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Dementia risk in renal dysfunction

A systematic review and meta-analysis of prospective studies

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ABSTRACT

Objective: Renal dysfunction has been linked with increased risk for cognitive impairment and dementia, but studies are conflicting. For that reason, the aim of the present systematic review and meta-analysis is to summarize the best available evidence on the prospective association between potential markers of renal dysfunction and development of cognitive impairment or dementia.

Methods: Medline, Embase, and Cochrane Database of Systematic Reviews were searched for potential publications until August 1, 2016. Studies were eligible if they fulfilled the following criteria: population-based study, prospective design, ≥ 100 participants, aged ≥ 45 years, ≥ 1 year follow-up, and cognition/dementia outcomes. Where appropriate, random effects meta-analyses were conducted yielding pooled odds ratios (OR) and 95% confidence intervals (CI).

Results: Twenty-two out of 8,494 abstracts fulfilled the eligibility criteria. Sufficient evidence was found for albuminuria, mixed results for estimated glomerular filtration rate (eGFR), insufficient support for cystatin C, and tentative evidence for serum creatinine and creatinine clearance. Meta-analyses of 5 studies representing 27,805 persons showed a 35% increased risk of cognitive impairment or dementia in those with albuminuria (OR 1.35, 95% CI 1.06–1.73, $p = 0.015$), whereas eGFR < 60 mL/min/1.73 m² showed no significant association (OR 1.28, 95% CI 0.99–1.65, $p = 0.063$). No meta-analyses could be done for serum creatinine, creatinine clearance, or cystatin C.

Conclusions: The overall evidence for an association between renal dysfunction and cognitive impairment or dementia is modest. Evidence suggests that albuminuria is associated with higher odds of developing cognitive impairment or dementia. *Neurology*® 2017;88:198–208

GLOSSARY

Ab = β -amyloid; **AD** = Alzheimer disease; **CCI** = creatinine clearance; **CI** = confidence interval; **CKD** = chronic kidney disease; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*; **eGFR** = estimated glomerular filtration rate; **MMSE** = Mini-Mental State Examination; **NOS** = Newcastle-Ottawa Scale; **OR** = odds ratio; **SCr** = serum creatinine.

Renal dysfunction has been considered a candidate risk factor for cognitive impairment and dementia.^{1–3} The kidneys and the brain, both being end organs, are susceptible to vascular damage due to broadly similar anatomic and hemodynamic features.⁴ Chronic kidney disease (CKD) and dementia share a similar risk factor profile including hypertension, diabetes mellitus, or hyperlipidemia, and in both conditions a high prevalence of small vessel disease, silent brain infarcts, white matter pathology, and microbleeds was reported.^{2,3,5–8} Hence, several pathways may underlie the association between CKD and cognitive impairment, including shared vascular factors or a direct neurotoxic effect of uremia.^{2,9}

Worldwide, the number of people with dementia has increased.¹⁰ Identification of determinants of dementia is important given the absence of effective treatments. There is sufficient

Supplemental data
 at Neurology.org

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evidence to support the associations between modifiable risk factors and cognitive decline or dementia later in life.^{11,12} The global prevalence of CKD in the general population is estimated to be 8%–16%, with the highest prevalence in older people.¹³ Both CKD and dementia are important public health problems with associated poor health outcomes and rising health care costs for our society.^{14,15}

A previous meta-analysis found a 39% increased odds for cognitive impairment in patients with CKD.¹⁶ Yet this study included only 6 prospective studies and only reported on estimated glomerular filtration rate (eGFR) as a marker of renal dysfunction, potentially excluding relevant studies using other markers like albuminuria or cystatin C. Therefore, we took a broader approach and systematically reviewed the best available evidence on the prospective association between potential markers of renal dysfunction and development of cognitive impairment or dementia.

METHODS Data sources and searches. The literature search was conducted in Medline, Embase, and Cochrane Database of Systematic Reviews. A deliberate choice was made for a broad search with minimal restrictions in order to harvest all potentially interesting publications. Some markers of renal function were specified within the search term due to their wide use in clinical practice.¹⁷ The search strategy included (1) terms related to predictors (e.g., renal, kidney, albuminuria, creatinine, cystatin), (2) terms for the outcomes (e.g., dementia, Alzheimer disease [AD], cognitive impairment), and (3) specific limitations (i.e., humans, language restrictions). See appendix e-1 at Neurology.org for the complete search strategy.

Study selection. All publications until August 1, 2016, were included that fulfilled the following inclusion criteria: population-based study, prospective design, ≥ 100 participants, age ≥ 45 years, ≥ 1 year follow-up, and cognition/dementia outcomes. Secondary literature (review articles, conference abstracts) and reference lists of publications were also scrutinized.

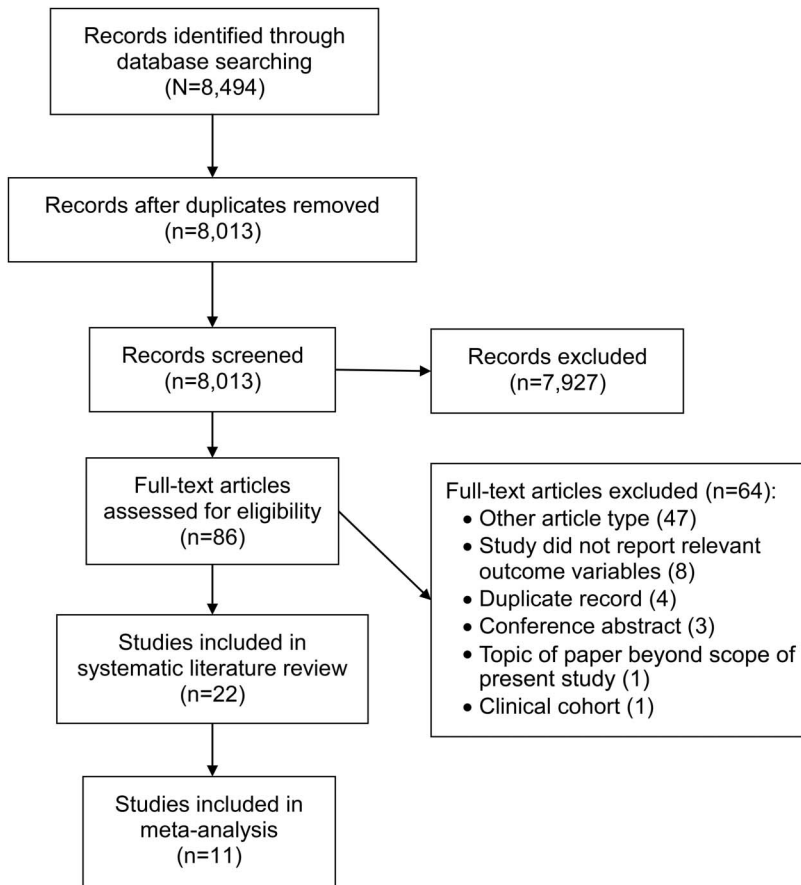
Data extraction and quality assessment. The selection process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (appendix e-2). First, 2 independent raters (S.K., K.D.) screened titles and abstracts for broad suitability and eligibility criteria. Second, 2 independent investigators (I.C., K.D.) reviewed the full-text versions of potentially relevant citations and extracted information such as sample size, setting, age range, follow-up period, outcome (dementia, cognitive impairment, or cognitive decline), predictors (marker of renal dysfunction), and effect estimate, according to a standardized data collection form. Discrepancies were resolved through consensus and discussion with the third reviewer (S.K.). Corresponding authors were contacted if full-text articles were not available or additional information was required (with 2 reminders in case of nonresponse). Quality aspects were assessed with the Newcastle-Ottawa Scale (NOS).¹⁸

