Kidney Medicine

# Acute Kidney Injury, Mild Cognitive Impairment, and Dementia: A Cohort Study of Patients from SPRINT

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**Rationale & Objective:** It is well accepted that acute cognitive dysfunction and delirium can occur with severe acute kidney injury (AKI). Recent evidence has indicated AKI can contribute to incident dementia years later. However, these observations were limited by lack of adjudication in most of these studies and greater severity of AKI.

**Study Design:** A retrospective cohort study.

**Setting & Participants:** 8,148 older adults at high cardiovascular risk enrolled in the Systolic Blood Pressure Intervention Trial (SPRINT).

**Predictor:** Adjudicated AKI as a time-varying predictor.

**Outcomes:** Incident mild cognitive impairment (MCI), probable dementia, and their composite.

**Analytical Approach:** Cox proportional hazard models.

**Results:** Participants were 68 ± 9 years, 65% male, 28% with prevalent chronic kidney disease), with a median (interquartile range) follow-up time for the composite of 4.0 (2.1-5.4) and 4.6 (3.6-5.9) years in the AKI and non-AKI groups, respectively. The incidence rate of MCI, probable dementia, and their composite was higher in participants who experienced an AKI event (n = 270). In the fully adjusted model, AKI was positively associated with probable dementia (hazard ratio, 1.72; 95% CI, 1.07-2.75) and the composite outcome (1.43 [1.01-2.04]).

**Limitations:** AKI before baseline was not captured; retrospective and associative.

**Conclusions:** Adjudicated AKI, which was largely mild and reversible, was independently associated with increased risk of probable dementia and the composite of probable dementia and MCI in older adults at high cardiovascular risk.

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There has been increased recognition in recent years that acute kidney injury (AKI) can have a sustained impact on health and long-term consequences,[1] including incident or progressive chronic kidney disease (CKD), long-term mortality, and myocardial infarction.[2,3] AKI is most prevalent in older patients in intensive care units, but can also be community-acquired in ambulatory patients, as well as occur in other levels of in-hospital care.[4]

CKD is associated with high risk of mild cognitive impairment (MCI)[5,6] and dementia.[7,8] It is also well accepted that acute cognitive dysfunction and delirium can occur with severe AKI as a result of uremic encephalopathy.[9] Recent evidence has supported the concept that AKI can contribute to incident dementia years later.[10-13] However, these observations were limited by lack of adjudication and severity of AKI.

The Systolic Blood Pressure Intervention Trial (SPRINT) was a large, randomized-controlled trial that included adjudicated AKI, MCI and probable dementia endpoints in older adults at high cardiovascular risk. An extended battery of cognitive function tests was also performed in participants in the substudy SPRINT Memory and Cognition in Decreased Hypertension (MIND). As complete or partial resolution of AKI occurred in the vast majority of participants (~90%), and only 5.6% of events required dialysis for treatment,[14] SPRINT affords a unique opportunity to evaluate the association of generally mild and reversible AKI with subsequent cognitive endpoints. We hypothesized that the occurrence of an AKI would be independently associated with incident probable dementia, MCI, and their composite, among SPRINT study participants.

## METHODS

### Study Design

The design of SPRINT and SPRINT MIND have been described in detail previously.[15-17] Briefly, the study randomized 9,361 participants 50 years of age or older at increased cardiovascular risk and with a systolic blood pressure (SBP) at screening between 130 and 180 mm Hg to a SBP goal of <120 mm Hg (intensive treatment group) or <140 mm Hg (standard treatment group). Participants did not have a history of diabetes or stroke. All major classes of antihypertensive medications were included to achieve blood pressure goals. Eligible participants were enrolled across the United States between November 2010 and March 2013. The study was approved by the institutional review board at each participating site, and all participants provided written informed consent.

