Title

Blood Pressure, Incident Cognitive Impairment, and Severity of CKD: Findings From the Chronic Renal Insufficiency Cohort (CRIC) Study.

Journal

American Journal of Kidney Diseases, 82(4)

Authors

Babroudi, Seda
Tighiouart, Hocine
Schrauben, Sarah
et al.

Publication Date

2023-10-01

DOI

10.1053/j.ajkd.2023.03.012

Peer reviewed

HHS Public Access

Author manuscript

Am J Kidney Dis. Author manuscript; available in PMC 2024 October 01.

Published in final edited form as:

Am J Kidney Dis. 2023 October ; 82(4): 443–453.e1. doi:10.1053/j.ajkd.2023.03.012.

Blood Pressure, Incident Cognitive Impairment, and Severity of CKD: Findings From the Chronic Renal Insufficiency Cohort (CRIC) Study

Seda Babroudi, MD[1], **Hocine Tighiouart, MS**[2], **Sarah J. Schrauben, MD, MSCE**[3], **Jordana B. Cohen, MD, MSCE**[3], **Michael J. Fischer, MD, MSPH**[4], **Mahboob Rahman, MD**[5], **Chi-yuan Hsu, MD, MS**[6], **Stephen M. Sozio, MD**[7], **Matthew Weir, MD**[8], **Mark Sarnak, MD, MS**[1], **Kristine Yaffe, MD**[9], **Manjula Kurella Tamura, MD, MPH**[10], **David Drew, MD, MS**[1] **CRIC Study Investigators**

[1.]William B. Schwartz Division of Nephrology, Tufts Medical Center, Boston, MA, USA

[2.]Tufts University School of Medicine, Boston, MA, USA; Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, MA, USA

[3.]Departments of Medicine and Epidemiology, Biostatistics and Informatics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

[4.]Department of Medicine/Nephrology, University of Illinois at Chicago, Chicago, IL, USA and Medical Service, Jesse Brown VA Medical Center, Chicago, IL, USA and the Center of Innovation for Complex Chronic Healthcare (CINCCH), Edward J. Hines VA Hospital, Hines, IL, USA

[5.]Case Western Reserve University, University Hospitals Cleveland Medical Center, Louis Stokes Cleveland VA Medical Center, Cleveland, OH, USA

[6.]Division of Nephrology, University of California San Francisco, San Francisco, CA, USA

[11.]Corresponding author: Seda Babroudi, William B. Schwartz Division of Nephrology, Tufts Medical Center, 800 Washington Street, Box 391, Boston, MA, USA, seda.babroudi@tuftsmedicine.org.

Authors' Contributions: Research area and study design: SB, MS, HT, KY, MKT, DD; Data acquisition: DD; Data analysis and interpretation: all authors; Statistical analysis: HT; Supervision or mentorship: DD. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Peer Review: Received September 7, 2022. Evaluated by 4 external peer reviewers, with direct editorial input from a Statistics/Methods Editor and editorial input from an Acting Editor-in-Chief (Editorial Board Member Ana Cristina Simões e Silva, MD, PhD). Accepted in revised form March 5, 2023. The involvement of an Acting Editor-in-Chief to handle the peer-review and decision-making processes was to comply with AJKD's procedures for potential conflicts of interest for editors, described in the Information for Authors & Journal Policies.

CRIC Study Investigators: Lawrence J. Appel, MD, MPH, Jing Chen, MD, MMSc, MSc, Debbie L Cohen, MD, Harold I. Feldman, MD, MSCE, Alan S. Go, MD, James P. Lash, MD, Robert G. Nelson, MD, PhD, MS, Panduranga S. Rao, MD, Vallabh O Shah, PhD, MS, Mark L. Unruh, MD, MS.

Additional Information: Authors Mahboob Rahman and Chi-yuan Hsu are CRIC Study Investigators.

[7]Division of Nephrology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA and Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[8]Division of Nephrology, University of Maryland School of Medicine, Baltimore, MD, USA

[9]University of California San Francisco, San Francisco, CA, USA

[10]Division of Nephrology, Stanford University School of Medicine, Palo Alto, CA and Geriatric Research and Education Clinical Center, VA Palo Alto Health Care System, Palo Alto, CA, USA

Abstract

Rationale and Objective: Hypertension is a known risk factor for dementia and cognitive impairment. There are limited data on the relation of systolic blood pressure (SBP) and diastolic blood pressure (DBP) with incident cognitive impairment in adults with chronic kidney disease. We sought to identify and characterize the relationship among blood pressure, cognitive impairment, and severity of decreased kidney function in adults with chronic kidney disease.

Study Design: Longitudinal Cohort study.

Setting & Participants: 3,768 participants in the Chronic Renal Insufficiency Cohort (CRIC) Study.

Exposures: Baseline SBP and DBP were examined as exposure variables, using continuous (linear, per 10-mm Hg higher), categorical (SBP <120 (reference), 120 to 140, >140 mm Hg; DBP <70 (reference), 70 to 80, >80 mm Hg) and non-linear terms (splines).

Outcome: Incident cognitive impairment defined as a decline in modified mini-mental state exam (3MS) score to greater than 1 standard deviation (SD) below the cohort mean.

Analytical Approach: Cox proportional hazard models adjusted for demographics as well as kidney disease and cardiovascular disease risk factors.

Results: The mean (SD) age of participants was 58 (11) years, eGFR was 44 mL/min/1.73m^2 (15) and the median (IQR) follow-up time was 11 (7, 13) years. In 3,048 participants without cognitive impairment at baseline and with at least one follow-up 3MS test, higher baseline SBP was significantly associated with incident cognitive impairment only in the eGFR >45 mL/min/1.73m^2 subgroup [adjusted hazard ratio (AHR) 1.13, 95% CI 1.05-1.22 per 10-mm Hg higher SBP]. Spline analyses, aimed at exploring non-linearity, showed that the relationship between baseline SBP and incident cognitive impairment was J-shaped and significant only in the eGFR >45 mL/min/1.73m^2 subgroup (p=0.02). Baseline DBP was not associated with incident cognitive impairment in any analyses.

Limitations: 3MS test as the primary measure of cognitive function.

Conclusions: Among patients with chronic kidney disease, higher baseline SBP was associated with higher risk of incident cognitive impairment specifically in those individuals with eGFR >45 ml/min/1.73m^2.

Plain Language Summary

High blood pressure (BP) is a strong risk factor for dementia and cognitive impairment (CI) in studies of adults without kidney disease. High BP and CI are common in adults with chronic kidney disease (CKD). The impact of BP on the development of future CI in patients with CKD remains unclear. We identified the relationship between BP and CI in 3076 adults with CKD. Baseline BP was measured, after which serial cognitive testing was performed over 11 years. Fourteen percent of participants developed CI. We found that higher baseline systolic BP was associated with an increased risk of CI. We found that this association was stronger in adults with mild-to-moderate CKD compared to those with advanced CKD.

Keywords

Systolic Blood Pressure; Diastolic Blood Pressure; Cognitive Impairment; Chronic Kidney Disease; Hypertension

Introduction

Hypertension is highly prevalent in the CKD population, and is a modifiable risk factor for the progression of CKD, cardiovascular disease, and stroke. Independent of stroke, hypertension is associated with the development of cognitive impairment in the general population.[1,2] The relationships between systolic and diastolic blood pressure (SBP and DBP) and risk of cognitive impairment and dementia, however, are complex. A recently published large meta-analysis investigating the effect of BP on cognitive impairment and dementia in the general population found a linear association between SBP and cognitive impairment.[3] In contrast, the same study and others have shown a non-linear, U-shaped association between DBP and cognitive impairment.[3,4] Supporting these observational relations, intensive blood pressure control is associated with a decreased risk of cognitive impairment in the general population.[5,6] However, optimal blood pressure targets have yet to be identified as data are lacking for low blood pressure readings.

Despite the increased prevalence of cognitive impairment in patients with CKD,[7,8] there are a paucity of data regarding the association between SBP and DBP and cognitive impairment in this population. In the interventional study SPRINT-MIND, an interaction with CKD was observed between intensive blood pressure control and the pre-specified outcomes of mild cognitive impairment or dementia, such that intensive BP control significantly reduced the outcomes only in those without CKD.[9] Thus, the precise relationship between blood pressure and cognitive impairment among those with CKD remains poorly understood.

The goal of our study was to investigate the association between blood pressure and cognitive impairment in patients with chronic kidney disease using data from the Chronic Renal Insufficiency Cohort (CRIC), which rigorously measured SBP and DBP and administered the modified mini-mental state (3MS) longitudinally at regular intervals. We also evaluated the interaction and performed pre-specified stratified analyses with estimated glomerular filtration rate (eGFR) > and ≤45 ml/min/1.73 m^2 to determine if eGFR modified the relationship between blood pressure and cognitive outcomes.

Methods

Study Design and Population

The Chronic Renal Insufficiency Cohort is a prospective multi-center observational cohort established to evaluate risk factors for the progression of chronic kidney disease and its complications.[10] To date, two recruitment phases of CRIC have reached completion: 2003-2008 and 2013-2015. Participants initially recruited in the CRIC study were between the ages of 21 and 74 years old, with baseline age-based eGFR as follows: 20 to 70 ml/min/1.73 m2 for ages 21 to 44 years, 20 to 60 ml/min/1.73 m2 for ages 45 to 64 years, and 20 to 50 ml/min/1.73 m2 for ages 65 to 74 years. Given more limited cognitive testing was available for subsequent recruitment phases, only participants in the initial recruitment phase were included in the analyses below. Participants were excluded if they had polycystic kidney disease or were on active immunosuppression for glomerulonephritis at the time of recruitment, as previously described in the CRIC study.[10] The study protocol was approved by institutional review boards of all participating centers and all participants provided informed consent.