Markers of renal dysfunction. eGFR is expressed as milliliter blood filtered per minute by the functioning nephrons in the kidney, with <60 mL/min/1.73 m² as moderately impaired and <45 mL/min/1.73 m² as moderately to severely impaired kidney function. An eGFR of 60–90 mL/min/1.73 m² represents mildly reduced kidney function (stage 2 CKD). In this study, we examine more advanced stages of CKD, namely eGFR levels <45 , 45–59, and <60 mL/min/1.73 m². eGFR <60 mL/min/1.73 m² is the most common indicator of CKD.¹⁹ eGFR can be derived according to different formulas, usually from serum creatinine (SCr).²⁰ Albuminuria or proteinuria refers to an abnormal amount of proteins (e.g., albumin) present in the urine.²¹ Normally, proteins are retained during the filtration process in the kidneys. Microalbuminuria is defined as excretion of 30–300 mg/24 h of albumin, whereas macroalbuminuria is defined as an excretion of more than 300 mg/24 h of albumin.²² The value of acceptable albumin excretion lies between 2 and 30 mg/24 hours.²³ In addition, albuminuria can be measured by using an albumin-to-creatinine ratio on a random (spot) urine sample. An albumin-to-creatinine ratio of 30 mg/g is considered clinically significant.²⁴ Cystatin C, a cysteine proteinase inhibitor, is a very small protein produced by all nucleated cells. It is freely filtered by the glomerulus and then metabolized in the tubules. Normal kidney functioning is characterized by a steady cystatin C blood level, whereas high levels of cystatin C indicate kidney dysfunction.²⁵ Creatinine is a waste product of creatine phosphate in muscles, and is relatively stable over time. An elevated level of SCr (for men >1.2 mg/dL; for women 1.0 mg/dL) may indicate that the kidneys are not working properly.⁷ However, SCr does not correlate linearly with eGFR and is a relatively poor measure of renal function.¹⁹ Creatinine clearance (CCl) is the measurement of the amount of creatinine excreted in the urine per unit of time (usually based on a 24-hour urine collection).¹⁷

Data synthesis and analysis. Random-effects meta-analysis was used to generate pooled odds ratios (OR) and their 95% confidence intervals (CI). Tests were 2-sided at an α level of 0.05. Estimates from crude as well as most fully adjusted models available were used. Heterogeneity among studies was assessed using the I^2 statistic. Possible publication bias was assessed by funnel plots and the Egger test. Separate meta-analyses were only conducted for different levels of eGFR and albuminuria. All analyses were done with Stata 13.1 (StataCorp, College Station, TX).

RESULTS We identified 8,494 abstracts, of which 86 (1%) were included for full-text scrutiny. Of these, 64 were excluded due to article type (e.g., review, editorial), study design (e.g., cross-sectional study), or they were conference abstracts or duplicate records. We contacted 17 authors to obtain full-text articles that were not available to us. Of these, 11 authors responded. The 6 unavailable full-text articles were patient-based studies, conference abstracts, or review articles. In addition, we contacted authors of 20 studies for additional information that was not included in full text, and 10 authors responded. This resulted in 22 prospective population-based studies (figure 1). One additional study was found from cross-references, but this study was excluded after full-text screening. Quality assessment of 22

Figure 1 Flow diagram



prospective studies was sufficient (mean NOS score 8.00, SD 0.62, range 7–9).

Renal dysfunction in the population-based studies was based on eGFR, albuminuria, cystatin C, SCr, and CCl. Cognitive functioning was most often defined as a decline in cognition between 2 time points (e.g., change in Mini-Mental State Examination [MMSE] scores). Other outcome measures such as cognitive impairment or dementia were diagnosed based on findings from neuropsychological examinations, clinical evaluations, diagnostic criteria (e.g., DSM-IV²⁶), and review of medical records. If studies investigated dementia subtypes, this was generally based on different criteria for AD dementia (National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria²⁷) and vascular dementia (National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche en l’Enseignement en Neurosciences criteria²⁸). All 22 studies and their results are summarized in the table and appendix e-3.

eGFR. Seventeen studies investigated the association between (change in) eGFR and cognitive decline or risk of cognitive impairment/dementia. Ten studies

focused on cognitive decline, of which 5 found more decline in cognitive capacity with lower eGFR as time progresses,^{29–33} and 5 studies found no effect.^{34–38} Two of these studies and 1 additional study looked at the association between longitudinal changes in eGFR and cognitive decline.^{34,35,39} One study found that faster eGFR decline was associated with cognitive decline and incident dementia with a vascular component,³⁵ 1 study reported an association between declining eGFR and a decline in several cognitive domains,³⁴ and 1 study found that higher eGFR was associated with slower cognitive decline.³⁹ Five studies focused on cognitive impairment, of which 1 study found an increased risk,⁴⁰ and 4 studies found no association.^{41–44} Three studies examined the relation between eGFR and dementia risk, 2 studies found no association between eGFR and dementia risk,^{35,45} while 1 study found an increased risk of all-cause dementia.⁴⁶ Rather than eGFR at baseline, age-related change in eGFR and type of dementia might play a role.