The primary outcome of SPRINT MIND was adjudicated probable dementia; prevalent dementia was a study exclusion. MCI and the composite of probable dementia and MCI were secondary outcomes. SPRINT was terminated early because of the benefit of intensive blood pressure control for the primary outcome of a composite

**PLAIN LANGUAGE SUMMARY**

It is well accepted that acute cognitive dysfunction and delirium can occur with severe acute kidney injury (AKI), and recent evidence has indicated that AKI can contribute to new onset of dementia years later. We examined whether having an AKI increased risk of adverse cognitive outcomes among 8,148 older adults at high cardiovascular risk enrolled who participated in the Systolic Blood Pressure Intervention Trial. AKI, although generally mild and reversible, independently associated with increased risk of probable dementia and a combined endpoint of probable dementia and mild cognitive impairment. These results suggest that cognitive function should be monitored following AKI in this patient population.

of cardiovascular events and all-cause mortality in August 2015. Cognitive outcomes continued to be followed until July 2018. A total of 8,563 participants were included in the original report of cognitive outcomes. Among the 8,563 participants with cognitive outcomes in SPRINT, 415 were missing covariates, for a final cohort of 8,148 in the current analysis.

## Study Variables

### Acute Kidney Injury

AKI was an adjudicated outcome that occurred in 270 participants; the details of ascertainment of AKI in SPRINT have been presented previously.[14] Briefly, AKI events were based on the modified Kidney Disease Improving Global Outcomes criteria, based only on serum creatinine level, and were included only if the AKI event was recorded as an adjudicated serious adverse event. AKI events occurred either in the emergency department or during hospitalization (either as a primary reason for hospitalization or as part of the hospitalization). All AKI events occurred temporally after the assessment of baseline cognitive function; however, history of AKI before study enrollment was not assessed.

### MCI and Probable Dementia

Ascertainment of cognitive status followed a 3-step process of cognitive assessment, with suspected cases identified by pre-determined scoring criteria assigned randomly to 2 members of the Adjudication Committee for review. Probable dementia and MCI were adjudicated endpoints as determined by a panel of experts consisting of neurologists, geriatricians, psychiatrists, and neuropsychologists with recognized expertise in dementia, as described in detail previously.[17] MCI was defined as 2 or more consecutive occurrences of an adjudicated classification of MCI occurring after the baseline visit. MCI and probable dementia events with a date before the date of AKI were excluded from this analysis. The trial planned for cognitive assessments at baseline, year 2, and year 4 of follow-up, as well as at study closeout if removed by more than one year from the 4-year follow-up visit. Many of the planned 4-year cognitive assessments had not been completed at the time of trial termination, thus, were completed at study closeout. After the trial ended and during closeout, blood pressure management was returned to the participants' primary care physicians. A final extended follow-up visit, which included cognitive testing, was conducted between October 2017 and July 2018.

### Covariates

Sex and race/ethnicity were self-reported using fixed categories to satisfy National Institutes of Health policies. Smoking status was classified as never, former, and current by self-report. History of cardiovascular disease was defined as detailed previously and assessed at baseline as a dichotomous variable.[16] Education was categorized as (1) high school or less, (2) some college, vocational training after high school, or an associate degree; and (3) college degree or higher education. Participants with prevalent CKD had an estimated glomerular filtration (eGFR) rate between 20 and 59 mL/min/1.73 $m^2$ based on the 4-variable Modification of Diet in Renal Disease equation (this was the equation used at the time of SPRINT trial). Blood pressure was based on the average of 3 automated measurements during a clinic visit in the seated position following 5 minutes of quiet rest (Model 907, Omron Healthcare). Albuminuria was measured by urinary albumin to creatinine ratio (UACR). The number of antihypertensive medications was determined at the baseline visit.

## Statistical Analyses

Incidence rate was calculated as the number of cognitive outcomes per 100 person-years for those with AKI before a cognitive outcome and those without AKI before a cognitive outcome. AKI was considered as a time-varying predictor, and the association of AKI with time to cognitive outcomes (MCI, probable dementia, and their composite) was analyzed using the counting process method in survival analysis using a Cox model. The survival process functions (ie, survival curves) were calculated using the counting process method, without and with adjustment for covariates.