Exposure

Primary exposures were baseline SBP and DBP. Three blood pressure measurements were obtained at rest following a standardized protocol.[11] The mean of the three blood pressure measurements was reported as the blood pressure value for that visit. This analysis examined baseline mean SBP as a continuous (per 10-mm Hg higher SBP), categorical (<120 [reference], 120 to 140, >140 mm Hg), and non-linear (splines) term. Baseline mean DBP was also analyzed as a continuous (per 10-mm Hg higher DBP), categorical (<70 [reference], 70 to 80, >80 mm Hg), and non-linear (splines) term.

Evaluation of Cognitive Function

All participants underwent the Modified Mini-Mental State exam (3MS) to evaluate global cognitive function, which was administered biennially from 2003-2013, and annually from 2013 onward for participants aged greater than 65 years.[10] The 3MS is a test of global cognitive function that contains components for orientation, concentration, language, praxis, and immediate and delayed memory with scores ranging from 0-100, with higher scores indicating better function.[12]

As part of an ancillary study (CRIC-COG), 825 of the original participants aged 55 years or older underwent additional cognitive testing including the 3MS, Trail-Making A and B (Trails A and B), Category Fluency (Verbal), Buschke Selective Reminding (Buschke a, b, c), Buschke Recall (Recall), and Modified Boston Naming tests annually for a maximum of four cognitive assessments from 2003 to 2007 (Table S1).[7] Trails A is primarily a test of attention, while Trails B is primarily a test of executive function. Trails A and B scores reflect the time to complete a task, therefore lower scores indicate better function.[13] Category Fluency (Verbal) is primarily a test of language, with higher scores indicating better function.[14] Buschke Selective Reminding Test (Buschke a, b, c) and Buschke Recall (Recall) primarily test verbal memory with immediate and delayed components, with higher

scores indicating better function.[15] The Modified Boston Naming test is primarily a test of language deficits in which higher scores indicate better function.[14]

Outcomes

Incident cognitive impairment: The primary outcome in this study was incident cognitive impairment defined as a subsequent 3MS score greater than 1 SD below the cohort mean (determined from baseline cognitive scores). We used 3MS score as the primary outcome because the 3MS test was administered to nearly the entire CRIC cohort and has previously been used as a marker for cognitive impairment.[7,16,17] We defined presence of cognitive impairment at baseline as a 3MS score of greater than or equal to 1 SD below the cohort mean.[7] In this study, 1 SD below the cohort mean was equal to 82.5, rounded to 83, therefore we used a baseline 3MS score cut-off for cognitive impairment of <83. We excluded participants with cognitive impairment at baseline from analyses. Secondary outcomes in this study were incident cognitive impairment defined as a cognitive score greater than 1 SD below the cohort mean on Category Fluency (Verbal), Buschke Selective Reminding (Buschke a, b, c), Buschke Recall (Recall), and Modified Boston Naming, and greater than 1 SD above the cohort mean on Trails A and B cognitive tests, because these tests were only administered to a subset of all CRIC participants.[7]

Cognitive Decline—We also evaluated cognitive decline by examining the change in cognitive test scores over time in the entire cohort across SBP and DBP categories.

Covariates

Covariates included demographic characteristics (age, sex, race, ethnicity, and education), baseline cognitive scores, diabetes, history of cardiovascular disease (coronary artery disease or peripheral arterial disease), stroke, current smoking, body mass index, estimated glomerular filtration rate by 2009 CKD-EPI equation,[18] and urine albumin to creatinine ratio (UACR).

Statistical Methods

Complete case analyses were performed, excluding participants with missing baseline and follow-up data (Figure 1). We examined the baseline characteristics of CRIC participants across the following categories of baseline SBP (SBP <120 mmHg [reference], 120-140 mmHg, and >140 mmHg) and DBP (DBP <70 mmHg [reference], 70-80 mmHg, and >80 mmHg), which were summarized with means and standard deviations for normally distributed variables, medians and interquartile ranges (IQR) for highly skewed variables, and frequency count and percentages for categorical variables (Table 1).

Incident Cognitive Impairment—For analysis of incident cognitive impairment defined as a cognitive test score of greater than 1 SD below the cohort baseline mean, participants with baseline cognitive scores less than 1 SD below the baseline mean were excluded (Figure 1). We examined the association between blood pressure and incident cognitive impairment using Cox proportional hazard models. In these models, individuals were censored at the last recorded cognitive testing date or by a recorded censoring event such as death or dropout. Event rates were calculated per 100 person-years. Models were

constructed as follows: Unadjusted, Model 1: adjusted for baseline cognitive score, age, sex, race, education, and Model 2: additionally adjusted for cardiovascular disease, stroke, current smoking, body mass index, diabetes, eGFR and UACR. Restricted cubic splines were constructed to explore the adjusted functional relationship between continuous SBP and DBP with incident cognitive impairment. We used five knots for both baseline SBP and DBP for the restricted cubic splines. The knots were selected at the default knot percentile locations of the rcs function in the rms R package and correspond to the following values for baseline SBP and DBP, respectively: 5% (98.00, 52.00), 27.5% (112.67, 63.33), 50% (124.00, 70.67), 72.5% (137.33, 78.67), and 95% (164.67, 92.00). The continuous variables age, BMI, eGFR, and UACR were analyzed as linear terms. To examine whether there was effect modification by eGFR on the observed associations, we performed stratified analyses in which the models above were repeated separately for those individuals with eGFR >45 ml/min/1.73m^2 and eGFR ≤45 ml/min/1.73 m^2. Significance testing was performed to evaluate both a non-linear (P_{global}) and linear (P_{linear}) relationship between blood pressure and incident cognitive impairment.

Cognitive Decline—Linear mixed models and shared parameter models accounting for drop-out due to death were used to explore the longitudinal changes of 3MS score.[19] We used splines terms for the time term in the mixed model to examine the shape of the 3MS trajectory; there was evidence for a two-slope model with an initial rise in 3MS score up to 3 years, and then a decline afterwards. The 3-year knot was identified by fitting successive two-slope mixed models for time varying the fixed knot across a range of values from 1 to 5 years, which yielded the best AIC and BIC model fit. To examine the effect of baseline SBP and DBP categories on the longitudinal changes of 3MS score, we included the main effect of categorical SBP and DBP in addition to the interaction of these categories with the two slopes terms for follow-up time in the mixed model.

Interactions and Sensitivity Analyses

Given varied definitions of cognitive impairment using the 3MS test in the literature, we repeated analyses defining incident cognitive impairment as a 3MS score of less than 80.[16] Additionally, we performed sensitivity analyses in which we re-ran all models with the variables age, BMI, eGFR, and UACR treated as restricted cubic splines in the aforementioned models. Lastly, to account for the potential for a competing risk of death, we conducted competing risks analyses using the same model structure describe above. All analyses were performed using R version 4.1.0.

Results

Cohort Participants

Out of 3,939 participants of the initial recruitment phase in CRIC, we included 3,768 participants in this study, with the main reasons for exclusion being missing covariates, 3MS, or blood pressure data in order of frequency (Figure 1). The average age of participants was 57.8 ± 10.9 years, 2,062 (54.7%) were male, 2,168 (57.5%) self-identified as racially non-white, 2,287 (60.7%) had some college or graduate education, and the mean eGFR by the CKD-EPI equation was 44.4 ± 15.0 mL/min/1.73m^2. There were 1,448 (38%)

study participants with SBP <120 mmHg, 1,340 (36%) had SBP 120-140 mmHg, and 980 (26%) had SBP >140 mmHg. Participants with SBP >140 mmHg were older, non-white, had lower eGFR, one or more cardiovascular risk factors, and higher urine albumin/creatinine ratios (Table 1). At baseline, the mean 3MS score at baseline was 91.4 (8.6), with scores of 93.2, 91.5, and 88.7 for participants with SBPs of <120, 120-140, and >140 mm Hg, respectively ($p < 0.0001$). The median (IQR) follow-up time was 10.9 (7.4, 12.8) years and the median (IQR) number of follow-up 3MS assessments was 5 (2, 7). 3,048 participants had two or greater longitudinal 3MS assessments and did not have cognitive impairment at baseline for evaluation of incident cognitive impairment and decline (Figure 1).

Blood Pressure and Incident Cognitive Impairment

417 out of 3048 (13.7%) participants developed incident cognitive impairment. The fully adjusted hazard ratios for baseline SBP with incident cognitive impairment by linear and categorical terms were 1.05 (0.99, 1.10) for each 10 mmHg higher SBP, and 1.10 (0.87, 1.39) and 1.19 (0.90, 1.57) for SBP 120-140 and SBP >140 mmHg, respectively compared to SBP <120 mm Hg (Table 2). There was a J-shaped relationship observed between baseline SBP and incident cognitive impairment in all models (Figure 2). When stratified by eGFR, a significant non-linear J-shaped relationship was observed between baseline SBP and incident cognitive impairment in the eGFR >45 ml/min/1.73m^2 subgroup ($p=0.02$), but not in the eGFR ≤45 ml/min/1.73m^2 subgroup. We also observed a significant linear relationship between SBP and incident cognitive impairment in the eGFR >45 ml/min/1.73m^2 subgroup but not the eGFR ≤45 ml/min/1.73m^2 subgroup [AHR 1.13 (1.02, 1.22) and 1.01 (0.94, 1.08) for each 10 mmHg higher SBP, respectively] (Table 2, Figure 2B, C).

