Albuminuria and Decline in Cognitive Function

The ONTARGET/TRANSCEND Studies

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Background: Microvascular disease of the kidney (manifesting as albuminuria) and of the brain (manifesting as cognitive decline) may share a common pathogenesis. Gaining an understanding of the concomitant history of these 2 conditions may inform clinical practice and lead to novel prevention and treatment approaches.

Methods: A total of 28 384 participants with vascular disease or diabetes mellitus were examined. At baseline and year 5, participants underwent a Mini-Mental State Examination (MMSE) and urine testing for albumin excretion. Multivariable logistic regression was used to determine the association between albumin excretion and MMSE score, cross-sectionally and prospectively, and whether angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker use modified the association.

Results: Compared with participants with normoalbuminuria, those with microalbuminuria (odds ratio [OR], 1.26; 95% confidence interval [CI], 1.11-1.44]) and macroalbuminuria (1.49; 1.20-1.85) were more likely to have a reduced MMSE score (<24). On follow-up, participants with baseline albuminuria had increased odds of cognitive decline (decrease in MMSE score ≥3 points) compared with those with normoalbuminuria (microalbuminuria: OR, 1.22; 95% CI, 1.07-1.38; macroalbuminuria: 1.21; 0.94-1.55). Participants who developed new albuminuria had increased odds of cognitive decline during follow-up compared with those who remained normoalbuminuric (new microalbuminuria: OR, 1.30; 95% CI, 1.12-1.52; new macroalbuminuria: 1.77; 1.24-2.54). Participants with baseline macroalbuminuria treated with an angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker had lower odds of MMSE decline than participants treated with placebo.

Conclusion: Factors that contribute to albuminuria may contribute to cognitive decline, supporting the notion that both conditions share a common microvascular pathogenesis.

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KIDNEYS THAT EXCRETE EXCESsive amounts of albumin have many of the same microvascular features that are found in the brains of people with cognitive impairment, eg, capillary basement membrane thickening, luminal narrowing, and leakiness.[1-3] These observations suggest that both conditions may share a common pathogenesis, and they may also share similar natural courses. Recently, several studies demonstrated that microalbuminuria and macroalbuminuria are associated with increased odds or risk of cognitive impairment. Given the cross-sectional nature of some of these studies[4-6] and the inconclusive results of the prospective studies (2 of which had <2 years of follow-up),[7-9] it would be of interest to perform larger studies with longer follow-up to confirm and quantify the prospective relationship between albuminuria and cognitive impairment. If such a relationship does exist, it will contribute to a better understanding of pathways leading to cognitive decline that may facilitate new approaches to prevention and possibly treatment.

The Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET) and the Telmisartan Randomized Assessment Study in ACE [Angiotensin-Converting Enzyme]–Intolerant Subjects With Cardiovascular Disease (TRANSCEND) provide an opportunity to address these questions because both trials included participants with baseline and follow-up measurement of albuminuria and cognitive function.[10] A significant proportion of participants had albuminuria. In this study we determined (1) the association between the presence and severity of albuminuria at baseline and cognitive function at baseline and follow-up, and (2) the relationship between an increase in albumin excretion and change in cognitive function during follow-up. Our hypothesis was that

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the presence and severity of albuminuria and its progression were independently associated with decline in cognitive function. We also examined whether use of ACE inhibitors and/or angiotensin receptor blocker (ARBs) modified the association of albuminuria with cognitive function.

METHODS

POPULATION

The ONTARGET was a double-blind, randomized cardiovascular outcome study of 25 620 participants with vascular disease or diabetes mellitus (DM) with end-organ damage, randomly assigned to receive the ARB telmisartan (80 mg/d), the ACE inhibitor ramipril (10 mg/day), or their combination. It reported that the 2 medications were equal in terms of cardiovascular and renal outcomes, whereas their combination was associated with more adverse effects and offered no benefit other than reducing the level of albuminuria.[11,12] A parallel study, the TRANSCEND, determined whether telmisartan was superior to placebo in 5926 patients who had the same eligibility criteria as in ONTARGET but were intolerant of ACE inhibitors. It demonstrated that telmisartan had no statistically significant effect on the primary cardiovascular outcome (cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure), but it reduced the risk of the secondary composite outcome of cardiovascular death, myocardial infarction, and stroke. It had no effect on cardiovascular or total mortality.[13,14] The median follow-up of both studies was 56 months. Nested within these studies was a cognition study with serial assessment of Mini-Mental State Examination (MMSE). Repeated measurements of albuminuria were also obtained. All participants signed informed consent on study entry.

OUTCOME MEASURES

Cognitive function was ascertained by use of the MMSE at baseline and at the penultimate study visit. The MMSE includes 10 domain items, which relate to orientation to time (5 points), orientation to place (5 points), registration of new information (3 points), attention and calculation (5 points), recall (3 points), naming and repetition (3 points), items assessing language skills (8 points [2 naming items, repeating a phrase, following a 3-step command, reading and following a written command, and writing a sentence]), and design copy (1 point), the last being a brief measure of visual construction. The MMSE scale ranges from 0 to 30, with higher scores indicating better cognitive performance. The MMSE is a screening instrument to discriminate cognitive impairment and dementia.[15] Contextually appropriate translations of the MMSE were used in several countries (Austria, Belgium, Czech Republic, Germany, Greece, the Netherlands, Finland, Norway, Sweden, South Africa, United Arab Emirates, and South Korea).