In all models, the initial model was unadjusted, then multivariable-adjusted models were fit to include age, sex, race, randomized treatment arm, and education (model 1); model 1 plus smoking status, cardiovascular disease history, SBP, and number of antihypertensive medications (model 2); and model 2 plus baseline eGFR and UACR (log-transformed) (model 3).

We evaluated the statistical interaction between AKI and clinical characteristics (sex, age [<75 or ≥75 years], randomization arm, race [White vs other], education, prevalent CKD, cardiovascular disease history, smoking

**Table 1.** Baseline Demographics and Clinical Characteristics According to Acute Kidney Injury Incidence

| | AKI Event (n = 270) | No AKI Event (n = 7,878) |
|---|---|---|
| Age, y | 71 ± 10 | 68 ± 9 |
| Male sex, n (%) | 203 (75%) | 5,099 (65%) |
| Race/ethnicity, n (%) | | |
| Black | 95 (35%) | 2,310 (29%) |
| Hispanic | 15 (6%) | 836 (11%) |
| Non-Hispanic White | 159 (59%) | 4,588 (58%) |
| Other | 1 (0.4%) | 144 (2%) |
| Intensive randomization arm, n (%) | 168 (62%) | 3,918 (50%) |
| Education, n (%) | | |
| High school or less | 92 (34%) | 1,955 (25%) |
| Some college, vocational training, or associates degree | 92 (34%) | 2,806 (36%) |
| College or higher education | 86 (32%) | 3,117 (40%) |
| Smoking Status, n (%) | | |
| Never | 92 (34%) | 3,500 (44%) |
| Former | 139 (52%) | 3,367 (43%) |
| Current | 39 (14%) | 1,011 (13%) |
| CVD History, n (%) | 86 (32%) | 1,552 (20%) |
| CKD, n (%) | 163 (60%) | 2,141 (27%) |
| SBP, mm Hg | 142 ± 16 | 140 ± 16 |
| eGFR, mL/min/1.73 $m^2$ | 57.2 ± 22.1 | 72.2 ± 20.2 |
| UACR, mg/g | 22.1 (8.5-101.8) | 9.3 (5.6-20.0) |
| Number of antihypertensives, n (%) | | |
| 0 | 15 (6%) | 733 (9%) |
| 1 | 57 (21%) | 2,503 (32%) |
| 2 | 83 (31%) | 2,712 (34%) |
| 3 | 93 (34%) | 1,530 (19%) |
| 4 | 22 (8%) | 400 (5%) |

Note: Data are mean ± SD, median (IQR), or n (%).
Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular diseases; eGFR, estimated glomerular filtration rate (Modification of Diet in Renal Disease); SBP, systolic blood pressure; UACR, urinary albumin to creatinine ratio.

history, and UACR), and presented stratified hazard ratios via forest plots. As a sensitivity analysis, we also considered all-cause mortality as a competing risk using the Fine and Gray method.

In all analyses, baseline characteristics were summarized by AKI categories (yes or no) and presented as mean ± standard deviation (SD) or median (interquartile range) for continuous variables and n (%) for categorical variables. Two-tailed values of $P < 0.05$ were considered statistically significant for all analyses. All statistical analyses were performed using SAS version 9.4.

## RESULTS

### Participant Characteristics at Baseline

Among the 8,148 participants included in this analysis, age was 68±9 years, 65% were male (n = 5,302), 58% (n = 4,747) were White, and 28% (n = 2,304) had prevalent CKD. Individuals with an AKI event during SPRINT were more likely to be older, male, Black race, in the intensive group, former smokers, have lower education, have prevalent CKD or cardiovascular disease, have lower eGFR, have higher SBP, have greater UACR, and be prescribed more antihypertensive medications at baseline (Table 1). Baseline memory and processing speed domain scores were slightly lower in the group that subsequently had an AKI.