The adjusted hazard ratios for baseline DBP and incident cognitive impairment by linear and categorical terms were 1.06 (0.98, 1.16) for each 10 mmHg higher DBP, and 0.86 (0.68, 1.09) and 1.17 (0.90, 1.52) for DBP 70-80 and DBP >80 mmHg, respectively compared to DBP <70 mmHg (Table 3). Similar to SBP, a non-linear association was observed between baseline DBP and incident cognitive impairment (Figure 3). When stratified by eGFR, a J-shaped curve was observed between baseline and continuous DBP and incident cognitive impairment specifically in the eGFR >45 ml/min/1.73m^2 subgroup, but not in linear analyses [AHR 1.04 (0.93, 1.17) and 1.12 (0.98, 1.28) for each 10 mmHg higher DBP, for eGFR >45 ml/min/1.73m^2 and eGFR ≤45 ml/min/1.73m^2, respectively] (Table 3, Figure 3B, C).

Qualitatively similar associations were observed between continuous and categorical baseline SBP and DBP and incident cognitive impairment, defined using Trails B, Buschke a, and Boston Naming testing (Table S3).

Blood Pressure and Cognitive Decline

Participants in the highest baseline SBP category had lower mean cognitive scores at baseline and exhibited greater cognitive decline over the study period as compared to the middle and lower SBP categories (Figure 4B). For DBP, those in the highest DBP category had slightly lower baseline cognitive scores while no difference was observed across categories in the rate of cognitive decline (Figure 4C).

Sensitivity Analyses

The relationships observed between baseline SBP, baseline DBP, and incident cognitive impairment were similar in sensitivity analyses where cognitive impairment was defined as 3MS score <80 (Table S4, S5). There was a minimal change in the effect of both continuous and categorical SBP and DBP for the primary outcome of 3MS score <83 and also the sensitivity outcome of 3MS <80 when the variables age, BMI, eGFR, and UACR were treated as restricted cubic splines as compared to linear terms. We also noted no significant difference in the associations between baseline BP measures and incident cognitive impairment when accounting for competing risks.

Discussion

We found a high rate of cognitive impairment as assessed by the 3MS test amongst participants with CKD. We observed an increasing prevalence of cognitive impairment in individuals with higher baseline systolic blood pressures but not for those individuals with higher baseline diastolic blood pressures. In longitudinal analyses, we found an association between baseline SBP and incident cognitive impairment, which was statistically significant in individuals with eGFR >45 ml/min/1.73m2. Analyses exploring the continuous hazards between SBP and cognitive impairment showed that the association may best be described as J-shaped. In contrast, we did not observe a significant association between baseline DBP and cognitive impairment or cognitive decline.

Our results are consistent with most studies in the general adult population, which have previously demonstrated a relationship between higher SBP and cognitive impairment, whether it be linear,[20] J-, or U-shaped.[21–23] In a smaller subset of this same CRIC cohort, Ghazi et al observed no significant association between blood pressure measures and cognitive impairment in patients with kidney disease.[17] However, their analyses focused primarily on 24-hour ambulatory blood pressure readings which were only performed in approximately one-third of participants in CRIC, several years into the cohort study, reducing the overall number of participants with both blood pressure measures as well as follow-up cognitive testing.

We observed a J-shaped association between baseline SBP and incident cognitive impairment amongst CRIC participants with an eGFR >45 ml/min/1.73m2, with increased risks when baseline SBP was below 100 mmHg or above 120 mmHg. The observed increased risk of incident cognitive impairment with baseline SBP <100 mmHg may be secondary to loss of cerebral autoregulation and low cerebral blood flow (CBF), promoting brain hypoperfusion and ultimately leading to cognitive impairment.[24] Conversely, elevated SBP is associated with all forms of vascular disease, including cerebrovascular disease, thereby resulting in cognitive impairment. In contrast, we did not observe a significant association between baseline DBP and incident cognitive impairment in the cohort. Glodzik et al previously identified an association between SBP and CBF in the general population, but no association between DBP and CBF, consistent with our findings.[25] This suggests that variation in DBP may not significantly affect CBF, and therefore may reduce its impact on cognitive impairment.

In subgroup analyses, the J-shaped association between baseline SBP and incident cognitive impairment was only apparent in the eGFR >45 ml/min/1.73m2 subgroup, suggesting that the impact of SBP on cognitive impairment in individuals with mild-to-moderate CKD is similar to the general population. In contrast, there was no association between baseline SBP and incident cognitive impairment in the eGFR ≤ 45 ml/min/1.73m2 subgroup. Although the lack of association could represent the effect of unmeasured confounding, Kurella Tamura et al observed a trend towards harm amongst participants in the SPRINT trial with baseline eGFR <45 when evaluating the effect of intensive blood pressure control (SBP <120) vs standard treatment (SBP <140) on the development of probable dementia, mild cognitive impairment, or the composite outcome as a function of baseline eGFR when modeled continuously.[26] Together, these findings suggest alternative mechanisms independent of blood pressure may increase the risk of cognitive impairment in advanced CKD.

One proposed mechanism for the observed concurrent dysfunction of the kidney and the brain is the presence of small vessel disease due to the low resistance, passive perfusion nature of both organs. In their cross-sectional study evaluating the association between CKD and MRI-markers of cerebral small vessel disease, Ikram et al observed greater white matter lesions on MRI only in the eGFR <45 ml/min/1.73m2 subgroup, even after adjustment for systolic and diastolic blood pressure.[27] Although hypertension is one cause of small vessel disease, other etiologies, including inflammation, exist. One such inflammatory marker is nitric oxide, which affects endothelial function in the brain and the kidney, and could contribute to small vessel disease in both organs independent of blood pressure.[28] Additionally, uremic metabolites have previously been associated with cognitive impairment in patients with ESKD on dialysis, and may play a role in the development of cognitive impairment in patients with advanced CKD.[29]

The significant association between SBP and cognitive impairment in individuals with mild-to-moderate CKD suggests that SBP is a potentially modifiable risk factor for cognitive impairment in this population. Long-term antihypertensive therapy in older adults has previously been shown to reduce the risk of dementia and mild cognitive impairment in the general population.[30] Similarly, there was a trend towards benefit in participants in the SPRINT-MIND study with eGFR >45 ml/min/1.73m2 when evaluating the effect of intensive versus standard BP treatment on probable dementia, mild cognitive impairment, and their composite outcome as a function of baseline eGFR when modeled continuously.[9] Taken together, these studies suggest that maintaining a normal SBP may limit cognitive decline, though the exact blood pressure targets and magnitude of benefit for blood pressure control in patients with mild-to-moderate versus advanced CKD remains uncertain.

The strengths of this study include the large number of well-characterized participants, the use of standardized office blood pressure measures, long-term cognitive testing follow-up, and detailed ascertainment of key covariates such as CVD and CKD risk factors. Limitations of this study include the use of the 3MS as the primary measure of cognitive function, which may have less sensitivity to detect mild cognitive impairment and early dementia compared to other cognitive tests,[31] and does not directly assess executive function. To account for these shortcomings, we also evaluated blood pressure with additional cognitive tests in a subgroup of the cohort. The results from this cohort support the associations identified

through use of the 3MS test, though the power to detect significant associations was reduced by the small number of individuals who performed the additional cognitive testing and shorter follow-up time. We also note that the same 3MS test was administered in follow-up visits, increasing the likelihood that there is a learning or practice effect,[32] which would decrease our ability to detect cognitive decline and incident cognitive impairment. Lastly, we did not specifically evaluate the relationship between blood pressure during follow-up, or number or class of antihypertensive medications used at baseline or during follow-up, and incident cognitive impairment in our cohort.

In conclusion, we demonstrated a J-shaped association between baseline SBP and incident cognitive impairment in people with CKD, which was significant only amongst individuals with eGFR > 45 ml/min/1.73m2. We saw no consistent association between DBP and cognitive outcomes, regardless of eGFR. Systolic blood pressure is therefore an important, modifiable risk factor for cognitive impairment in individuals without advanced kidney disease. Future studies should focus on identifying underlying causative mechanisms that may mediate the observed difference in cognitive impairment risk as a function of blood pressure in the advanced CKD population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Support:

Funding for the CRIC Study was obtained under a cooperative agreement from National Institute of Diabetes and Digestive and Kidney Diseases (*U01DK060990, U01DK060984, U01DK061022, U01DK061021, U01DK061028, U01DK060980, U01DK060963, U01DK060902 and U24DK060990*). The project was additionally supported by the National Center for Advancing Translational Sciences, National Institutes of Health, Award Numbers UL1TR002544 and TL1TR002546 *(SB)*. The funders had no role in study design, data collection, analysis, reporting, or the decision to submit for publication.