A decrease of 3 points or more in the MMSE score was considered a significant change in cognitive function and is a cutoff point that has been used previously.[16] An MMSE score of less than 24 has been used as a conventional cutoff point for clinically significant cognitive impairment.[14]

MEASUREMENT OF ALBUMINURIA AND OTHER LABORATORY TESTING

Albuminuria was measured as urine albumin to creatinine ratio before run-in and at the penultimate visit. A value between 30 and 299 mg per gram of creatinine (to convert to milligrams per millimole, multiply by 0.113) was defined as microalbuminuria. A value of 300 mg or more per gram of creatinine was defined as macroalbuminuria. Urine albumin was measured centrally by a turbidimetric method (Unicel DxC600 Synchron Systems; Beckman Coulter, Brea, California). The coefficient of variation was 4.4% at 32.2 mg/L and 2.4% at 105.5 mg/L. A human serum pool at a concentration of 10.9 mg/L gave a coefficient of variation of 9.2%, and at 159.8 mg/L gave a coefficient of variation of 2.7%. Creatinine in urine was measured centrally by a modified Jaffe method (Unicel DxC600 Synchron Systems). The coefficient of variation was 2.9% at 7.9 mg/L and 2.8% at 23.1 mg/L. A human serum pool at a concentration of 10.8 mg/L gave a coefficient of variation of 2.6%, and at 103 mg/L gave a coefficient of variation of 1.8%.

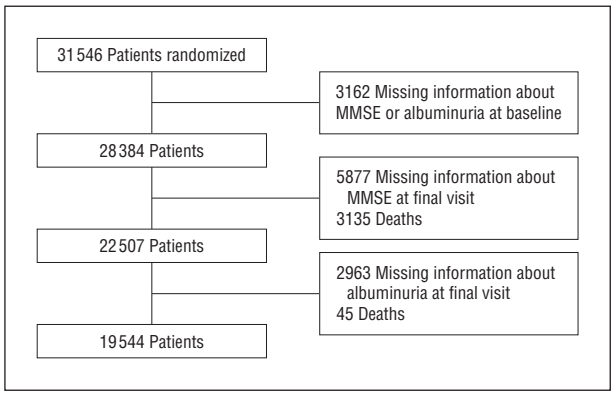

Figure 1. Flow diagram of study participants in whom the relationship of Mini-Mental State Examination (MMSE) scores and change in MMSE scores with baseline albuminuria and change in albuminuria was analyzed.

Serum creatinine was measured before run-in, 6 weeks after randomization, after 2 years, and at study conclusion. Serum creatinine was measured locally at study sites. From these values, the estimated glomerular filtration rate (eGFR) was calculated by means of the 4-item Modification of Diet in Renal Disease formula.[17]

BASELINE AND INCIDENT COVARIATES

Baseline characteristics were obtained through questionnaires and clinical assessment. Fasting glucose and lipid values were obtained locally. Depression was considered present if the participant answered positively to the questions "Have you felt sad, in low spirits or depressed for the past 2 weeks or more?" and "Have you thought of death or required treatment for depression?" Regular alcohol use was defined as 3 or more drinks per week; binge drinking was defined as more than 5 drinks per day. Being physically active was defined as doing exercise 2 to 4 times a week or more. Education level was categorized by the highest attained level. Data were sought regarding prevalent and incident cardiac events (myocardial infarction, angina, hospitalization for heart failure), stroke/transient ischemic attacks, peripheral artery disease, coronary artery bypass grafting, and percutaneous coronary intervention, as well as medication use.

STATISTICAL METHODS

Continuous data were summarized by means and standard deviations, and the comparison across normoalbuminuria, microalbuminuria, and macroalbuminuria was performed via analysis of variance method. Categorical data were presented as frequencies and percentages and then compared with the χ^2 test. Multivariable logistic regression was used to determine (1) the association between presence and severity of albuminuria (at baseline) and cognitive function at baseline and at follow-up and (2) the association between an increase in albumin excretion during follow-up and decline in cognitive function during follow-up (**Figure 1**). Only participants with available urine albumin to

Table 1. Baseline Characteristics of the ONTARGET/TRANSCEND Cohorts Included in the Cognition Evaluation Study Categorized as Having Normoalbuminuria, Microalbuminuria, or Macroalbuminuria[a]