**Table 2.** Incidence Rates of Mild Cognitive Impairment, Probably Dementia, and Their Composite, Stratified by Acute Kidney Injury Incidence

| | # Events | Years (median) | Person-Years | Event Rate/ 100 Person-Years |
|---|---|---|---|---|
| MCI | | | | |
| No AKI | 583 | 4.4 | 36,081 | 1.6 |
| AKI | 19 | 2.6 | 607 | 3.1 |
| Probable dementia | | | | |
| No AKI | 286 | 5.0 | 37,890 | 0.8 |
| AKI | 21 | 2.7 | 666 | 3.0 |
| Composite | | | | |
| No AKI | 783 | 4.4 | 36,424 | 2.1 |
| AKI | 34 | 2.6 | 619 | 5.5 |

Abbreviations: AKI; acute kidney injury; MCI, mild cognitive impairment.
Note: Incidence rates in the AKI group refer to a time interval and events for those with an AKI event and cognitive event occurring after AKI and in the no AKI group refer to events any time after baseline.

### Relation Between an AKI event and MCI, Probable Dementia, and Their Composite

The median (interquartile range) follow-up time for probable dementia was 5.0 (3.9-6.0) years, for MCI was 4.4 (3.6-5.9) years, and for the composite was 4.4 (3.6-5.9) years from baseline in the non-AKI group and 3.2 (3.2-5.4) years for probable dementia, 4.0 (3.3-5.4) for MCI, and 3.9 (3.3-5.4) years for the composite from the time of AKI in the AKI group. The incidence rate of MCI, probable dementia, and their composite was higher in participants who experienced an AKI event (Table 2). Participants with an AKI event also had a shorter time to occurrence of probable dementia, MCI, and their composite (Fig 1). The association of AKI with time to probable dementia and their composite remained statistically significant in fully adjusted models (Table 3). The associations were slightly attenuated after considering death as a competing risk (Table S1). In total, 123, 113, and 113 participants died of any cause before developing probable dementia, MCI, or their composite, respectively.

### The Interaction of AKI With Clinical Characteristics on Cognitive Endpoints

The interaction P values and stratified hazard ratios according to baseline clinical characteristics are shown in Figure 2. There was greater risk of the composite and MCI outcomes in White participants (interaction $P = 0.004$ and $P = 0.03$, respectively), with no other significant interactions.