In the meta-analysis, a total of 8 studies, representing 36,636 persons, could be included.^{31,33,35,37,40,42,43,46} For this, 4 studies reporting both eGFR <45 mL/min/1.73 m² and eGFR 45–59 mL/min/1.73 m² levels were pooled individually (within 1 study) in order to be included in the eGFR <60 mL/min/1.73 m² meta-analysis.^{35,40,42,43} eGFR <60 mL/min/1.73 m² was not associated with risk of cognitive impairment or dementia ($p = 0.063$; figure 2). There were signs of heterogeneity based on the I^2 statistic ($I^2 = 69.0\%$, $p = 0.002$). The funnel plot of the adjusted estimates was broadly symmetrical (see figure 1 of appendix e-4) and the Egger test ($p = 0.105$) was not significant, suggesting no signs of publication bias. Exclusion of 2 relatively small influential studies (logarithm of standard error >0.4) reduced heterogeneity modestly (OR 1.13, 95% CI 0.91–1.40, $p = 0.258$; $I^2 = 58.8\%$, $p = 0.033$). Separate meta-analyses were conducted for eGFR <45 mL/min/1.73 m² and eGFR 45–59 mL/min/1.73 m². No significant associations were observed in these analyses (appendix e-5). It was not possible to perform a meta-analysis for eGFR 60–89 mL/min/1.73 m² since there were only 2 studies.^{33,42} Overall, heterogeneity in outcomes across studies was reduced in all analyses for adjusted estimates in comparison with unadjusted estimates (e.g., eGFR <60 mL/min/1.73 m²: $I^2 = 69.0\%$ vs $I^2 = 91.6\%$, respectively). See figures 1–3 of appendix e-6 for the results of the unadjusted estimates.

Albuminuria. Seven studies reported on albuminuria, of which 4 found a faster rate of cognitive decline,^{33,36,38,47} 1 found an increased risk of cognitive impairment,⁴² and 3 showed mixed results for incident dementia.^{35,45,47}

Table Characteristics of population-based studies assessing the relation between (markers of) renal dysfunction and cognitive impairment or dementia

Authors	Sample; mean age, y; follow-up, y	Cognitive test/diagnostic criteria	Predictor/methods of assessment/reference group	Adjustment for confounders	Most important results
Buchman et al., 2009 ²⁹	Rush Memory and Aging Project (n = 886); 80.6; mean 3.4	Five cognitive domains (episodic memory, semantic memory, working memory, perceptual speed, and visuospatial abilities) were based on 19 cognitive tests	CKD = eGFR <60/4-variable MDRD/eGFR ≥60	Age, sex, education, BMI, hemoglobin, physical activity, late-life social activity, hypertension, diabetes, smoking, myocardial infarction, congestive heart failure, claudication, stroke, depression, baseline eGFR	Lower eGFR (estimate 0.0008, SE <0.001, p = 0.017) or impaired kidney function (estimate -0.028, SE <0.009, p = 0.003) at baseline is associated with a more rapid rate of cognitive decline
Darsie et al., 2014 ³⁰	Cardiovascular Health Study (n = 3,907); >72; mean 5.3	3MS, DSST	eGFR _{cys} <60, eGFR _{cys} 60-89.9/CKD-EPI/eGFR _{cys} ≥ 90	Age, sex, education, race, smoking, BMI, diabetes, hypertension, C-reactive protein, APOE4 genotype, depression, myocardial infarction, stroke, congestive heart failure, eGFR _{cys} × year	eGFR _{cys} <60 associated with a 0.64 (0.51-0.77) points/year faster decline in MMSE score and a 0.42 (0.28-0.56) points/year faster decline in DSST
Davey et al., 2013 ³⁴	Maine-Syracuse Longitudinal Study (n = 590); 62.1; 5	Factor analysis of 17 cognitive tests led to 5 cognitive composite scores	Baseline eGFR, change in eGFR (>3 mL per year)/4-variable MDRD (other formulas for sensitivity analyses) ≤3 mL per year	Age, sex, education, race, systolic blood pressure, diabetes, BMI, high-density lipoproteins, total cholesterol, smoking, baseline cognitive functioning, baseline renal functioning	No significant association between baseline eGFR and cognitive decline; change in eGFR was associated with a decreased global cognitive performance, verbal episodic memory, and abstract reasoning
Etgen et al., 2009 ⁴¹	Intervention Project on Cerebrovascular Disease and Dementia in the Community of Ebersberg (INVADE) study (n = 3,154); >54; mean 784 d	6CIT (cognitive impairment: score >7)	Mild CKD = CCI 45-59; moderate to severe CKD = CCI <45/CG/CCI ≥60; SCr/ not described/not described; eGFR <45/MDRD/eGFR >60	Age, sex, baseline 6CIT, depression, physical activity, drinking, diabetes, history of ischemic heart disease or stroke, hyperlipidemia, hypertension, smoking	Significant association between moderate to severe CKD and cognitive impairment: OR 2.14 (1.18-3.87); significant association between SCr and cognitive impairment: OR 1.67 (1.04-2.70); no significant association between eGFR <45 and cognitive impairment: OR 1.43 (0.61-3.32)
Feng et al., 2012 ³¹	Singapore Longitudinal Aging Study (n = 1,186; cognitive normal subgroup); 65.6; 4	MMSE (cognitive decline: MMSE score drop ≥2 from baseline)	CKD = eGFR <60/4-variable MDRD/eGFR ≥60	Age, sex, race, education, time since baseline, baseline MMSE score, diabetes, hypertension, cardiovascular disease or stroke, other chronic illnesses, depression, IADL disability, smoking, drinking, physical exercise, obesity, albumin hemoglobin	Significant association between CKD and cognitive decline (OR 2.01 [1.26-3.23])
Helmer et al., 2011 ³⁵	Three City Study (n = 7,839); 73.9; 5.8	MMSE; diagnosis of dementia based on neuropsychological assessment and neurologic examination; etiology based on several diagnostic criteria	eGFR 45-60, eGFR <45/CKD-EPI/eGFR ≥60; proteinuria = UACR >30 mg albumin/g creatinine/fresh urine samples/≤30 mg albumin/g creatinine	Age, sex, education, center, APOE4 genotype, hypertension, cardiovascular disease, stroke, hypercholesterolemia, hypertriglyceridemia, diabetes, smoking, BMI, baseline eGFR (only for proteinuria and eGFR decline analyses)	No significant association between low baseline eGFR and incident dementia or cognitive decline; significant association for eGFR decline over the first 4-year period and dementia with vascular component; proteinuria was significantly associated with dementia with vascular component: RR 8.26 (1.26-54.2)
Higuchi et al., 2015 ⁴⁷	Honolulu-Asia Aging Study (n = 3,538); >77; 8	CASI; diagnosis of dementia based on history, neuropsychological test battery, and neurologic examination; etiology based on several diagnostic criteria	Proteinuria/urine dipstick/no proteinuria	Age, education, APOE4 genotype, stroke, hypertension, systolic blood pressure, diabetes, fasting blood glucose, physical activity index, baseline CASI score, time of follow-up	Positive proteinuria: higher annual change in CASI (-1.24, p = 0.02); significant association with all-cause dementia: RR 2.66 (1.09-6.53); no significant association with AD or VaD
Jassal et al., 2010 ³⁶	Rancho Bernardo Study (n = 759); 74.9; mean 6.6	MMSE, TMT-B, Animals Naming Category Fluency test	Moderate to severe CKD = eGFR <60/MDRD/eGFR ≥60, albuminuria = UACR ≥30 mg/g/kinetic alkaline picrate method/UACR <30 mg/g	Age, systolic blood pressure, hemoglobin, education, exercise, drinking, baseline cognitive score, estrogen, depression, antihypertensive, lipid-lowering medication use, eGFR	No significant associations for eGFR; for men, baseline albuminuria associated with reduced cognitive function