Variable	Overall	Albuminuria			*P* Value
		Normal	Micro	Macro	
Participants, No. (%)	28 384	23 829 (84.0)	3551 (12.5)	1004 (3.5)	
Demographics, mean (SD)					
Female, No. (%)	8339 (29.4)	6963 (29.2)	1066 (30.0)	310 (30.9)	.35
Age, y	66.51 (7.21)	66.34 (7.16)	67.59 (7.46)	66.70 (7.23)	<.001
SBP at entry, mm Hg	141.70 (17.32)	140.65 (17.07)	146.36 (17.53)	150.17 (17.47)	<.001
DBP at entry, mm Hg	82.08 (10.34)	81.88 (10.28)	82.91 (10.65)	83.71 (10.39)	<.001
BMI	28.10 (4.55)	27.98 (4.46)	28.66 (4.79)	29.00 (5.39)	<.001
Waist circumference, cm	96.06 (13.18)	95.63 (12.92)	98.00 (13.99)	99.38 (15.15)	<.001
Laboratory values, mean (SD)					
Glucose, mg/dL	119.6 (45.8)	115.1 (40.2)	138.6 (59.5)	158.0 (71.5)	<.001
Creatinine, mg/dL	1.06 (0.27)	1.04 (0.25)	1.12 (0.34)	1.29 (0.44)	<.001
eGFR, mL/min/1.73 m^2	73.19 (19.60)	74.07 (18.82)	70.47 (22.34)	62.02 (22.76)	<.001
eGFR <60 mL/min/m^2, No. (%)	6990 (24.6)	5270 (22.1)	1208 (34.0)	512 (51.0)	<.001
TC, mg/dL	191.5 (43.6)	190.7 (42.3)	193.8 (47.1)	201.9 (50.2)	<.001
Triglycerides, mg/dL	154.0 (101.8)	150.4 (94.7)	169.0 (131.9)	184.1 (123.9)	<.001
HDL-C, mg/dL	48.6 (15.8)	49.0 (15.8)	47.9 (15.4)	47.1 (17.4)	<.001
LDL-C, mg/dL	113.1 (37.8)	112.7 (37.5)	113.9 (40.5)	119.7 (43.6)	<.001
Albuminuria, mg/g of creatinine	47.2 (215.0)	5.9 (5.9)	94.1 (65.9)	860.4 (762.5)	<.001
Ethnicity, No. (%)					
Asian	4443 (15.7)	3616 (15.2)	635 (17.9)	192 (19.1)	<.001
Arab	268 (0.9)	183 (0.8)	59 (1.7)	26 (2.6)	
African	685 (2.4)	501 (2.1)	132 (3.7)	52 (5.2)	
European	20 200 (71.2)	17 243 (72.4)	2347 (66.1)	610 (60.8)	
Native or aboriginal	2525 (8.9)	2071 (8.7)	343 (9.7)	111 (11.1)	
Other	258 (0.9)	210 (0.9)	35 (1.0)	13 (1.3)	
Smoking status, No. (%)					
Never	10 522 (37.1)	8819 (37.0)	1342 (37.8)	361 (36.0)	.007
Formerly	14 400 (50.7)	12 159 (51.0)	1750 (49.3)	491 (48.9)	
Current	3429 (12.1)	2821 (11.8)	456 (12.8)	152 (15.1)	
Cardiovascular disease, No. (%)					
History of hypertension	19 889 (70.1)	16 229 (68.1)	2816 (79.3)	844 (84.1)	<.001
CAD (MI, angina, PCI, CABG)	21 305 (75.1)	18 346 (77.0)	2342 (66.0)	617 (61.5)	<.001
Stroke/TIA	6028 (21.2)	4959 (20.8)	857 (24.1)	212 (21.1)	<.001
PAD (angioplasty/claudication/limb amputation)	4107 (14.5)	3176 (13.3)	679 (19.1)	252 (25.1)	<.001
LVH	3697 (13.0)	2858 (12.0)	598 (16.8)	241 (24.0)	<.001
Diabetes mellitus	10 561 (37.2)	7671 (32.2)	2095 (59.0)	795 (79.2)	<.001
Alcohol consumption, No. (%)					
≥3 Drinks/wk	7990 (28.1)	6868 (28.8)	908 (25.6)	214 (21.3)	<.001
No alcohol	17 184 (60.5)	14 206 (59.6)	2272 (64.0)	706 (70.3)	
Some alcohol	10 652 (37.5)	9152 (38.4)	1219 (34.3)	281 (28.0)	
Binge alcohol	546 (1.9)	469 (2.0)	60 (1.7)	17 (1.7)	<.001

(continued)

creatinine ratio and MMSE scores at baseline or baseline and 5 years were included in the corresponding regression analyses. The characteristics of included patients and other participants were compared by unpaired, 2-tailed *t* tests for continuous variables and χ^2 test for categorical variables. Multivariate analyses were also used to examine whether ACE inhibitor and/or ARB use modified the association of albuminuria with cognition change.

All models were adjusted for demographic factors (age, sex, and ethnicity [European, Arab, African, native or aboriginal, and other]) and level of education [none, 1-8 years, 9-12 years, trade/technical school, and college/university]), previous cardiovascular disease (CVD), and risk factors, including the following: history of myocardial infarction, angina, coronary artery bypass grafting, and stroke/transient ischemic attacks; eGFR as a continuous variable; hypertension and baseline systolic blood pressure; smoking (never, former, or current); body mass index; lipid levels; and DM and fasting glucose levels. Other factors affecting or possibly affecting cognition were also adjusted for: (1) alcohol use (none, binge [>5 drinks/d], once a week, 2-4/wk, 5-6/wk, or every day); (2) depression (yes/no); and (3) use of medications: statins, β-blockers, antiplatelet agents, calcium-channel blockers, and anticoagulants. For incident changes in MMSE, additional adjustment was made for incident CVD events and for change in eGFR. A 2-tailed $P < .05$ was considered statistically significant. Analyses were performed with SAS version 8.2 (SAS Institute, Inc, Cary, North Carolina).

RESULTS

In total, 28 384 participants with baseline albuminuria levels and MMSE scores were included, of whom 84.0% had normoalbuminuria, 12.5% microalbuminuria, and 3.5% macroalbuminuria (**Table 1**). Compared with participants with normoalbuminuria, those with albuminuria were older; had higher blood pressure, body mass index, and waist circumference; had higher glucose and creatinine levels, lower eGFR, increased low-density lipoprotein cholesterol levels, and reduced high-density lipoprotein cholesterol levels; were less likely to be of European ethnicity; were more likely to currently smoke; more frequently had a history of hypertension, left ventricular hypertrophy, and DM; had less clinical vascular

Table 1. Baseline Characteristics of the ONTARGET/TRANSCEND Cohorts Included in the Cognition Evaluation Study Categorized as Having Normoalbuminuria, Microalbuminuria, or Macroalbuminuria (continued)