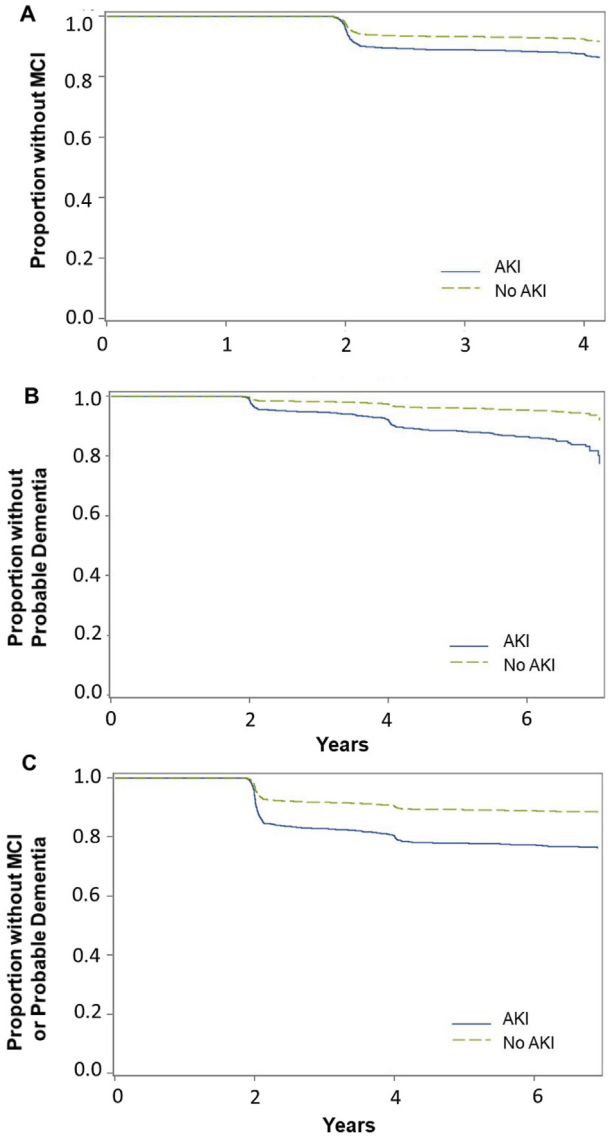


**Figure 1.** Survival curves of time (in years) to mild cognitive impairment (MCI, A), probable dementia (PD, B), and the composite of MCI or PD (C) in participants who developed a serious adverse event acute kidney injury (AKI; solid blue) as compared with those who did not (no AKI; dashed green). Outcomes were evaluated at continuous stop points over time with AKI as a time-varying predictor variable.

**Table 3.** Associations (Hazard Ratios; 95% CI) of Acute Kidney Injury With Time to Mild Cognitive Impairment, Probable Dementia, and Their Composite, Excluding Those with Outcomes before AKI

| | No AKI | AKI |
|---|---|---|
| MCI | | |
| Unadjusted | Ref | 1.70 (1.08-2.69) |
| Model 1 | Ref | 1.22 (0.77-1.92) |
| Model 2 | Ref | 1.22 (0.77-1.93) |
| Model 3 | Ref | 1.18 (0.74-1.89) |
| Probable dementia | | |
| Unadjusted | Ref | 3.10 (1.97-4.87) |
| Model 1 | Ref | 2.12 (1.34-3.34) |
| Model 2 | Ref | 2.06 (1.30-3.26) |
| Model 3 | Ref | 1.72 (1.07-2.75) |
| Composite | | |
| Unadjusted | Ref | 2.19 (1.56-3.09) |
| Model 1 | Ref | 1.54 (1.09-2.18) |
| Model 2 | Ref | 1.54 (1.09-2.18) |
| Model 3 | Ref | 1.43 (1.01-2.04) |

Abbreviations: AKI, acute kidney injury; MCI, mild cognitive impairment.
Note: Model 1: age, race, sex, randomization arm, and education. Model 2: model 1, smoking status, CVD history, systolic blood pressure, and number of antihypertensive medications. Model 3: model 2, estimated glomerular filtration rate (Modification of Diet in Renal Disease), and urinary albumin to creatinine ratio (log-transformed).

## DISCUSSION

In older adults at high cardiovascular risk who participated in SPRINT, an adjudicated AKI event was independently associated with a faster time to probable dementia and the composite of probable dementia and MCI. There was a high incidence rate of the composite outcome (5.5 per 100 person-years) in participants who experienced AKI. The association of AKI with cognitive outcomes was slightly attenuated after considering death as a competing risk.

In the SPRINT trial results, intensive blood pressure control versus standard blood pressure control did not reduce incident dementia (primary cognitive endpoint), but the trial was terminated early because of strong cardiovascular efficacy of intensive blood pressure lowering.[15] Notably, the incidence of both MCI and the composite endpoint were lower in the intensive group.

We observed no interaction of AKI with risk factors including CKD, nor with study group, to modify the association with probable dementia and the composite outcome, although there was a stronger association of AKI with MCI and the composite outcome in White participants. AKI occurred more commonly in the intensive group in SPRINT, and those with prevalent CKD were also slightly more likely to develop AKI with intensive treatment (interaction P value for group and CKD was 0.06).[14] Notably, AKI was generally mild and reversible in SPRINT.[14] The most common proximate cause of AKI was dehydration and/or intravascular volume depletion, followed by hypotension.[14]

AKI, defined by ICD-9 codes, has been previously associated with incident dementia in several cohorts.[10-13] Our findings extend this knowledge in several important ways. First, both AKI and dementia were adjudicated endpoints in SPRINT, unlike most prior studies, enhancing rigor.[14,17] Second, the severity of AKI was much less in SPRINT; the majority of AKI was stage 1 and completely or partially resolved without dialysis.[14] Prior research has focused on more severe AKI requiring hospitalization, including studies of intensive care unit patients requiring dialysis.[10-13] The observed increased risk of dementia despite largely mild and resolvable AKI is clinically significant and advances prior knowledge. Additionally, we examined MCI and a composite of MCI/probable dementia as outcomes, whereas other studies focused solely on dementia.