Continued

Table Continued

Authors	Sample; mean age, y; follow-up, y	Cognitive test/diagnostic criteria	Predictor/methods of assessment/reference group	Adjustment for confounders	Most important results
Khatri et al., 2009 ³²	Northern Manhattan Study (n = 2,172); 71.5; mean 2.9	TICS-m	SCr/kinetic Jaffe reaction/continuous variable; eGFR <60, eGFR 60-90/MDRD/eGFR >90; CCI <60, CCI 60-90/CG/CCI >90	Age, sex, race, education, insurance status, hypertension, diabetes, homocysteine, drinking, smoking, cardiac disease	Relative to the reference group, participants with CKD (all measures) had lower cognitive scores over time
Kurella et al., 2005 ⁴⁰	Health, Aging, and Body Composition Study (n = 2,406); 74; 2 or 4	3MS (cognitive impairment: 3MS score <80 or a decline in 3MS >5 points at follow-up)	eGFR categories: 45-59 and <45/MDRD/eGFR ≥60; CCI categories: 45-59 and <45/CG/CCI ≥60; sex-specific serum creatinine cutoffs were also measured	Age, sex, race, education, baseline 3MS score, cardiovascular disease, diabetes, blood pressure, lipids, inflammatory markers, hematocrit, stroke	Significant association between cognitive impairment and eGFR 45-59 (OR 1.32 [1.03-1.69]) and eGFR <45 (OR 2.43 [1.38-4.29]); significant association between cognitive impairment and CCI 45-59 (OR 1.44 [1.17-1.78]) and CCI <45 (OR 2.03 [1.46-2.83])
Kurella Tamura et al., 2011 ⁴²	Reasons for Geographic and Racial Disparities in Stroke Study (n = 19,399); >62; mean 3.8	6-Item Screener (cognitive impairment score ≤4)	eGFR categories <45, 45-59, 60-89/CKD-EPI/eGFR ≥90; UACR categories (mg/g) 10-29, 30-299, ≥300/BN ProSpec nephelometer/UACR <10	Age, sex, race, education, region, diabetes, hypertension, cardiovascular disease, stroke, smoking, drinking, UACR, eGFR	No significant associations for eGFR; significant association between cognitive impairment and UACR 30-299 (OR 1.31 [1.12-1.55]) and UACR ≥300 (OR 1.57 [1.15-2.14])
Lipnicki et al., 2013 ³⁷	Sydney Memory and Ageing Study (n = 889); 78.59; mean 23 mo, 12 d	Four cognitive domains (attention/processing speed, memory, language, executive function) were based on a neuropsychological test battery	Kidney disease/not described/no kidney disease; eGFR <60/MDRD (with 175 as first coefficient)/eGFR ≥60	Age, sex (significant main effect factors, age and sex interaction)	Kidney disease was associated with less memory decline; nonsignificant association between eGFR <60 and incident MCI or dementia (decline) (OR 0.871 [0.53-1.43]) ^a
O'Hare et al., 2012 ⁴⁵	Adult Changes in Thought (n = 2,968); 74; median 6	Dementia diagnosis based on CASI, neuropsychological test battery, clinical evaluations	Average eGFR/CKD-EPI/eGFR = 60; proteinuria/not described/no proteinuria; eGFR trajectory and eGFR variability analyses were also conducted	Age, sex, race, study cohort, age at enrollment, depression, diabetes, hypertension, congestive heart failure or other heart disease, cerebrovascular disease, self-rated health	No significant associations for eGFR; positive proteinuria: no statistically significant association between proteinuria and all-cause dementia (HR 1.15 [0.91-1.45])
Sajjad et al., 2012 ³⁸	Nurses' Health Study (n = 1,764); median 74; 4 or 6 y	Four primary outcome measures (global cognition, verbal memory, verbal fluency, TICS score) were based on a neuropsychological test battery	eGFR <60/CKD-EPI (results also available for other formulas)/eGFR ≥60; UACR ≥5 mg/g/immunoassay (urine albumin), Yaffe method (urine creatinine)/<5 mg/g	Age, education hypertension, BMI, diabetes, smoking cardiovascular disease, drinking, physical activity, hypercholesterolemia, spouse's education, postmenopausal hormone use	No significant associations for eGFR; for UACR ≥5, mean annual decline in global cognition -0.003 (-0.05 to -0.01)
Sasaki et al., 2011 ⁴⁶	Osaki-Tajiri project (n = 256); >72; 5	Dementia diagnosis was based on several diagnostic criteria: DSM-IV, NINCDS-ADRDA, NINDS-AIREN	CKD = eGFR <60 or presence of kidney impairment (e.g., albuminuria)/not described/eGFR ≥60	Age, sex, education, hypertension, diabetes, dyslipidemia, ischemic heart disease, anemia	Significant association between CKD and conversion to dementia (OR 5.3 [1.7-16.2])
Seliger et al., 2004 ⁴⁸	Cardiovascular Health Cognition Study (n = 3,349); >74; median 6	Dementia diagnosis based on neuropsychological test battery, clinical evaluation (similar to DSM-IV criteria); subtypes of dementia based on MRI findings	Moderate renal impairment = SCr ≥1.3 mg/dL in women, ≥ 1.5 mg/dL in men/not described/<1.3 mg/dL in women, <1.5 mg/dL in men; primary predictor was 1/SCr	Age, sex, education, race, body weight, coronary heart disease, diabetes, hypertension, smoking, APOE4 genotype	Significant association between elevated SCr and dementia risk (OR 1.37 [1.06-1.78])
Seliger et al., 2015 ³⁹	Baltimore Longitudinal Study of Aging (n = 2,116); 53.9; mean 7.7	BVRT, BNT, CVLT (learning slope, free recall [short and long delay]), DST (forward, backward), category and letter fluency, TMT (part A, part B)	Change in 1/SCr/not described/continuous variable; change in eGFR/4-variable MDRD/continuous variable	Age, sex, education, mean arterial pressure, hemoglobin, smoking, comorbidity score, NSAID use, use of aspirin	Increased SCr was associated with more rapid decline in verbal learning and visual memory; higher eGFR was associated with slower cognitive decline
Slinin et al., 2008 ⁴³	Osteoporotic Fractures in Men Study (n = 3,722); 73.6; mean 4.6	3MS (incident cognitive impairment <80 or decline in 3MS ≥5 points at next examination), TMT-B (incident cognitive impairment ≥1 SD above mean change)	Mild CKD = eGFR 45-59/MDRD/eGFR ≥60; moderate CKD = eGFR <45/MDRD/eGFR ≥60	Age, race, education, health status, IADL, drinking, diabetes, hypertension, stroke, cardiovascular disease, BMI, peripheral arterial disease, time to complete TMT-B at baseline, baseline 3MS score	No significant associations for eGFR on both tests