Variable	Overall	Albuminuria			*P* Value
		Normal	Micro	Macro	
Study, No. (%)					
ONTARGET	23 039 (81.2)	19 104 (80.2)	3004 (84.6)	931 (92.7)	<.001
TRANSCEND	5345 (18.8)	4725 (19.8)	547 (15.4)	73 (7.3)	
Education completed, No. (%)					
None	959 (3.4)	723 (3.0)	171 (4.8)	65 (6.5)	
1-8 y	8440 (29.7)	6898 (28.9)	1201 (33.8)	341 (34.0)	
9-12 y	8402 (29.6)	7069 (29.7)	1025 (28.9)	308 (30.7)	<.001
Trade/technical school	5101 (18.0)	4396 (18.4)	550 (15.5)	155 (15.4)	
College/university	5480 (19.3)	4741 (19.9)	604 (17.0)	135 (13.4)	
Depression, No. (%)	4142 (14.6)	3491 (14.7)	498 (14.0)	153 (15.2)	.52
Physical activity level, No. (%)					
Active	18 882 (66.5)	16 269 (68.3)	2074 (58.4)	539 (53.7)	
Mainly sedentary	6361 (22.4)	5018 (21.1)	1024 (28.8)	319 (31.8)	
<Once/wk	3137 (11.1)	2538 (10.7)	453 (12.8)	146 (14.5)	<.001
2-4 times/wk	6550 (23.1)	5626 (23.6)	719 (20.2)	205 (20.4)	
5-6 times/wk	2211 (7.8)	1934 (8.1)	221 (6.2)	56 (5.6)	
Every day	10 121 (35.7)	8709 (36.5)	1134 (31.9)	278 (27.7)	<.001
Medications, No. (%)					
Statin	17 230 (60.7)	14 726 (61.8)	1963 (55.3)	541 (53.9)	<.001
β-Blocker	16 226 (57.2)	13 870 (58.2)	1843 (51.9)	513 (51.1)	<.001
Aspirin or antiplatelet drug	22 912 (80.7)	19 541 (82.0)	2667 (75.1)	704 (70.1)	<.001
Diuretic	8148 (28.7)	6464 (27.1)	1249 (35.2)	435 (43.3)	<.001
Calcium-channel blocker	9818 (34.6)	7790 (32.7)	1540 (43.4)	488 (48.6)	<.001
Anticoagulant	2106 (7.4)	1641 (6.9)	364 (10.3)	101 (10.1)	<.001
Ramipril (ONTARGET)	7711 (27.2)	6420 (26.9)	1001 (28.2)	290 (28.9)	
Telmisartan (ONTARGET and TRANSCEND)	10 342 (36.4)	8700 (36.5)	1264 (35.6)	378 (37.6)	
Combination of ACEI and ARB	7647 (26.9)	6335 (26.6)	1019 (28.7)	293 (29.2)	
Placebo	2684 (9.5)	2374 (10.0)	267 (7.5)	43 (4.3)	<.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, coronary artery bypass grafting; CAD, coronary artery disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; macro, macroalbuminuria; micro, microalbuminuria; MI, myocardial infarction; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TC, total cholesterol; TIA, transient ischemic attack; TRANSCEND, Telmisartan Randomized Assessment Study in ACE [Angiotensin-Converting Enzyme]–Intolerant Subjects With Cardiovascular Disease.

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; creatinine to micromoles per liter, multiply by 88.4; triglycerides to millimoles per liter, multiply by 0.0113; TC, HDL-C, and LDL-C to millimoles per liter, multiply by 0.0259; and albuminuria to milligrams per millimole, multiply by 0.113.

[a] Because of rounding, percentages may not total 100.

disease; drank alcohol less often; had lower attained levels of education; and were less physically active at baseline. Those with microalbuminuria or macroalbuminuria were also less likely to be taking a statin, a β-blocker, or aspirin but were more likely to be taking a diuretic, calcium-channel blocker, or anticoagulant.

BASELINE ALBUMINURIA AND COGNITIVE FUNCTION

Mean (SD) baseline MMSE scores were 27.8 (2.7), 27.2 (3.3), and 26.8 (3.7) in participants with normoalbuminuria, microalbuminuria, and macroalbuminuria, respectively (**Table 2**; eFigure, http://www.archinternmed.com). There was a graded increase in MMSE score less than 24 with increasing severity of albuminuria. On multivariable analyses (**Table 3**), the presence of albuminuria was associated with impaired cognitive function (MMSE score <24), with odds ratios (ORs) of 1.27 (95% confidence interval [CI], 1.12-1.45) for microalbuminuria and 1.51 (1.22-1.87) for macroalbuminuria. When these analyses were repeated (eTable 1), categorized by sex, English or non-English speaker, white or nonwhite, or highest level of attained education, a similar effect was noted. There was no relationship between baseline MMSE scores and quartiles of urine albumin in participants with albuminuria levels less than 30 mg/g of creatinine (data not shown).

Table 2. Distribution of MMSE Scores and Mean MMSE Scores Categorized by Baseline Level of Albuminuria

Baseline MMSE Score	No. (%)			
	All	Albuminuria		
		Normal	Micro	Macro
≥28	18 832 (66.3)	16 111 (67.6)	2158 (60.8)	563 (56.1)
≥24	26 019 (91.7)	22 032 (92.5)	3131 (88.2)	856 (85.3)
<24	2365 (8.3)	1797 (7.5)	420 (11.8)	148 (14.7)
20 to <24	1757 (6.2)	1374 (5.8)	289 (8.1)	94 (9.4)
<20	608 (2.1)	423 (1.8)	131 (3.7)	54 (5.4)
Mean (SD)	27.7 (2.9)	27.8 (2.7)	27.2 (3.3)	26.8 (3.7)

Abbreviations: macro, macroalbuminuria; micro, microalbuminuria; MMSE, Mini-Mental State Examination.