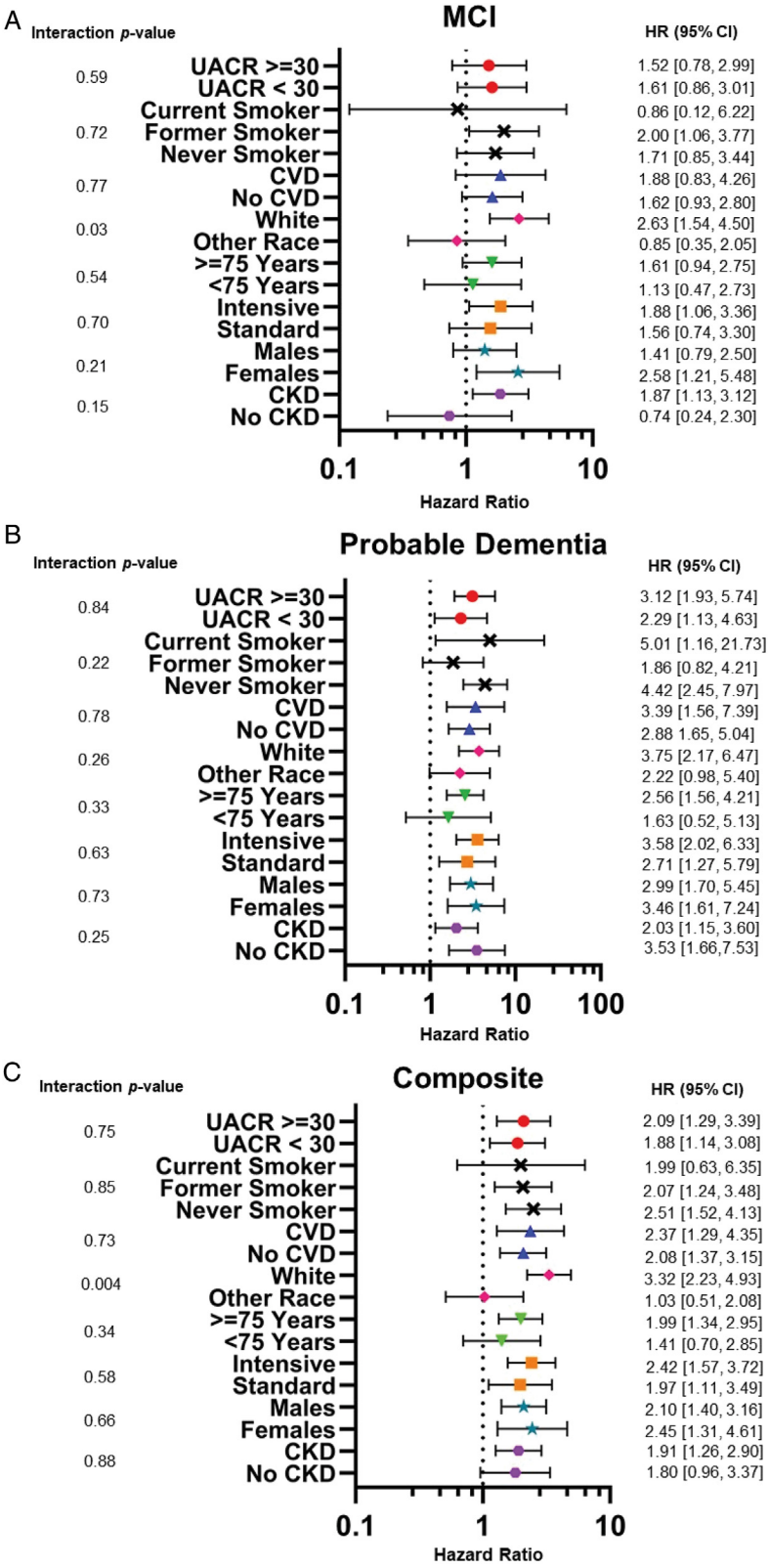


**Figure 2.** Forest Plots of unadjusted hazard ratios (HR [95% confidence intervals]) for time to mild cognitive impairment (MCI, A), probable dementia (B), and the composite of MCI or probable dementia (C) in participants who developed a serious adverse event acute kidney injury (AKI) as compared with those who did not, stratified by urinary albumin to creatinine ration (UACR; red circles), smoking status (black x's), prevalent cardiovascular disease (CVD) at baseline (blue triangles), Race (pink diamonds), age (green upside down triangles), randomization arm (orange squares), sex (turquoise stars), and prevalent chronic kidney disease (CKD) at baseline (purple hexagons). *P* value for the interaction of each stratification variable with AKI are shown for each of the outcomes. The X-axis is on a logarithmic scale.

There are several proposed mechanisms by which AKI may promote dementia and MCI. In a mouse model of AKI (ischemic reperfusion injury), functional decline in locomotor activity as an index of brain function is associated with a disruption of the blood-brain barrier promoting infiltration of chemokines and cytokines, neuronal pyknosis, and brain microgliosis.[18] Additional mechanisms may include oxidative stress, apoptosis, leukocyte activation and infiltration, neurotransmitter derangement, and hippocampus inflammation and cytotoxicity.[18-21] Important crosstalk between the nervous system and the kidney also exists.[22] It is plausible that a bout of inflammatory stimuli from AKI increases the risk of MCI and dementia years later, rather than via progression of AKI to CKD increasing risk of adverse cardiovascular endpoints.[23]

There are several limitations to our findings. The results are correlational, and we were unable to provide mechanistic insight. Participants may have had a history of an AKI event before study participation, which was not assessed, and treating AKI as a one-time exposure may not fully capture its longitudinal