References

1. Skoog I, Nilsson L, Persson G, et al. 15-year longitudinal study of blood pressure and dementia. The Lancet. 1996;347(9009):1141–1145. doi: 10.1016/s0140-6736(96)90608-x
2. Harrington F, Saxby BK, McKeith IG, Wesnes K, Ford GA. Cognitive performance in hypertensive and normotensive older subjects. Hypertension. 2000;36(6):1079–1082. doi: 10.1161/01.hyp.36.6.1079 [PubMed: 11116128]
3. Ou Y-N, Tan C-C, Shen X-N, et al. Blood pressure and risks of cognitive impairment and dementia: a systematic review and meta-analysis of 209 prospective studies. Hypertension. 2020;76(1):217–225. doi: 10.1161/HYPERTENSIONAHA.120.14993 [PubMed: 32450739]
4. Lv YB, Zhu PF, Yin ZX, Kraus VB, Threapleton D, Chei CL, Brasher MS, Zhang J, Qian HZ, Mao C, Matchar DB, Luo JS, Zeng Y, Shi XM. A U-shaped Association Between Blood Pressure and Cognitive Impairment in Chinese Elderly. J Am Med Dir Assoc. 2017;18(2):193.e7–192. doi: 10.1016/j.jamda.2016.11.011
5. Hughes D, Judge C, Murphy R, et al. Association of blood pressure lowering with incident dementia or cognitive impairment: a systematic review and meta-analysis. JAMA. 2020;323(19):1934–1944. doi: 10.1001/jama.2020.4249 [PubMed: 32427305]
6. Forette F, Seux M-L, Staessen JA, et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. Arch Intern Med. 2002;162(18):2046–2052. doi: 10.1001/archinte.l62.18.2046 [PubMed: 12374512]

7. Yaffe K, Ackerson L, Tamura MK, et al. Chronic kidney disease and cognitive function in older adults: findings from the chronic renal insufficiency cohort cognitive study. J Am Geriatr Soc. 2010;58(2):338–345. doi: 10.1111/j.1532-5415.2009.02670.x [PubMed: 20374407]
8. Kurella Tamura M, Wadley V, Yaffe K, McClure LA, Howard G, Go R, Allman RM, Warnock DG, McClellan W. Kidney function and cognitive impairment in US adults: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Am J Kidney Dis. 2008 Aug;52(2):227–34. doi: 10.1053/j.ajkd.2008.05.004. [PubMed: 18585836]
9. Williamson JD, Pajewski NM, Auchus AP, et al. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. JAMA. 2019;321(6):553–561. doi: 10.1001/jama.2018.21442 [PubMed: 30688979]
10. Feldman HI, Appel LJ, Chertow GM, et al. The chronic renal insufficiency cohort (CRIC) study: design and methods. J Am Soc Nephrol. 2003;14(suppl 2):S148–S153. doi: 10.1097/01.asn.0000070149.78399.ce [PubMed: 12819321]
11. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA. 2003;289(19):2560–2571. doi: 10.1001/jama.289.19.2560 [PubMed: 12748199]
12. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. J Clin Psychiatry. 1987 Aug;48(8):314–8. [PubMed: 3611032]
13. Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. Percept Mot Skills. 1958;8:271–276.
14. Welsh KA, Butters N, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery. Neurology. 1994;44:609–614. [PubMed: 8164812]
15. Buschke H, Fuld PA. Evaluating storage, retention, and retrieval in disordered memory and learning. Neurology. 1974;24:1019–1025 [PubMed: 4473151]
16. Kurella M, Chertow GM, Fried LF, et al. Chronic kidney disease and cognitive impairment in the elderly: the health, aging, and body composition study. J Am Soc Nephrol. 2005;16(7):2127–2133. doi: 10.1681/ASN.2005010005 [PubMed: 15888561]
17. Ghazi L, Yaffe K, Tamura MK, et al. Association of 24-Hour Ambulatory Blood Pressure Patterns with Cognitive Function and Physical Functioning in CKD. Clin J Am Soc Nephrol. 2020;15(4):455–464. doi: 10.2215/CJN.10570919 [PubMed: 32217634]
18. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Lente FV, Zhang YL, Coresh J, Levey AS, CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012;367(1):20–9. doi: 10.1056/NEJMoal114248 [PubMed: 22762315]
19. Rizopoulos D JM: An R Package for the Joint Modelling of Longitudinal and Time-to-Event Data. Journal of Statistical Software. 2010;35(9):1–33. 10.18637/jss.v035.i09 [PubMed: 21603108]
20. Launer LJ, Masaki K, Petrovitch H, Foley D, Havlik RJ. The association between midlife blood pressure levels and late-life cognitive function: the Honolulu-Asia Aging Study. JAMA. 1995;274(23):1846–1851. [PubMed: 7500533]
21. Waldstein SR, Giggey PP, Thayer JF, Zonderman AB. Nonlinear relations of blood pressure to cognitive function: the Baltimore Longitudinal Study of Aging. Hypertension. 2005;45(3):374–379. doi: 10.1161/01.HYP.0000156744.44218.74 [PubMed: 15699446]
22. Glynn RJ, Beckett LA, Hebert LE, Morris MC, Scherr PA, Evans DA. Current and remote blood pressure and cognitive decline. JAMA. 1999;281(5):438–445. doi: 10.1001/jama.281.5.438 [PubMed: 9952204]
23. Morris MC, Scherr PA, Hebert LE, et al. Association between blood pressure and cognitive function in a biracial community population of older persons. Nenroepidemiology. 2002;21(3):123–130. doi: 10.1159/000054809
24. Ruland S, Aiyagari V. Cerebral autoregulation and blood pressure lowering. Hypertension. 2007 May;49(5):977–8. doi: 10.1161/HYPERTENSIONAHA.107.087502. Epub 2007 Mar 12. [PubMed: 17353508]
25. Glodzik L, Rusinek H, Tsui W, Pirraglia E, Kim HJ, Deshpande A, Li Y, Storey P, Randall C, Chen J, Osorio RS, Butler T, Tanzi E, McQuillan M, Harvey P, Williams SK, Ogedegbe G,

Babb JS, de Leon MJ. Different Relationship Between Systolic Blood Pressure and Cerebral Perfusion in Subjects With and Without Hypertension. Hypertension. 2019 Jan;73(1):197–205. doi: 10.1161/HYPERTENSIONAHA.118.11233. [PubMed: 30571554] Erratum in: Hypertension. 2020 Jun;75(6):e29. [PubMed: 32401650]

26. Kurella Tamura M, Gaussoin SA, Pajewski NM, Chelune GJ, Freedman BI, Gure TR, Haley WE, Killeen AA, Oparil S, Rapp SR, Rifkin DE, Supiano M, Williamson JD, Weiner DE; SPRINT Research Group*. Kidney Disease, Intensive Hypertension Treatment, and Risk for Dementia and Mild Cognitive Impairment: The Systolic Blood Pressure Intervention Trial. J Am Soc Nephrol. 2020 Sep;31(9):2122–2132. doi: 10.1681/ASN.2020010038. Epub 2020 Jun 26. [PubMed: 32591439]
27. Ikram MA, Vernooij MW, Hofman A, Niessen WJ, van der Lugt A, Breteler MM. Kidney function is related to cerebral small vessel disease. Stroke. 2008 Jan;39(1):55–61. doi: 10.1161/STROKEAHA.107.493494. Epub 2007 Nov 29. [PubMed: 18048865]
28. Seliger SL, Longstreth WT Jr. Lessons about brain vascular disease from another pulsating organ, the kidney. Stroke. 2008 Jan;39(1):5–6. doi: 10.1161/STROKEAHA.107.496000. Epub 2007 Nov 29. [PubMed: 18048859]
29. Kurella Tamura M, Chertow GM, Depner TA, Nissenson AR, Schiller B, Mehta RL, Liu S, Sirich TL; FHN Study. Metabolic Profiling of Impaired Cognitive Function I Patients Receiving Dialysis. J Am Soc Nephrol. 2016 Dec;27(12):3780–3787. Doi: 10.1681/ASN.2016010039. Epub 2016 Jul 21. [PubMed: 27444566]
30. Group SR, Wright JT Jr, Williamson JD, et al. A randomized trial of intensive versus standard blood-pressure control. N Eng J Med. 2015;373(22):2103–16. doi: 10.1056/NEJMoa1511939
31. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool for Mild Cognitive Impairment. J AM Geriatric Soc. 2019;53(4):695–99. doi: 10.1111/j.1532-5415.2005.53221.x
32. Salthouse TA. Robust Cognitive Change. J Int Neuropsychol Soc. 2012;18(4):749–56. doi: 10.1017/S1355617712000380 [PubMed: 22595019]

