# Microalbuminuria, peripheral artery disease, and cognitive function

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**Kidney disease may be linked to a decline in cognitive activity. We examined the association of microalbuminuria and cognitive function in a general population of older adults in the United States drawn from the National Health and Nutrition Examination Survey of 1999–2002. Cognitive function was measured by digit symbol substitution in 2386 participants 60 years of age and older of whom 448 had microalbuminuria. Covariates included age, gender, race/ethnicity, education, smoking, diabetes, and hypertension. Among participants with peripheral artery disease, those with microalbuminuria had a significantly lower cognitive function score compared to those with a normal albumin-to-creatinine ratio. The association between microalbuminuria and cognitive function was weak in those without peripheral artery disease. But in those with peripheral artery disease, the odds of microalbuminuria associated with cognitive function in the lowest and middle tertiles was 6.5 and 3.5, respectively.**

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Decline in cognitive function is a growing public health problem for the elderly population. Approximately 15% of the US population over 65 years of age have frank dementia, while estimates suggest that 30–45% of the elderly population experience milder forms of cognitive impairment.[1–3] Cognitive impairment is associated with disability, increased home health-care use, hospitalization, entry into skilled nursing facilities, and mortality.[1,4–6] In addition, persons with cognitive function loss may experience adverse psychosocial and economic burdens.

There is growing evidence that chronic kidney disease (CKD) is associated with cognitive impairment in older adults.[7–14] Patients undergoing treatment for end-stage renal disease are at greater risk for having cognitive impairment than the general population.[8,10,12,15] Furthermore, the presence of even mild kidney dysfunction (estimated by a glomerular filtration rate (GFR) of 45–59 $ml\,min^{-1}\,1.73\,m^{-2}$) independently predicts the development of cognitive impairment.[7]

Albuminuria may be one of the earliest markers of CKD. It is generally thought to arise as a consequence of glomerular capillary leak, and likely also represents a marker for systemic atherosclerosis and endothelial dysfunction.[16,17] Yet, there are currently no studies examining the relationship of albuminuria with cognitive dysfunction.

We therefore examined the association of microalbuminuria and cognitive impairment in a general population sample of older adults.

## RESULTS

The characteristics of the study population are shown in Table 1. The population had a mean age of 71 years (range: 60–85 years), was predominantly white (90% white, 7% African American, and 3% Mexican American), and had slightly more women (56%) than men. Of the 2386 participants included in the study, 18.8% ($N=448$) had evidence of microalbuminuria and 81.2% ($N=1938$) had normal levels of urinary albumin-to-creatinine ratio concentrations. Differences in the distributions of age, education, alcohol use, diabetes, blood pressure, C-reactive protein, ankle-brachial index, and peripheral artery disease were observed between persons with and without microalbuminuria (Table 1). Also, participants with microalbuminuria demonstrated significantly lower mean levels of cognitive

**Table 1 | Characteristics[a] of NHANES 1999–2002 study participants 60 years of age and older, overall and by MA**

| | Total N=2386 | No MA N=1938 | MA N=448 | P-value |
|---|---|---|---|---|
| Age, years | 70.6 (0.272) | 69.9 (0.270) | 73.1 (0.456) | <0.001 |
| *Ethnicity, %* | | | | |
| White | 90.1 | 90.5 | 88.9 | 0.100 |
| African American | 7.0 | 6.6 | 8.0 | |
| Mexican American | 3.0 | 2.9 | 3.2 | |
| Gender, % male | 43.5 | 41.4 | 49.4 | <0.001 |
| High school education, % | 71.7 | 74.0 | 64.5 | 0.001 |
| Alcohol use, % | 61.9 | 62.6 | 59.1 | 0.253 |
| Current smoking, % | 12.2 | 12.0 | 12.6 | 0.741 |
| Hypertension, % | 65.7 | 62.4 | 76.0 | <0.001 |
| Diabetes, % | 13.1 | 11.0 | 19.6 | <0.001 |
| % glycohemoglobin | 5.7 | 5.7 | 6.0 | <0.001 |
| Systolic BP, mm Hg | 138 (0.772) | 135 (0.687) | 146 (1.38) | <0.001 |
| Diastolic BP, mm Hg | 69.0 (0.538) | 69.1 (0.488) | 68.3 (1.21) | 0.488 |
| Serum glucose,[b] mg per 100 ml | 103 (0.861) | 99.8 (0.869) | 112 (2.26) | <0.001 |
| Body mass index, kg $m^{-2}$ | 28.23 (0.138) | 28.3 (0.158) | 28.1 (0.333) | 0.625 |
| C-reactive protein, mg per 100 ml | 0.52 (0.027) | 0.488 (0.024) | 0.623 (0.042) | 0.010 |
| Ankle-brachial index | 1.10 (0.004) | 1.10 (0.004) | 1.09 (0.006) | 0.268 |
| Peripheral artery disease,[c] % | 10.4 | 9.90 | 12.4 | 0.109 |
| DSS score | 47.7 (0.670) | 49.6 (0.752) | 41.6 (0.923) | <0.001 |
| Serum creatinine, mg per 100 ml | 0.96 (0.008) | 0.938 (0.007) | 1.02 (0.018) | <0.001 |
| ACR, mg $g^{-1}$ | 21.5 (0.772) | 8.27 (0.184) | 60.4 (1.96) | <0.001 |
| Estimated GFR | 75.4 (0.644) | 76.1 (0.591) | 73.2 (1.44) | 0.063 |
| Estimated GFR<60 ml $min^{-1}$ 1.73 $m^{-2}$, % | 18.9 | 17.2 | 23.7 | 0.004 |