Continued

Table Continued

Authors	Sample; mean age, y; follow-up, y	Cognitive test/diagnostic criteria	Predictor/methods of assessment/reference group	Adjustment for confounders	Most important results
Slinin et al., 2015 ⁴⁴	Study of Osteoporotic Fractures (n = 1,332; 77.7; mean 9.8)	Cognitive impairment (new onset of MCI or dementia) was based on a screening phase (e.g., neuropsychological test battery) and diagnostic phase (e.g., panel of clinical experts, diagnostic criteria)	Cystatin C quartile 1: 0.61–0.91, quartile 4: 1.15–2.37 mg/L/N latex cystatin C/quartiles 2–3: 0.92–1.14 mg/L; eGFR _{Cr} , quartile 1: 21.6–66.4; quartile 4: 86.1–115.1/CKD-EPI/quartiles 2–3: 66.5–86.0; eGFR _{Cr+cys} quartile 1: 21.8–55.5, quartile 4: 76.1–109.4/CKD-EPI/quartiles 2–3: 55.6–76.0; eGFR _{Cr+cys} quartile 1: 23.5–61.8; quartile 4: 81.2–116.4/CKD-EPI/quartiles 2–3: 61.9–81.1	Age, race, education, self-reported health status, GDS, IADL, smoking, alcohol intake, BMI, history of coronary vascular disease, history of diabetes, history of hypertension, history of stroke	Significant association between cystatin C (quartile 1 and 4) and cognitive impairment, but not in the fully adjusted model; both lower and higher eGFR _{Cr+cys} were associated with an increased risk of cognitive impairment, although only the highest quartile was still associated after multivariable adjustment
Sundelöf et al., 2008 ⁵⁰	Uppsala Longitudinal Study of Adult Men (n = 1,153) (age 70 y)/(n = 761) (age 77 y); 70/77; median 11.3 (age 70)/5.3 (age 77)	Dementia diagnosis was based on cognitive screening (MMSE) and clinical evaluations (subtypes according to DSM-IV and NINCDS-ADRDA criteria)	Cystatin C in $\mu\text{mol/L}$ (lowest and middle tertile)/N latex cystatin C/highest tertile	Age, education, APOE4 genotype, diabetes, hypertension, stroke, serum cholesterol, BMI, smoking, β -amyloid protein 40 and 42	Significant association between cystatin C (lowest tertile and risk of AD at age 70) (HR 2.67 [1.22–5.83]) and age 77 (HR 2.83 [1.03–7.74])
Wang et al., 2010 ³³	Sample of community-based Chinese population (n = 1,243; 58.8; 4)	Cognitive decline was defined as ≥ 2 MMSE points at follow-up	eGFR 30–59, eGFR 60–89/modified MDRD equation based on data from Chinese CKD patients/eGFR ≥ 90 ; UACR ≥ 25 mg/g for females, UACR ≥ 17 mg/g for males/immunoturbidimetric methods/not described	Age, sex, education, BMI, systolic blood pressure, diabetes, UACR (only for eGFR analysis)	Significant association between cognitive decline and eGFR 30–59 (OR 2.73 [1.00–7.56]) and albuminuria (OR 1.03 [0.67–1.72]); nonsignificant association between eGFR 60–89 and cognitive decline (OR 1.35 [0.69–2.65])
Yaffe et al., 2008 ⁴⁹	Health, Aging, and Body Composition Study (n = 3,030); >73; 7	3MS, DSST (cognitive impairment was defined as decline in score of ≥ 1 SD at follow-up)	Intermediate cystatin C (1.0–1.25 mg/L)/N latex cystatin C/low cystatin C (0–1.00 mg/L); high cystatin C (>1.25 mg/L)/N latex cystatin C/low cystatin C (0–1.00 mg/L)	Age, sex, race, education, BMI, C-reactive protein, hypertension, diabetes, stroke	Significant associations between intermediate and high levels of cystatin C for both cognitive tests; intermediate cystatin C (1.0–1.25 mg/L): 3MS: OR 1.25 (0.98–1.61); DSST: OR 1.18 (0.93–1.50); high cystatin C (>1.25 mg/L): 3MS: OR 1.92 (1.37–2.69); DSST: OR 1.54 (1.10–2.15)