Compared with participants with baseline albuminuria and MMSE values, participants who did not have measured baseline albuminuria and/or MMSE scores had a

Table 3. Logistic Regression Models of Odds of MMSE Score Less Than 24 at Baseline in Participants With Microalbuminuria or Macroalbuminuria vs Without Albuminuria[a]

Variable	Model, OR (95% CI)			
	1	2	3	4
No albuminuria	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Microalbuminuria	1.64 (1.47-1.84)	1.34 (1.18-1.52)	1.29 (1.14-1.47)	1.27 (1.12-1.45)
Macroalbuminuria	2.12 (1.77-2.54)	1.63 (1.33-2.00)	1.57 (1.27-1.94)	1.51 (1.22-1.87)

Abbreviations: CI, confidence interval; MMSE, Mini-Mental State Examination; OR, odds ratio.

[a]Models were sequentially adjusted for confounders: model 1, unadjusted; model 2, adjusted for age, sex, ethnicity (European, Asian, African, Arab, native, or other), and education (none, 1-8 years, 9-12 years, trade/technical school, or college); model 3, further adjusted for history of cardiovascular disease at baseline (myocardial infarction, angina, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, stroke, and transient ischemic attack), history of diabetes mellitus and hypertension, baseline systolic blood pressure, smoking (never, past, or current), body mass index, and estimated glomerular filtration rate as a continuous variable; and model 4, further adjusted for alcohol use (yes/no, binge), exercise (none, once a week, 2-4 times/wk, 5-6 times/wk, or daily), depression, and medication use (statins, β-blockers, antiplatelet drugs, diuretics, calcium-channel blockers, and anticoagulants). The following factors were also significantly ($P < .03$) associated with a significantly increased odds of MMSE score less than 24 in model 4: increasing age, being non-European, having no education vs any education, history of stroke/transient ischemic attack, nonsmoker vs former or current smoker, lower body mass index, no alcohol vs use of alcohol or binge alcohol, no exercise vs any amount of exercise, depression, and use of diuretics.

Table 4. Logistic Regression Model of Odds of a 3-Point or Greater Decrease in MMSE Score From Baseline to Year 5 of Follow-up in Participants With Microalbuminuria or Macroalbuminuria vs Without Albuminuria[a]

Variable	Model, OR (95% CI)			
	1	2	3	4
No albuminuria	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Microalbuminuria	1.38 (1.22-1.55)	1.29 (1.14-1.46)	1.23 (1.08-1.39)	1.23 (1.08-1.39)
Macroalbuminuria	1.43 (1.13-1.80)	1.35 (1.07-1.72)	1.25 (0.98-1.59)	1.25 (0.98-1.59)

Abbreviations: CI, confidence interval; MMSE, Mini-Mental State Examination; OR, odds ratio.

[a]Models were sequentially adjusted for confounders: model 1, unadjusted; model 2, adjusted for age, sex, ethnicity (European, Asian, African, Arab, native, or other), and education (none, 1-8 years, 9-12 years, trade/technical school, or college); model 3, further adjusted for history of cardiovascular disease at baseline and incident cardiovascular disease during follow-up (myocardial infarction, angina, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, stroke, and transient ischemic attack), history of diabetes mellitus and hypertension, baseline systolic blood pressure, smoking (never, past, or current), body mass index, and estimated glomerular filtration rate as a continuous variable; and model 4, further adjusted for alcohol use (yes/no, binge), exercise (none, once a week, 2-4 times/wk, 5-6 times/wk, or daily), depression, and medication use (statins, β-blockers, antiplatelet drugs, diuretics, calcium-channel blockers, and anticoagulants). The following factors were also significantly ($P < .04$) associated with a significantly increased odds of a 3-point or greater decrease in MMSE score from baseline to year 5 of follow-up in model 4: increasing age, being African or native vs European, having any education vs no education, a history of stroke/transient ischemic attack or diabetes, no alcohol consumption vs any consumption, and no exercise vs any amount of exercise.

greater burden of CVD risk factors, lower levels of achieved education, and lower activity levels (eTable 2).

BASELINE ALBUMINURIA AND DECLINE IN COGNITIVE FUNCTION ON FOLLOW-UP

For this analysis, 22 507 participants who had albuminuria and MMSE values at baseline and at follow-up were examined (**Table 4**). A decrease in MMSE score of 3 points or more occurred in 11.0% of participants without albuminuria, 14.5% with microalbuminuria, and 15.0% with macroalbuminuria. On multivariable analyses, baseline microalbuminuria (OR, 1.23; 95% CI, 1.08-1.39), but not macroalbuminuria (OR, 1.25; 95% CI, 0.98-1.59), was significantly associated with a 3-point or greater decline in MMSE score compared with those without albuminuria. When these analyses were repeated (eTable 3), categorized by sex, English or non-English speaker, white or nonwhite, or highest level of attained education, a similar effect was noted. Compared with participants with baseline and follow-up MMSE values, participants without follow-up MMSE values had higher levels of CVD risk factors, more prevalent CVD, lower renal function, higher levels of albuminuria, and lower levels of attained education (eTable 4).

We further examined whether the use of medications (telmisartan from ONTARGET and TRANSCEND, n=8240; ramipril from ONTARGET, n=6184; and the combination of ramipril and telmisartan from ONTARGET, n=6027) vs placebo (TRANSCEND, n=2056) modified the association of albuminuria with cognitive decline (**Table 5**). In unadjusted analyses, there was no overall effect in each treatment group. However, when groups were subdivided by albuminuria status, there was a decrease in the odds of MMSE decline in participants with macroalbuminuria, especially with telmisartan. The overall interaction term of treatment on the odds of MMSE decline approached statistical significance ($P=.055$) and was significant with adjustment ($P=.02$).