ACR, urinary albumin-to-creatinine-ratio; BP, blood pressure; DSS, digit symbol substitution; GFR, glomerular filtration rate; MA, microalbuminuria (defined as ACR 17–250mg $g^{-1}$ in men and 25–350mg $g^{-1}$ in women).
[a]Mean (s.e.) for continuous variables and percentages for categorical variables.
[b]Nonfasting serum glucose.
[c]Peripheral artery disease defined as ankle-brachial index <0.90 in at least one leg.

function than those without microalbuminuria as demonstrated by the digit symbol substitution (DSS) scores of 41.6 and 49.6, respectively. Due to the statistically significant interaction of peripheral artery disease with microalbuminuria, all further analyses were stratified on the basis of peripheral artery disease status. This interaction was ordinal, indicating that the effect estimates for the association between microalbuminuria and cognitive function were in the same direction for persons with and without peripheral artery disease, but were of greater magnitude for the former. There were 231 persons with peripheral artery disease and 1803 persons without peripheral artery disease in a total of 2034.

The relationship between cognitive function and microalbuminuria varied by the presence or absence of peripheral artery disease. Cognitive functioning based on DSS scores was higher among persons with peripheral artery disease (mean DSS score: $41.1 \pm 1.1$) than those without it (mean DSS score: $49.9 \pm 0.7$) (not shown). The prevalence of microalbuminuria was also higher among persons with peripheral artery disease (18.7%) compared to those without it (13.6%). Figure 1 shows the prevalence of microalbuminura by tertile of DSS score and stratified by peripheral artery disease status. As shown, the percentage of study participants with microalbuminuria decreased with greater cognitive function among persons with and without peripheral artery disease.

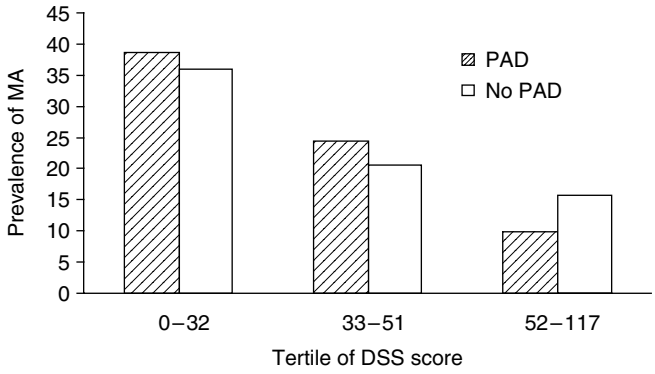


**Figure 1 | Prevalence of microalbuminuria (MA) by peripheral artery disease (PAD) status and tertile of cognitive function.**

In unadjusted linear regression models (Table 2), lower cognitive function levels were associated with microalbuminuria among persons with and without peripheral artery disease (−8.7 (95% confidence interval (CI): −13.9, −3.6) and −6.6 (95% CI: −8.7, −4.4), respectively). After adjusting for confounders in a base model (including age, race/ethnicity, gender, education, smoking, diabetes, and hypertension), the magnitude of the difference in cognitive function associated with microalbuminuria among persons with peripheral artery disease was attenuated slightly to −6.7 (95% CI: −9.9, −3.5). The association between micro-