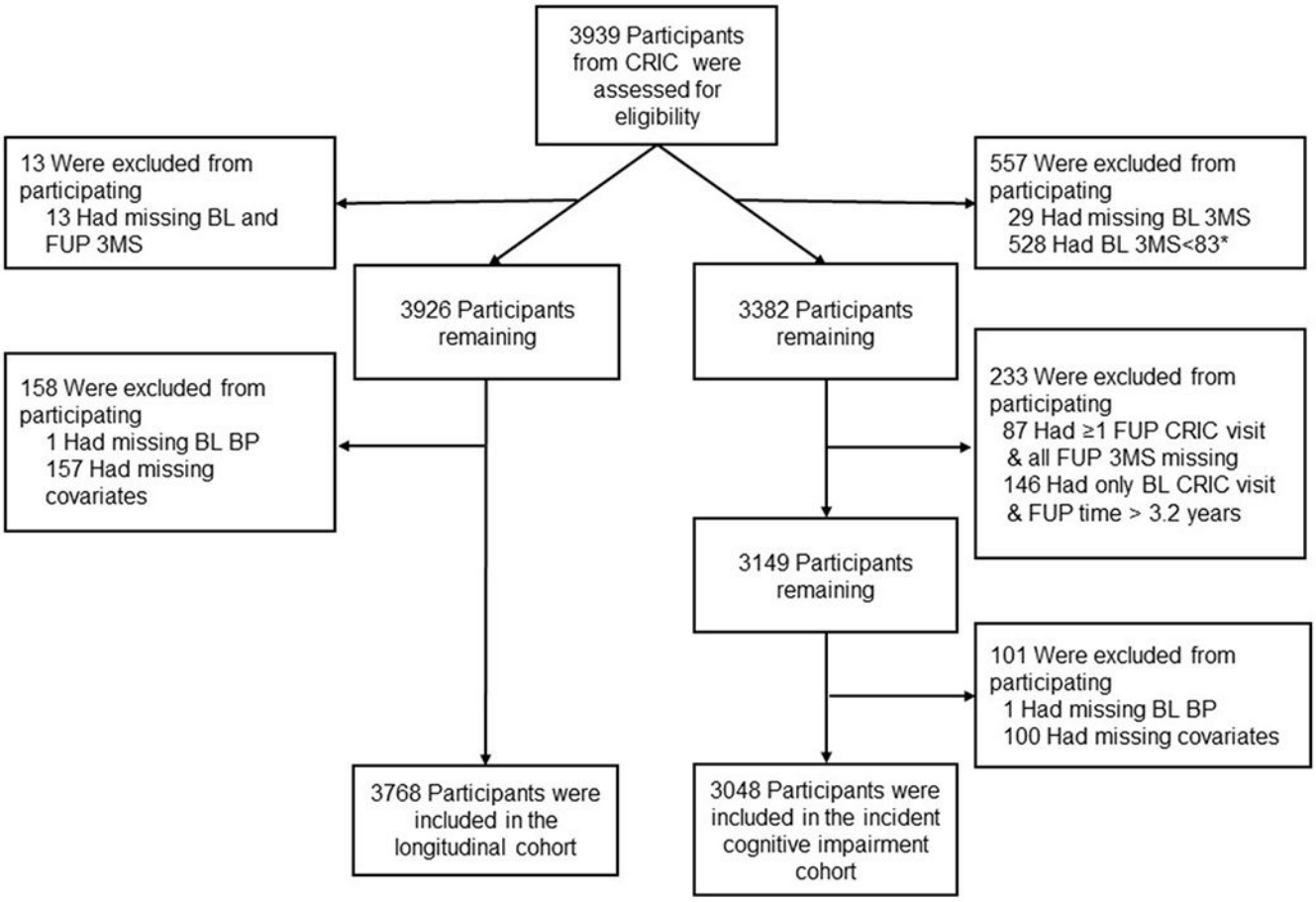
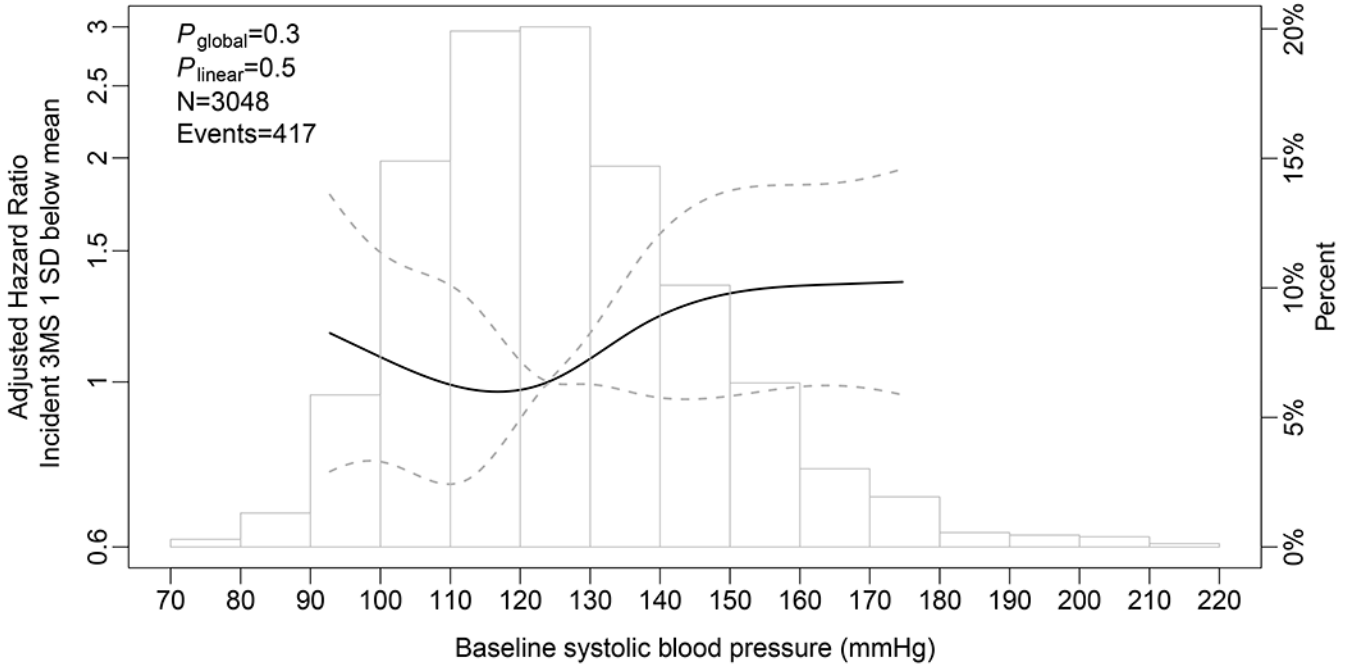
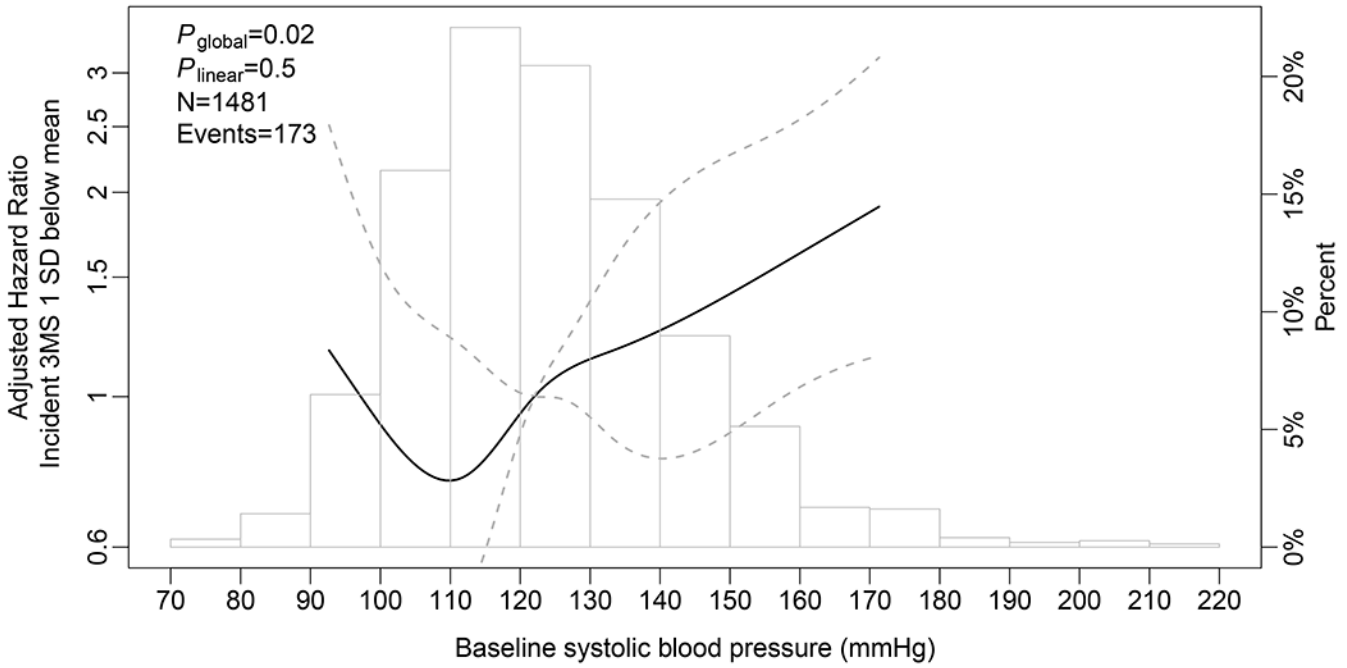


Figure 1.

Study flow diagram. Eligibility for longitudinal cohort on left, and incident cognitive impairment cohort on right. *1 SD below the cohort mean 3MS score = 82.5, rounded to 83. Abbreviations: CRIC, Chronic Renal Insufficiency Cohort; 3MS, modified mini-mental state exam; BL, baseline; FUP, follow-up; BP, blood pressure.