CHANGE IN URINARY ALBUMIN EXCRETION AND DECLINE IN COGNITIVE FUNCTION ON FOLLOW-UP

This analysis included 19 544 participants with both urine albumin and MMSE measurements at baseline and at follow-up. During follow-up, 83.0% (16 216 of 19 544 participants) had no change in albuminuria status (normo-

Table 5. Odds Ratios (ORs) (Logistic Regression Analyses) of a 3-Point or Greater Decline in MMSE Score From Baseline to the Penultimate Visit by Treatment in the ONTARGET and TRANSCEND Studies Combined[a]

		Baseline Albuminuria Status			Interaction *P* Value
	Overall	Normal	Micro	Macro	
Overall					
No.	22 507	19 393	2533	581	
Event,[b] No. (%)	2587 (11.49)	2132 (10.99)	368 (14.53)	87 (14.97)	
Telmisartan (OT + TR)					
No.	8240	7111	912	217	
Event, No. (%)	952 (11.55)	782 (11.00)	146 (16.01)	24 (11.06)	
Ramipril					
No.	6184	5290	731	163	
Event, No. (%)	717 (11.59)	601 (11.36)	91 (12.45)	25 (15.34)	
Combination					
No.	6027	5141	711	175	
Event, No. (%)	686 (11.38)	547 (10.64)	108 (15.19)	31 (17.71)	
Placebo					
No.	2056	1851	179	26	
Event, No. (%)	232 (11.28)	202 (10.91)	23 (12.85)	7 (26.92)	
Unadjusted ORs					
Telmisartan (OT + TR) vs placebo					.05
OR (95% CI)	1.03 (0.88-1.20)	1.01 (0.86-1.19)	1.29 (0.81-2.07)	0.34 (0.13-0.89)	
P value	.73	.92	.29	.03	
Ramipril vs placebo					.31
OR (95% CI)	1.03 (0.88-1.21)	1.05 (0.88-1.24)	0.96 (0.59-1.57)	0.49 (0.19-1.29)	
P value	.70	.60	.88	.15	
Combination vs placebo					.39
OR (95% CI)	1.01 (0.86-1.18)	0.97 (0.82-1.15)	1.21 (0.75-1.97)	0.58 (0.23-1.51)	
P value	.90	.74	.43	.27	
Interaction *P* value				.055	
Adjusted ORs					
Telmisartan (OT + TR) vs placebo					.02
OR (95% CI)	1.10 (0.94-1.28)	1.08 (0.91-1.28)	1.43 (0.87-2.33)	0.26 (0.09-0.76)	
P value	.25	.39	.15	.01	
Ramipril vs placebo					.17
OR (95% CI)	1.14 (0.97-1.34)	1.17 (0.98-1.39)	1.03 (0.62-1.72)	0.38 (0.13-1.14)	
P value	.12	.08	.90	.08	
Combination vs placebo					.23
OR (95% CI)	1.10 (0.94-1.30)	1.07 (0.90-1.28)	1.29 (0.78-2.13)	0.45 (0.15-1.31)	
P value	.24	.42	.33	.14	
Interaction *P* value				.02	

Abbreviations: CI, confidence interval; macro, macroalbuminuria; micro, microalbuminuria; MMSE, Mini-Mental State Examination; OT, ONTARGET; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial; OR, odds ratio; TR, TRANSCEND; TRANSCEND, Telmisartan Randomized Assessment Study in ACE [Angiotensin-Converting Enzyme]–Intolerant Subjects With Cardiovascular Disease.

[a] Adjustments are made for the same factors as in model 4 from Table 4.

[b] "Event" was a decrease in MMSE score of 3 points or more.

albuminuria, 15 022 participants; microalbuminuria, 924; and macroalbuminuria, 270); 5.9% (1155 of 19 544) had improvement in albuminuria status (macroalbuminuria to microalbuminuria, 131 participants; macroalbuminuria to normoalbuminuria, 94; and microalbuminuria to normoalbuminuria, 930); and 11.1% (2173 of 19 544) had worsening (normoalbuminuria to microalbuminuria, 1642 participants; normoalbuminuria to macroalbuminuria, 224; and microalbuminuria to macroalbuminuria, 307). Among those with normoalbuminuria at baseline who progressed to microalbuminuria or macroalbuminuria, there was a stepwise increase in the odds of a 3-point or greater MMSE score decrease compared with those who remained normoalbuminuric (OR [95% CI], 1.30 [1.12-1.52] and 1.77 [1.24-2.54], respectively) (**Table 6** and **Figure 2**). Compared with those whose microalbuminuria regressed to normoalbuminuria, those who remained microalbuminuric or had progression to macroalbuminuria had an increased odds of a 3-point or greater decrease in MMSE score (OR [95% CI], 1.33 [1.00-1.78] and 1.57 [1.07-2.32]). Last, compared with those whose macroalbuminuria regressed to normoalbuminuria, those who remained with macroalbuminuria or had regression to microalbuminuria were 1.50 (95% CI, 0.65-3.50) and 1.73 (0.70-4.29) more likely to have a 3-point or greater decrease in MMSE score.

Compared with participants with baseline and follow-up albuminuria and MMSE values, those without either or both of these values had a higher burden of CVD risk factors, more prevalent CVD, lower renal function, higher levels of albuminuria, and lower levels of attained education (eTable 5).