Abbreviations: 3MS = modified Mini-Mental State Examination; 6CIT = 6-Item Cognitive Impairment Test; AD = Alzheimer disease; BMI = body mass index; BN = Behring Nephelometer; BNT = Boston Naming Test; BVRT = Benton Visual Retention Test; CASI = Cognitive Abilities Screening Instrument; CCI = creatinine clearance; CG = Cockcroft-Gault equation; CKD = chronic kidney disease; CKD-EPI = CKD Epidemiology Collaboration equation; CVLT = California Verbal Learning Test; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*; DSST = Digit Symbol Substitution Test; DST = Digit Span Test; eGFR = estimated glomerular filtration rate; eGFR_{Cr} = estimated glomerular filtration rate based on creatinine; eGFR_{Cr+cys} = estimated glomerular filtration rate based on creatinine and cystatin C; eGFR_{cys} = estimated glomerular filtration rate based on cystatin C; GDS = Geriatric Depression Scale; HR = hazard ratio; IADL = instrumental activities of daily living; MCI = mild cognitive impairment; MDRD = modification of diet in renal disease formula; MMSE = Mini-Mental State Examination; N latex cystatin C = particle-enhanced immunonephelometric assay; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria; NINDS-AIREN = National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria; NSAID = nonsteroidal anti-inflammatory drugs; OR = odds ratio; RR = relative risk; SCr = serum creatinine; TICS-m = modified Telephone Interview for Cognitive Status; TMT = Trail-Making Test; UACR = urine albumin-creatinine ratio; VaD = vascular dementia.

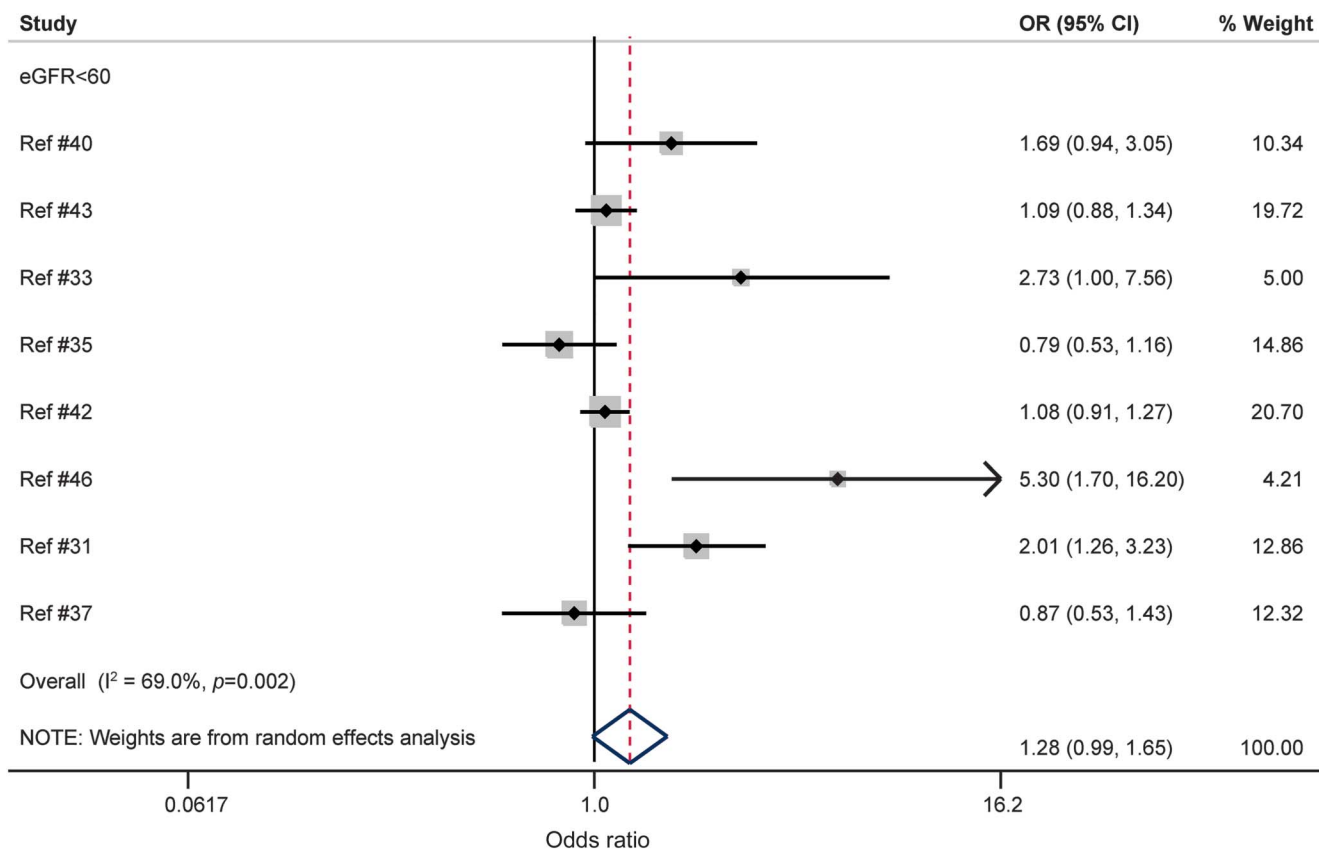
^aORs obtained after contact with the corresponding author.

In the meta-analysis, 5 studies, representing 27,805 persons, could be included.^{33,35,42,45,47} Based on the fully adjusted estimates, albuminuria was associated with a 35% increased risk of cognitive impairment or dementia ($p = 0.015$; figure 3). There was mild to moderate heterogeneity ($I^2 = 38.2$). There were no signs of publication bias based on visual inspection of the funnel plot (see figure 2 of appendix e-5) and the Egger test ($p = 0.274$). Four of these studies reported unadjusted estimates (see figure 4 of appendix e-6). Heterogeneity in outcomes across studies was reduced for adjusted

estimates in comparison with unadjusted estimates ($I^2 = 38.2\%$ vs $I^2 = 74.8\%$, respectively).

Creatinine. Five studies reported on SCr, of which 2 found an increased risk of cognitive impairment,^{40,41} 1 found an increased risk of dementia,⁴⁸ 1 found a faster rate of cognitive decline,³² and 1 found that an increase in SCr was associated with more rapid cognitive decline.³⁹ No meta-analysis could be conducted for this association due to different methods of exposure and outcome formulations across studies.