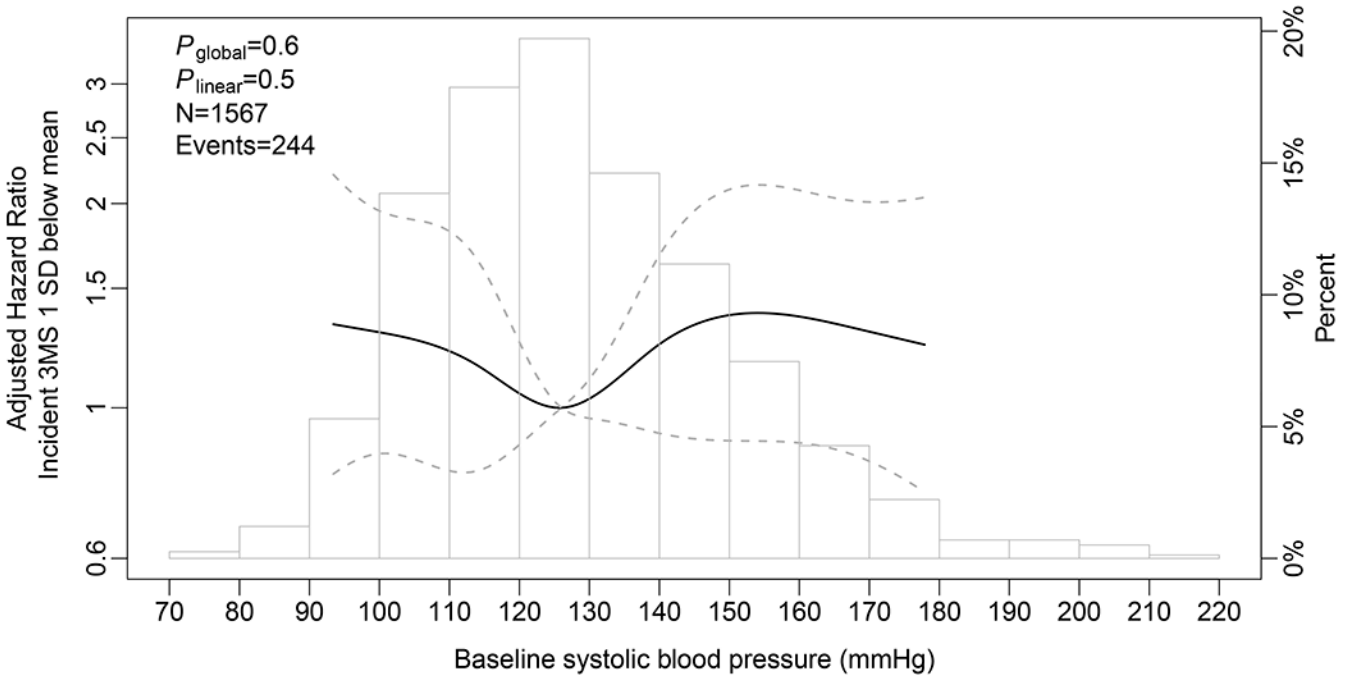


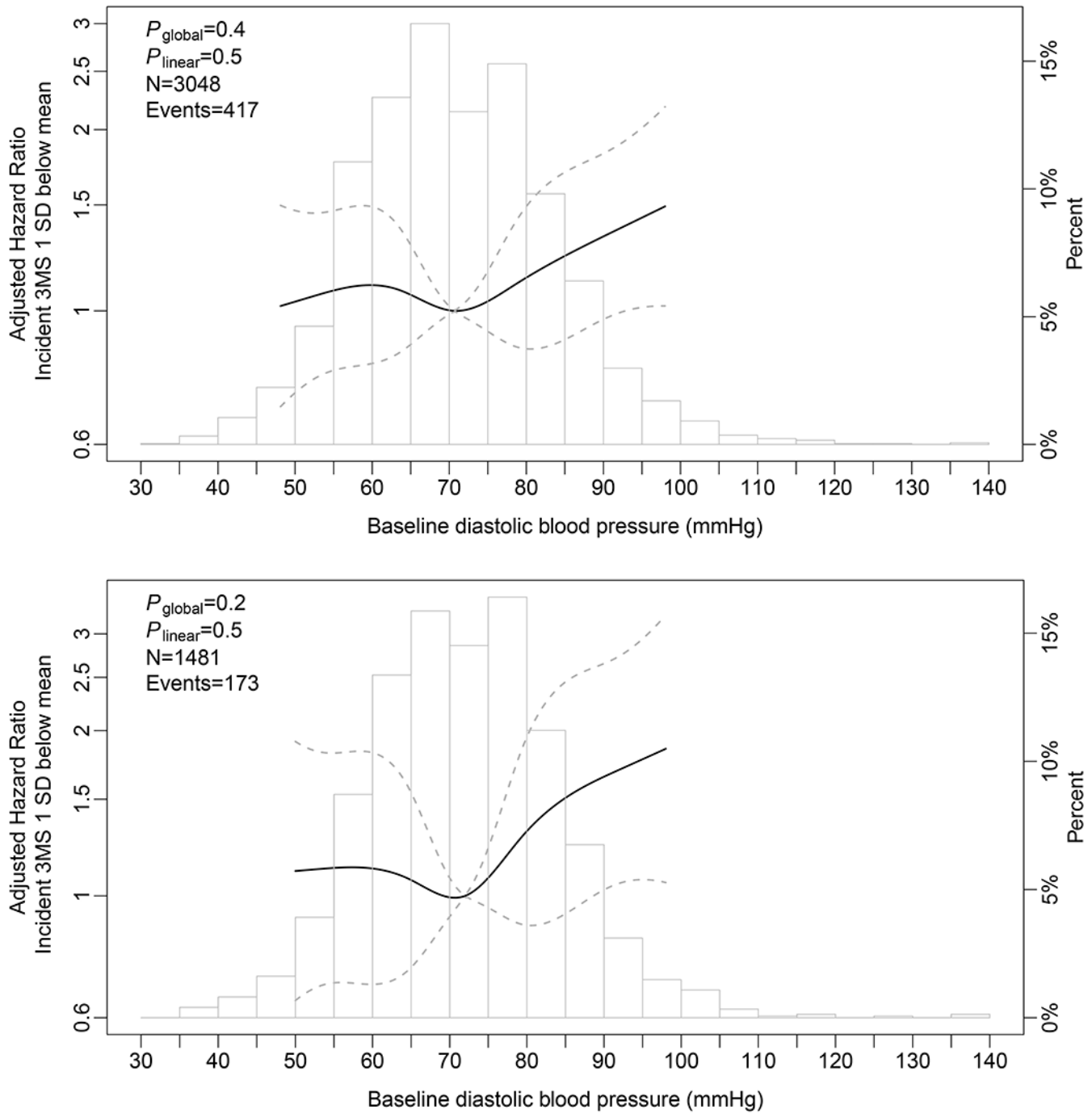
Figure 2.

A) Adjusted Association of Baseline Systolic Blood Pressure with Incident Cognitive Impairment in the CRIC**. **B)** Adjusted Association of Baseline Systolic Blood Pressure with Incident Cognitive Impairment among Participants with eGFR >45 ml/min/1.73m2**. **C)** Adjusted Association of Baseline Systolic Blood Pressure with Incident Cognitive Impairment among Participants with eGFR ≤45 ml/min/1.73m2**

Relationship between baseline systolic blood pressure (*x* axis), histogram demonstrating percent of participants with baseline systolic blood pressure within the indicated intervals (*y* axis, right), and adjusted hazard ratio of incident cognitive impairment (*y* axis, left). The dotted lines represent 95% confidence intervals. P_{global} reflects level of significance of a non-linear relationship. P_{linear} reflects level of significance of a linear relationship. N reflects number of participants with 2 or more 3MS assessments for evaluation of decline with baseline 3MS >83. Cognitive impairment defined as a 3MS score less than 83 (approximately 1 SD below the cohort mean).

** Adjusted for baseline 3MS, age, sex, race, education, cardiovascular disease, stroke, current smoking, BMI, DM2, eGFR, and UACR.

Abbreviations: CRIC, Chronic Renal Insufficiency Cohort; 3MS, Modified Mini-Mental State exam; BMI, body mass index; DM2, type 2 diabetes mellitus; eGFR, estimated glomerular filtration rate; UACR, urine albumin to creatinine ratio.