Table 6. Logistic Regression Model of the Odds of a 3-Point or Greater Decrease in MMSE Score From Baseline to Year 5 of Follow-up in Participants Whose Albuminuria Status Changed[a]

Variables	OR (95% CI)			
	Model 1	Model 2	Model 3	Model 4
[Normal to micro] vs [stay normal]	1.46 (1.26-1.70)	1.32 (1.14-1.54)	1.31 (1.12-1.53)	1.30 (1.12-1.52)
[Normal to macro] vs [stay normal]	1.94 (1.37-2.74)	1.87 (1.31-2.66)	1.84 (1.29-2.64)	1.77 (1.24-2.54)
[Stay micro] vs [micro to normal]	1.36 (1.04-1.79)	1.32 (1.00-1.73)	1.31 (0.98-1.74)	1.33 (1.00-1.78)
[Micro to macro] vs [micro to normal]	1.59 (1.11-2.27)	1.56 (1.08-2.25)	1.57 (1.07-2.31)	1.57 (1.07-2.32)
[Macro to micro] vs [macro to normal]	1.50 (0.64-3.51)	1.64 (0.69-3.91)	1.69 (0.70-4.11)	1.73 (0.70-4.29)
[Stay macro] vs [macro to normal]	1.69 (0.79-3.63)	1.70 (0.78-3.70)	1.34 (0.59-3.06)	1.50 (0.65-3.50)

Abbreviations: CI, confidence interval; macro, macroalbuminuria; micro, microalbuminuria; MMSE, Mini-Mental State Examination; OR, odds ratio.
[a]Models were sequentially adjusted for confounders: model 1, unadjusted; model 2, adjusted for age, sex, ethnicity (European, Asian, African, Arab, native, other), education (none, 1-8 years, 9-12 years, trade/technical school, or college), and baseline MMSE score; model 3, further adjusted for history of cardiovascular disease at baseline and incident cardiovascular disease during follow-up (myocardial infarction, angina, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, stroke, and transient ischemic attack), history of diabetes mellitus and hypertension, baseline systolic blood pressure, smoking (never, past, or current), body mass index, baseline estimated glomerular filtration rate as a continuous variable, and change in estimated glomerular filtration rate; and model 4, further adjusted for alcohol use (yes/no, binge), exercise (none, once a week, 2-4 times/wk, 5-6 times/wk, or daily), depression, and medication use (statins, β-blockers, antiplatelet drugs, diuretics, calcium-channel blockers, and anticoagulants). The following factors were also significantly ($P < .04$) associated with significantly increased odds of a 3-point or greater decrease in MMSE score from baseline to year 5 of follow-up in model 4: in the normal to micro/macro group: baseline MMSE score, increased age, African vs European, no education vs any education, previous or incident stroke/transient ischemic attack, lower systolic blood pressure, lower body mass index, history of diabetes mellitus, and no exercise vs any exercise; in the micro to normal/macro group: baseline MMSE score, increased age, no previous myocardial infarction/angina/revascularization, previous or incident stroke/transient ischemic attack, and no statin use; and in the macro to micro/normal group: no education vs 9 to 12 years or trade/technical school.

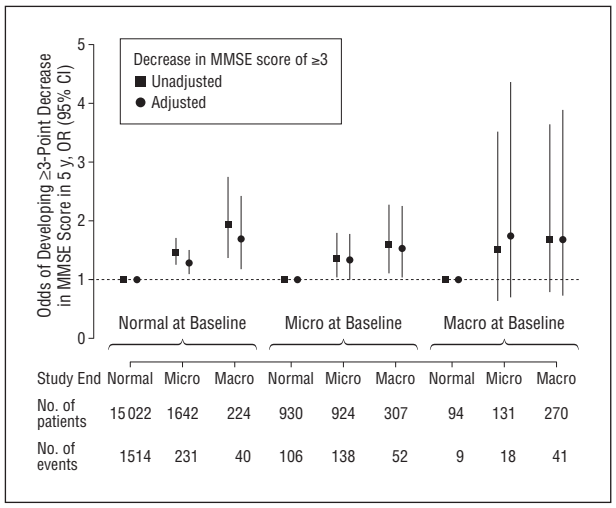

Figure 2. Odds ratios (ORs) and 95% confidence intervals (CIs) of developing a 3-point or greater decrease in Mini-Mental State Examination (MMSE) score during 5 years categorized by baseline normoalbuminuria (normal), microalbuminuria (micro), and macroalbuminuria (macro) and the change in albuminuria status during 5 years of follow-up.

COMMENT

This is, to our knowledge, the first study to report both a cross-sectional and a prospective, graded association between a marker of microvascular disease—albuminuria—and the development of cognitive decline. Importantly, this association was independent of clinical cardiovascular and renal disease (prevalent and incident) and cardiovascular risk factors, which cluster with albuminuria. These results are consistent with the notion that albuminuria and cognitive decline may share a common microvascular pathogenesis and progression.

It is hypothesized that changes in the cerebral microcirculation contribute to cognitive changes. Owing to the difficulty of studying such changes ante mortem and the lack of specific symptoms referable to them, most evidence for their role is indirect. Such evidence includes magnetic resonance imaging–defined silent strokes, white matter lesions, and white matter hyperintensity in the absence of clinical stroke events[18] and the presence of microvascular risk factors (such as hypertension, DM, and smoking) in people with cognitive impairment. Further evidence comes from cross-sectional studies of the retinal vasculature. Retinal arterioles share common anatomical and physiological characteristics with cerebral arterioles and are affected by hypertension and age. In the Atherosclerosis Risk in Communities Study, any form of retinopathy was associated with increased odds of cognitive impairment.[19] The greater the severity of the retinopathy (microaneurysms, hemorrhages, and exudates), the greater were the odds of impaired cognition. Similar findings were observed in the Cardiovascular Health Study in an older cohort.[20] One study demonstrated retinopathy to be associated with brain white matter hyperintensity.[21] Finally, 3 cross-sectional studies of albuminuria have shown it to be associated with dementia, white matter hyperintensity on magnetic resonance imaging, or poor executive functioning.[4-6]