Figure 2 Forest plot of population-based prospective studies assessing the relation between estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² and cognitive impairment or dementia (fully adjusted estimates)



CI = confidence interval; OR = odds ratio.

Creatinine clearance. Three studies investigated the association between CCI and cognitive decline or cognitive impairment. The Northern Manhattan Study in 2,172 community-dwelling participants found that persons with a baseline CCI <60 mL/min showed significantly more decline compared with individuals with a CCI >90 mL/min over the 2.9 years of follow-up.³² The Health ABC Study in 2,406 elderly individuals found a significant association between CCI (45–59 and <45 mL/min/1.73 m²) and cognitive impairment.⁴⁰ The INVADE study demonstrated a significant association between CCI <45 mL/min/1.73 m² and cognitive impairment after 2 years of follow-up.⁴¹ No meta-analysis could be conducted because of differences in exposure and outcome definitions between studies.

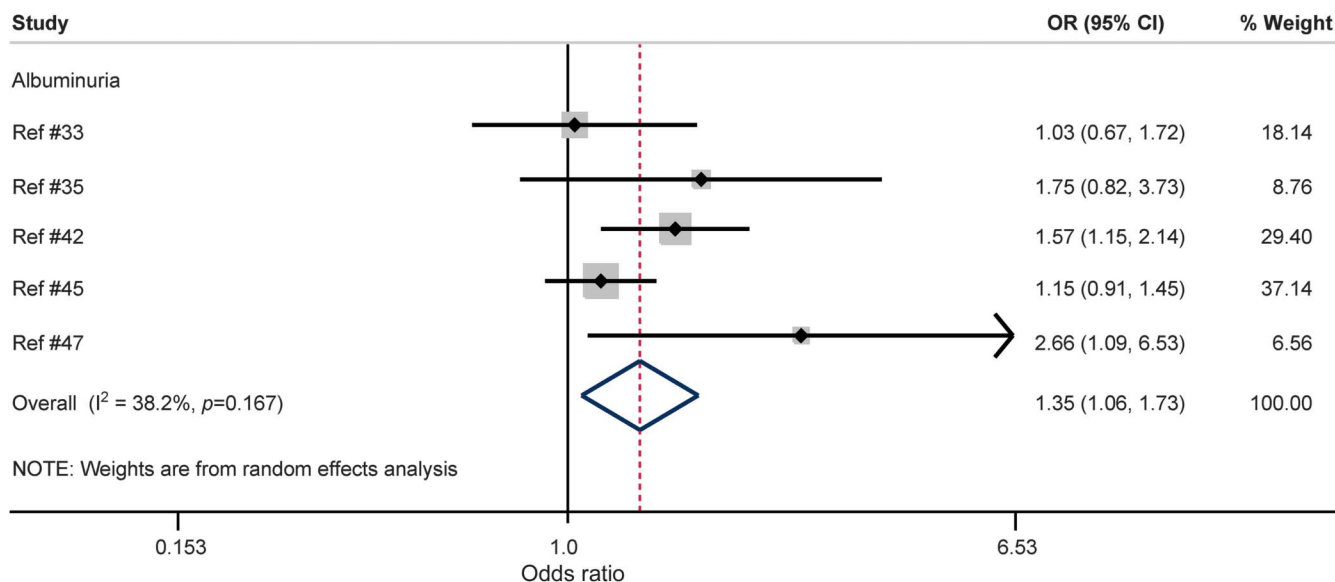
Cystatin C. Three studies focused on cystatin C and cognitive impairment or dementia. The Health ABC Study found an increased risk of cognitive impairment among 3,030 older adults if they had high levels of cystatin C.⁴⁹ In contrast, in men aged 70 and 77 years from the Uppsala Longitudinal Study of Adult Men, high levels of serum cystatin C were associated with a decreased risk of AD.⁵⁰ The Study of

Osteoporotic Fractures in 1,332 elderly women found a U-shape association between cystatin C and cognitive impairment, but after adjustment for covariates, these associations were no longer significant.⁴⁴ No valid meta-analysis could be conducted due to different methods of exposure (e.g., cutoffs, tertiles, quartiles) and outcome formulations across studies.

DISCUSSION This systematic review and meta-analysis suggested that individuals with albuminuria have, on average, a 35% increased risk of cognitive impairment or dementia. Separate meta-analyses for different levels of eGFR yielded nonsignificant results, possibly due to substantial heterogeneity among studies. The literature on eGFR is mixed in general, with studies showing a positive or no association between low levels of eGFR with cognitive decline or dementia risk. For SCr, tentative evidence suggests an association between elevated SCr levels with faster cognitive decline and higher risk for dementia, but too few high-quality studies exist for meta-analysis. In contrast, the review on cystatin C yielded only 3 studies with different methodology and contradictory results.

The substantial heterogeneity observed in the meta-analyses of eGFR might be due to several

Figure 3 Forest plot of population-based prospective studies assessing the relation between albuminuria and cognitive impairment or dementia (fully adjusted estimates)



CI = confidence interval; OR = odds ratio.

methodologic issues, such as (1) the difference in formulas used to measure kidney function (e.g., Modification of Diet in Renal Disease formula, Chronic Kidney Disease Epidemiology Collaboration equation); (2) the variation in study population (e.g., sex-specific, age range, concurrent medication); (3) the inclusion of possible confounders (e.g., including a few [sociocultural demographics] or the choice of covariates [exercise, depression, genotype]); and (4) the assessment of cognitive functioning (e.g., generic screening [MMSE], multidomain test battery, dementia diagnosis).^{2,9}

The exact mechanisms relating renal dysfunction to dementia are not fully understood, but may include shared risk factors, some of which are better documented than others.⁹ Traditional risk factors include cardiovascular disease (e.g., myocardial infarction, atrial fibrillation), stroke, type 2 diabetes mellitus, isolated systolic hypertension, age, smoking, and hypercholesterolemia.^{9,51} Other factors include anemia, albumin, and hyperhomocysteinemia, whereas inflammation, oxidative stress, cerebral small vessel disease, silent brain infarcts, microbleeds, and white matter lesions are possible underlying mechanisms leading to cognitive impairment or dementia.^{2,9} It seems not surprising that the prevalence of the above-mentioned risk factors is higher in patients with CKD than in the general population.^{2,3,6–8} On the other hand, CKD also appears to be a risk factor for cardiovascular or cerebrovascular diseases. For instance, persons with renal insufficiency have an increased risk of stroke or carotid atherosclerosis.^{52,53} In addition, a recent MRI study found that renal dysfunction

was associated with poor cognitive performance and volume deficits in the brain's white matter.⁷ A recent longitudinal study in 600 patients with vascular risk factors found that CKD was related to all-cause dementia independent from vascular risk factors and baseline cerebral small vessel disease.⁵⁴ These findings suggest that vascular damage is not the only possible explanation of the association.