impact. Additionally, covariates were assessed at baseline rather than at the time of AKI in the AKI group, and eGFR was calculated in SPRINT using the Modification of Diet in Renal Disease equation. Although a substudy in SPRINT participated in brain magnetic resonance imaging, less than 10 participants from this subcohort had an AKI event; thus, we were unable to assess the association of AKI with changes in cerebral white matter lesions or total brain volume.[24] Participants in SPRINT were nondiabetic, older adults at high cardiovascular results, and risk may not be generalizable to other populations. Additionally, there were fewer than anticipated dementia endpoints in SPRINT MIND, given the early termination of SPRINT because of cardiovascular efficacy of intensive blood pressure control; however, it is notable that we observed an association of AKI with incident dementia despite this lower than anticipated event rate. It is also possible that patients with MCI are more susceptible to volume depletion leading to AKI, rather than mild transient AKI causing cognitive impairment. Finally, there may be residual confounding not fully captured by the adjustment for covariates, such as the severity of vascular disease.

In conclusion, adjudicated AKI, which was largely mild and reversible, was independently associated with increased risk of probable dementia, the composite of probable dementia and MCI. These results suggest that cognitive function should be monitored following AKI in this patient population. Further research is needed to continue to elucidate the mechanisms by which AKI may increase susceptibility to cognitive impairment.

## SUPPLEMENTARY MATERIALS

### Supplementary File (PDF)

**Table S1:** Associations (Hazard Ratios; 95% CI) of Acute Kidney Injury With Time to Mild Cognitive Impairment, Probable Dementia, and Their Composite, With Death as a Competing Risk, Excluding Those With Outcomes Before AKI.

## ARTICLE INFORMATION

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