Additional evidence of an association of microvascular disease and cognitive change comes from several cross-sectional studies of albuminuria. In a study of 2316 adults 65 years or older, drawn from the Cardiovascular Health Study, the risk of mild cognitive impairment was increased by 10% and that of dementia by 22% in univariate analysis for each doubling of the urine albumin to creatinine ratio.[4] The association of albuminuria with dementia remained significant in multivariate analysis. In a different study,[5] of 335 elderly participants, the presence of albuminuria was associated with worse executive functioning. In both studies the degree of albuminuria was associated with a graded increase in white matter

hyperintensity score. A third study, based on the National Health and Nutrition Examination Survey III data set, also reported an association between albuminuria and cognition but only in people with peripheral artery disease.[6]

Three studies have prospectively assessed the association of baseline albuminuria with cognitive change. A study from Australia found that cognitive decline in 204 older diabetic individuals was predicted across 1.5 years by increased urinary albumin excretion.[7] In a study of 140 elderly participants with impaired glucose tolerance, baseline urine albumin to creatinine ratio was associated with a 10% to 20% increased risk, during 1 year, of developing poor cognitive function.[8] Another report[9] showed no cross-sectional association between albuminuria and low cognitive scoring in older adults but a statistically significant prospective (6.6 years) association in men. In the largest of these studies,[9] there were only 90 participants with albuminuria. None had the ethnic and geographic diversity of our cohort or the large number of participants, with or without DM and CVD; nor were as many adjustments for covariates done as in our study.

A causal relationship between albuminuria and the development of cognitive change cannot be derived from our study. It is likely, however, that the 2 disorders arose concomitantly. The cerebral and renal circulations are characterized by high flow and low impedance. Autoregulation of the microvasculature serves to bring blood flow to these organs, at the same time limiting excess pressure exposure in the capillaries (reviewed by Mitchell[22]). Endothelial dysfunction and loss of microvascular autoregulation can disrupt the normal milieu within the extracellular matrix of the brain and kidney.[23] Strain in the microcirculation, for example, can increase the generation of reactive oxygen species.[22]

With regard to the modification of study drug on the association of albuminuria with MMSE decline, lower odds of MMSE decline compared with placebo were found with all treatments, especially telmisartan, in the presence of macroalbuminuria. These results are in keeping with our previous analyses that showed renin angiotensin system (RAS) blockade to be consistently effective in lowering proteinuria only in participants with greater than 1 g of protein per gram of creatinine in the urine.[14] The results suggest that, in this relatively small subgroup of study participants, RAS blockade may have been protective of cognitive function. Given the nonrandomized, observational nature of our analyses, such a conclusion should be viewed with caution. However, there is indirect support for our findings. A retrospective analysis of the Cardiovascular Health Study has shown that certain RAS blockers are protective of cognitive decline in people with hypertension. The effect was hypothesized to be due to decreased brain RAS activity.[24] A small, prospective study reported that patients treated with a combination of telmisartan and hydrochlorothiazide showed improvement in cognitive function compared with those treated with a combination of lisinopril and hydrochlorothiazide.[25] The Observational Study on Cognitive Function and Systolic Blood Pressure Reduction demonstrated antihypertensive therapy based on ARB use to be associated with preservation of cognitive function.[26] On the other hand, in the Study on Cognition and Prognosis in the Elderly, ARB use was not associated with lower rates of cognitive decline compared with placebo.[27] None of these studies examined albuminuria and cognition.

Of interest is to view our findings from a population perspective. Studies from the United States estimate that 14.6% to 32.7% of adults 60 years to 80 years or older have microalbuminuria or macroalbuminuria.[28] Among similarly aged adults with DM, the rates are 37.6% to 48.6%. Assuming that the presence of microalbuminuria or macroalbuminuria increases the odds of cognitive impairment by 22% to 44%, it follows that 3.2% to 14.4% of diminished cognitive function is associated with or explained by microalbuminuria or macroalbuminuria and in 8.3% to 21.4% of those with DM. Likewise, assuming that microalbuminuria or macroalbuminuria increases the risk of a decrease in cognitive function by approximately 18%, we estimate that 2.6% to 5.9% of cases of cognitive decline in the general population, and 6.8% to 8.7% in those with DM, are associated with microalbuminuria or macroalbuminuria. These estimates are in accord with estimates of cognitive decline in association with high white matter intensity scores.[29] It should be noted that our estimates apply to a population whose mean age is approximately 10 years younger than the "usual" age at which cognitive impairment appears.

There are several limitations to this study. First, participants in ONTARGET and TRANSCEND had vascular disease or were at high risk for it. These characteristics by themselves can increase the risk of cognitive disease.[2] Our results, therefore, may not be applicable to people with albuminuria without known vascular disease. Second, the MMSE is a general test of cognition, weighted mostly to memory and orientation; it does not capture deficiencies in various domains of cognitive function, nor can it detect subtle changes in frontal lobe executive function, a common early feature of vascular-related cognitive impairment. A simple screening tool such as the MMSE is used in large trials to minimize cost and to lessen inconvenience to the participant. Last, the cohorts for each of the 3 sets of analysis were healthier than those excluded from the analyses for lack of albuminuria or MMSE values. This makes our estimates conservative.

Our findings have clinical implications. They suggest that, among people with macrovascular disease, microvascular disease in one organ system may reflect microvascular disease in another. This may explain why dementia and mild cognitive impairment are more common in people with DM,[30] who have a high prevalence of albuminuria. Our findings offer a possible avenue for screening of people at risk for cognitive impairment. Our findings regarding treatment require confirmation by a dedicated prospective study.

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