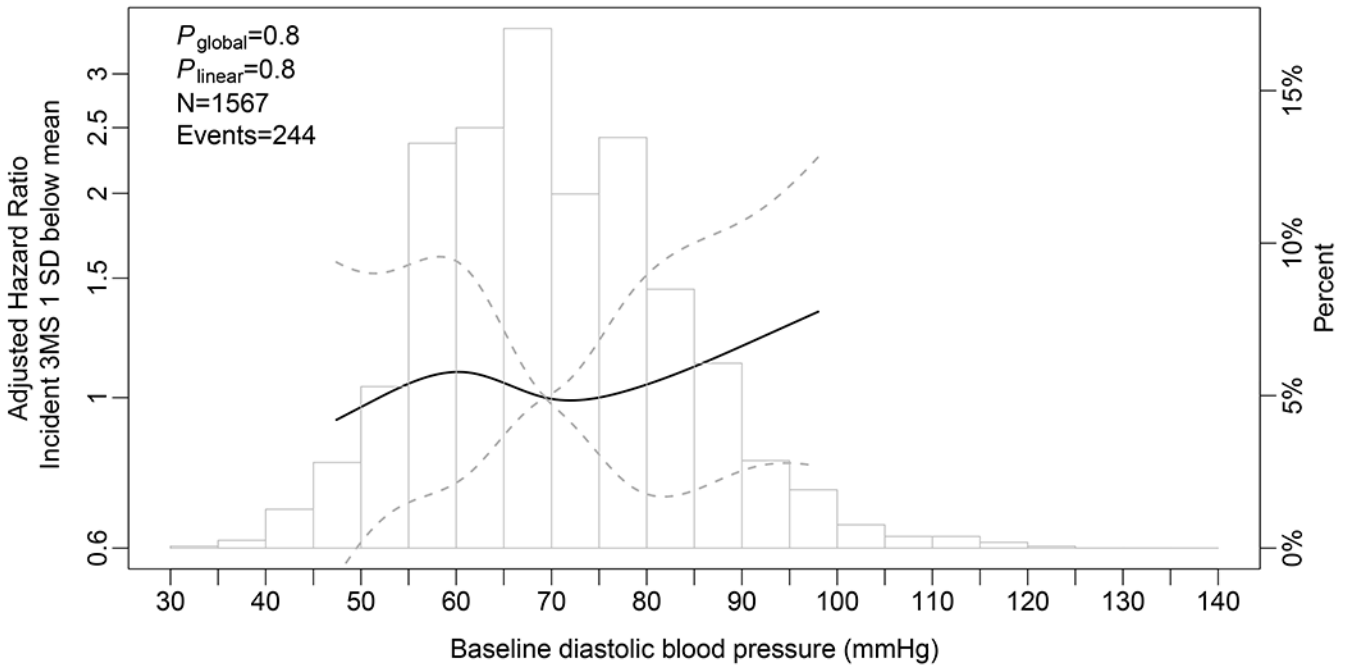


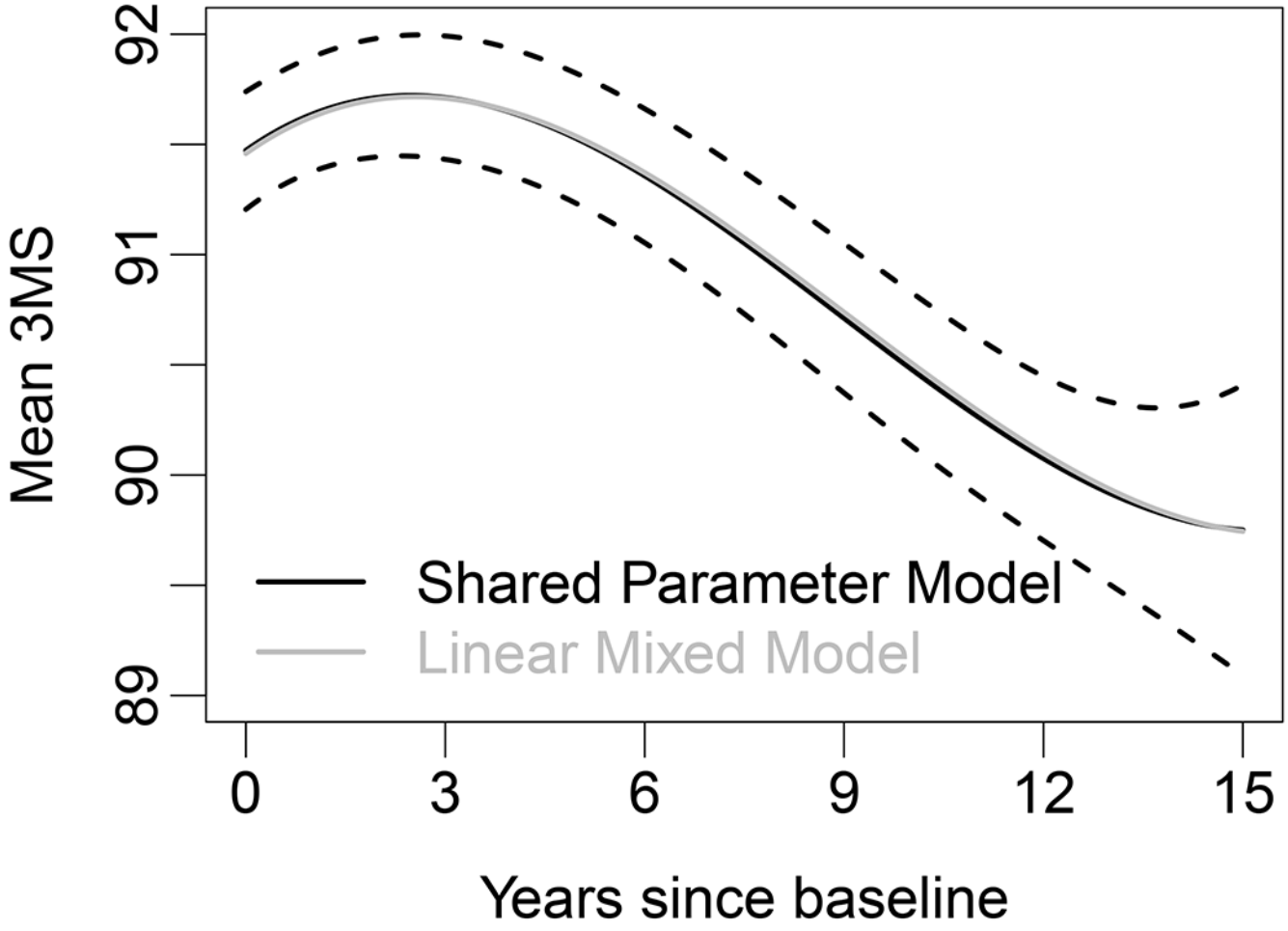
Figure 3.

A) Adjusted Association of Baseline Diastolic Blood Pressure with Incident Cognitive Impairment in the CRIC**. **B)** Association of Baseline Diastolic Blood Pressure with Incident Cognitive Impairment among Participants with eGFR >45 ml/min/1.73m2**. **C)** Association of Baseline Diastolic Blood Pressure with Incident Cognitive Impairment among Participants with eGFR ≤45 ml/min/1.73m2**

Relationship between baseline diastolic blood pressure (*x* axis), histogram demonstrating percent of participants with baseline diastolic blood pressure within the indicated intervals (*y* axis, right), and adjusted hazard ratio of incident cognitive impairment (*y* axis, left). The dotted lines represent 95% confidence intervals. P_{global} reflects level of significance of a non-linear relationship. P_{linear} reflects level of significance of a linear relationship. N reflects number of participants with 2 or more 3MS assessments for evaluation of decline with baseline 3MS >83. Cognitive impairment defined as a 3MS score less than 83 (approximately 1 SD below the cohort mean).

** Adjusted for baseline 3MS, age, sex, race, education, cardiovascular disease, stroke, current smoking, BMI, DM2, eGFR, and UACR.

Abbreviations: CRIC, Chronic Renal Insufficiency Cohort; 3MS, Modified Mini-Mental State exam; BMI, body mass index; DM2, type 2 diabetes mellitus; eGFR, estimated glomerular filtration rate; UACR, urine albumin to creatinine ratio.



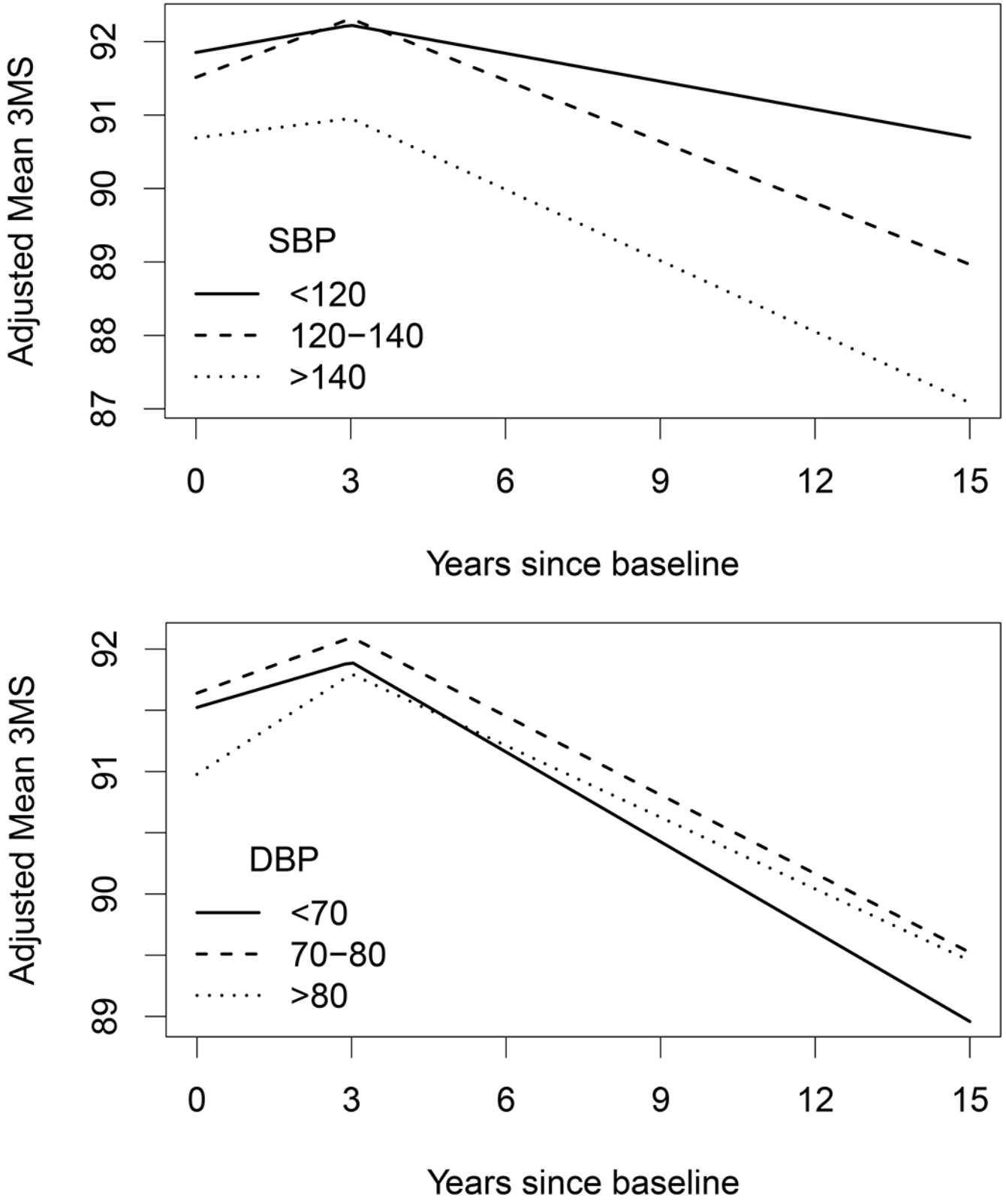


Figure 4.

A) Adjusted Cognitive Decline by 3MS Score in All Participants in the CRIC**. **B)** Adjusted Association of Systolic Blood Pressure Category and Cognitive Decline by 3MS Score in the CRIC**. **C)** Adjusted Association of Diastolic Blood Pressure Category and Cognitive Decline by 3MS Score in the CRIC**.