We were not able to pool enough studies that reported on cystatin C. A growing body of evidence demonstrated the involvement of cystatin C in neuroprotective processes in the brain, including its colocalization with β -amyloid (A β) in parenchymal and vascular amyloid deposits, and the inhibition of A β aggregation and deposition by binding to the amyloid precursor protein or the A β 40 and A β 42 peptides.⁵⁵ In addition, the Icelandic form of the hereditary cystatin C amyloid angiopathy is caused by a mutation in the cystatin C gene and is characterized by low levels of serum and CSF cystatin C, intracerebral hemorrhages, stroke, dementia, and death before the age of 40 years.⁵⁶ The study by Yaffe et al.⁴⁹ found that individuals with high levels of serum cystatin C had a 92% increased risk of developing cognitive impairment over 7 years of follow-up. This is in line with results from the Cardiovascular Health Study Cognition Study, which found that high serum levels of cystatin C were associated with poorer cognitive performance 6 years later, greater prevalence of brain infarcts, more white matter lesions, and lower gray matter volume. However, this study only measured cognition at a single time point.⁵⁷

In contrast, the study by Sundelöf et al.⁵⁰ indicated that lower serum levels of cystatin C were associated with increased odds of AD. A recent study demonstrated the presence of low CSF levels of cystatin C in patients with AD in comparison with healthy controls.⁵⁸ Although serum levels of cystatin C are presumably more related to renal dysfunction and CSF levels of cystatin C more to AD pathology, it is difficult to establish a one-to-one relationship due to intercorrelations.

On the other hand, it is also possible that a direct neuronal toxicity of the uremic state is involved.⁹ Concentrations of uremic toxins in brain areas related to cognition (e.g., thalamus, cerebral cortex) are about 10 times higher in patients with CKD than in healthy people.⁵⁹ The aforementioned association with cystatin C might also support the idea of a direct neural toxic effect.⁶⁰ Yet it is important to note that the pathways linking CKD and dementia are not mutually exclusive but might work additively or even synergistically. Clearly, more studies into plausible underlying pathways are needed.

The present results for various eGFR levels differ substantially from the findings of a previous meta-analysis by Etgen et al.¹⁶ This inconsistency in findings can be explained by the fact that we only included the most rigorously adjusted model for each study in our analysis of fully adjusted estimates, while some of the risk estimates reported by Etgen et al. were based on crude data,^{35,41} including the large study by Helmer et al.,³⁵ which found almost a significant protective effect of eGFR.

Our study has a number of strengths. By using large population-based studies with prospective designs including long follow-up periods and adjustment for a large number of known confounders, our study adds to the growing evidence that renal dysfunction is an independent risk factor for cognitive impairment or dementia. A number of limitations in this study must also be mentioned. First, most of the included studies used different methods for estimating renal function (e.g., formulas, equations, or sex-specific cutoffs), probably increasing heterogeneity among studies. In addition, most studies assessed kidney function only once, usually at study entry. Yet renal function is complex and dynamic (e.g., day-to-day variability) and cannot be fully captured at one point in time, potentially leading to exposure misclassification. Since such misclassification is likely nondifferential (i.e., independent from dementia outcome), this might have diluted stronger associations in the population. Future studies should use multiple baselines. In addition, it would be informative to study longitudinal changes in renal functioning in relation to changes in cognitive performance to learn how

trajectories correlate over time. We could identify only 3 prospective studies that reported on longitudinal measures of renal function, but due to the differences in applied methodology (e.g., annual eGFR decline, change in logged eGFR), we were unable to pool these results.^{34,35,39} Second, studies adjusted for different sets of possible confounders (all adjusted minimally for age, sex, and education). For instance, some studies reporting on non-eGFR markers adjusted for eGFR levels while others did not. However, adjusting for eGFR levels had virtually no effect on risk estimates within individual studies. Third, we were unable to include 6 studies (30% of the total included studies) that incorporated markers of renal function as continuous variables in the meta-analyses because of the differences in scaling exposure (e.g., per 0.1 mg/dL increase, decrease of 1 SD), and outcomes (e.g., β coefficients, change per unit increase), next to diversity in cognitive domains tested (e.g., MMSE, Trail-Making Test B). Fourth, various measures were used across studies to operationalize the dichotomous cognitive impairment or dementia outcomes (e.g., MMSE cutoffs, diagnostic criteria). Fifth, although we used fully adjusted models, it is possible that the association is influenced by residual confounding. Sixth, we did not contact authors to conduct additional analyses (e.g., to provide results for specific cutoffs of markers of renal dysfunction not provided in the original article). While this could have increased the number of studies for pooling of data, using only reported estimates increases transparency. Finally, both renal function and cognition may decline with age, making it difficult to separate the effects of aging from a direct effect of renal function on cognition.

Albuminuria was associated with a modestly increased risk of cognitive impairment or dementia. Results for different levels of eGFR were nonsignificant, probably due to heterogeneity across studies. More research is needed to examine whether the association with albuminuria is causal or due to shared mechanisms, and to establish the underlying pathophysiology.

AUTHOR CONTRIBUTIONS

Kay Deckers: study concept and design, acquisition of data, analysis and interpretation of data, drafting the manuscript. Ileana Camerino: acquisition of data, critical revision of manuscript for intellectual content. Martin P.J. van Boxtel: study concept and design, critical revision of manuscript for intellectual content. Frans R.J. Verhey: study concept and design, critical revision of manuscript for intellectual content. Kate Irving: critical revision of manuscript for intellectual content. Carol Brayne: critical revision of manuscript for intellectual content. Miia Kivipelto: critical revision of manuscript for intellectual content. John M. Starr: critical revision of manuscript for intellectual content. Kristine Yaffe: critical revision of manuscript for intellectual content. Peter W. de Leeuw: critical revision of manuscript for intellectual content. Sebastian Köhler: study concept and design, analysis and interpretation of data, critical revision of manuscript for intellectual content, study supervision.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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