Relationship between time from study onset (*x* axis) and adjusted mean 3MS score (*y* axis) overall and by systolic and diastolic blood pressure category (solid, dashed, and dotted lines).

** Adjusted for baseline 3MS, age, sex, race, education, cardiovascular disease, stroke, current smoking, BMI, DM2, eGFR, and UACR.

Abbreviations: CRIC, Chronic Renal Insufficiency Cohort; 3MS, modified mini-mental state exam; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; DM2, type 2 diabetes mellitus; eGFR, estimated glomerular filtration rate; UACR, urine albumin to creatinine ratio.

Table 1.

Demographics and Clinical Characteristics of the CRIC Study Population Stratified by Systolic Blood Pressure Category

	Total (N=3768)	SBP<120 mmHg N=1448 (38.4%)	SBP 120-140 mmHg N=1340 (35.6%)	SBP>140 mmHg N=980 (26.0%)	Trend *p*
SBP (mmHg)	128.3 (22.0)	107.8 (8.6)	129.2 (6.0)	157.2 (15.5)	<.001
DBP (mmHg)	71.4 (12.8)	65.2 (9.7)	72.3 (11.2)	79.3 (14.0)	<.001
3MS	91.4 (8.6)	93.2 (7.2)	91.5 (8.3)	88.7 (10.1)	<.001
Age (year)	57.8 (10.9)	55.7 (11.7)	58.7 (10.4)	59.7 (9.8)	<.001
Male	2062 (54.7%)	787 (54.4%)	751 (56.0%)	524 (53.5%)	0.8
Race					<.001
White	1779 (47.2%)	835 (57.7%)	632 (47.2%)	312 (31.8%)	
Black	1577 (41.9%)	483 (33.4%)	569 (42.5%)	525 (53.6%)	
Other	412 (10.9%)	130 (9.0%)	139 (10.4%)	143 (14.6%)	
Ethnicity					<.001
Non-Hispanic White	1600 (42.5%)	779 (53.8%)	584 (43.6%)	237 (24.2%)	
Non-Hispanic Black	1570 (41.7%)	480 (33.2%)	568 (42.4%)	522 (53.3%)	
Hispanic	453 (12.0%)	131 (9.1%)	137 (10.2%)	185 (18.9%)	
Other	145 (3.9%)	58 (4.0%)	51 (3.8%)	36 (3.7%)	
Education					<.001
Less than high school	768 (20.4%)	196 (13.5%)	275 (20.5%)	297 (30.3%)	
High school	713 (18.9%)	256 (17.7%)	249 (18.6%)	208 (21.2%)	
Some college	1096 (29.1%)	424 (29.3%)	391 (29.2%)	281 (28.7%)	
College graduate or higher	1191 (31.6%)	572 (39.5%)	425 (31.7%)	194 (19.8%)	
Cause of kidney disease					<.001
Diabetes	971 (25.8%)	245 (16.9%)	337 (25.2%)	389 (39.7%)	
Hypertension	612 (16.2%)	228 (15.8%)	202 (15.1%)	182 (18.6%)	
Other	525 (13.9%)	281 (19.4%)	176 (13.1%)	68 (6.9%)	
Unknown	1660 (44.1%)	694 (47.9%)	625 (46.6%)	341 (34.8%)	
Diabetes	1812 (48.1%)	531 (36.7%)	650 (48.5%)	631 (64.4%)	<.001
Cardio-Vascular Disease	1259 (33.4%)	409 (28.3%)	454 (33.9%)	396 (40.4%)	<.001
Stroke	371 (9.9%)	109 (7.5%)	133 (9.9%)	129 (13.2%)	<.001

	Total (N=3768)	SBP<120 mmHg N=1448 (38.4%)	SBP 120-140 mmHg N=1340 (35.6%)	SBP>140 mmHg N=980 (26.0%)	Trend *p*
Peripheral Vascular Disease	248 (6.6%)	65 (4.5%)	87 (6.5%)	96 (9.8%)	<.001
Current Smoker	491 (13.0%)	184 (12.7%)	164 (12.2%)	143 (14.6%)	0.2
BMI (kg/m^2)	32.1 (7.8)	31.5 (7.7)	32.4 (7.7)	32.4 (8.1)	<.001
eGFR CKD-EPI (mL/min/1.73m^2)	44.4 (15.0)	46.5 (15.6)	44.7 (14.5)	40.7 (14.0)	<.001
UACR (ug/mg)	51 (8, 456)	19 (6, 143)	47 (8, 407)	357 (42, 1654)	<.001

Data shown as n (%) or mean (SD) or median (25th, 75th percentiles)

Abbreviations: CRIC, Chronic Renal Insufficiency Cohort; SBP, systolic blood pressure; DBP, diastolic blood pressure; 3MS, Modified Mini-Mental State exam; BMI, body mass index; eGFR, estimated glomerular filtration rate; UACR, urine albumin to creatinine ratio

Am J Kidney Dis. Author manuscript; available in PMC 2024 October 01.

Table 2.

Unadjusted and Adjusted Cox Proportional Hazard Models for Incident Cognitive Impairment Defined as 3MS<83 (1 SD below the mean) Across Systolic Blood Pressure as a Categorical and Continuous Variable in the CRIC (n= 3048[#])

	Continuous (per 10 mmHg)	SBP<120 mmHg	SBP 120-140 mmHg	SBP>140 mmHg
Overall				
N	3048	1247	1102	699
Events	417	129	166	122
Total years FUP	24557	10726	9084	4747
Event rate per 1000py	16.98	12.03	18.27	25.7
Unadjusted HR (95%CI)	1.18 (1.13, 1.23)	1.00	1.52 (1.21, 1.92)	2.21 (1.72, 2.83)
Model 1 HR (95%CI)	1.09 (1.04, 1.14)	1.00	1.21 (0.96, 1.53)	1.42 (1.11, 1.83)
Model 2 HR (95%CI)	1.05 (0.99, 1.10)	1.00	1.10 (0.87, 1.39)	1.19 (0.90, 1.57)
eGFR≤45				
N	1567	582	559	426
Events	244	79	91	74
Total years FUP	11227	4399	4196	2632
Event rate per 1000py	21.73	17.96	21.69	28.12
Unadjusted HR (95%CI)	1.11 (1.05, 1.18)	1.00	1.21 (0.89, 1.63)	1.63 (1.18, 2.24)
Model 1 HR (95%CI)	1.05 (0.99, 1.11)	1.00	0.97 (0.72, 1.31)	1.24 (0.90, 1.71)
Model 2 HR (95%CI)	1.01 (0.94, 1.08)	1.00	0.88 (0.64, 1.20)	1.04 (0.72, 1.50)
eGFR>45				
N	1481	665	543	273
Events	173	50	75	48
Total years FUP	13331	6327	4888	2115
Event rate per 1000py	12.98	7.90	15.34	22.69
Unadjusted HR (95%CI)	1.26 (1.18, 1.35)	1.00	1.94 (1.36, 2.78)	2.95 (1.98, 4.38)
Model 1 HR (95%CI)	1.16 (1.08, 1.25)	1.00	1.62 (1.12, 2.33)	1.79 (1.19, 2.70)
Model 2 HR (95%CI)	1.13 (1.05. 1.22)	1.00	1.57 (1.08. 2.28)	1.64 (1.07. 2.53)

[#]Indicates number of participants with two or more 3MS assessments for evaluation of decline with baseline 3MS >83

Model 1: Adjusted for baseline 3MS, age, sex, race and education

Model 2: Model 1 + cardiovascular disease, stroke, current smoking, BMI, DM2, eGFR and UACR

Abbreviations: CRIC, Chronic Renal Insufficiency Cohort; SBP, systolic blood pressure; 3MS, Modified Mini-Mental State exam; BMI, body mass index; DM2, type 2 diabetes mellitus; eGFR, estimated glomerular filtration rate; UACR, urine albumin to creatinine ratio; py, patient-years

Table 3.

Unadjusted and Adjusted Cox Proportional Hazard Models for Incident Cognitive Impairment Defined as 3MS<83 (1 SD below the mean) Across Diastolic Blood Pressure as a Categorical and Continuous Variable in the CRIC (n=3048[#])

	Continuous (per 10 mmHg)	DBP<70 mmHg	DBP 70-80 mmHg	DBP>80 mmHg
Overall				
N	3048	1440	916	692
Events	417	201	111	105
Total years FUP	24557	11292	7684	5582
Event rate per 1000py	16.98	17.80	14.45	18.81
Unadjusted HR (95%CI)	0.99 (0.92, 1.07)	1.00	0.80 (0.64, 1.01)	1.04 (0.83, 1.32)
Model 1 HR (95%CI)	1.05 (0.97, 1.14)	1.00	0.84 (0.66, 1.06)	1.09 (0.85, 1.39)
Model 2 HR (95%CI)	1.06 (0.98, 1.16)	1.00	0.86 (0.68, 1.09)	1.17 (0.90, 1.52)
eGFR≤45				
N	1567	811	425	331
Events	244	137	51	56
Total years FUP	11227	5634	3212	2381
Event rate per 1000py	21.73	24.32	15.88	23.52
Unadjusted HR (95%CI)	0.96 (0.87, 1.06)	1.00	0.64 (0.47, 0.89)	0.96 (0.70, 1.31)
Model 1 HR (95%CI)	1.02 (0.92, 1.14)	1.00	0.80 (0.58, 1.12)	1.06 (0.76, 1.48)
Model 2 HR (95%CI)	1.04 (0.93, 1.17)	1.00	0.76 (0.55, 1.07)	1.15 (0.81, 1.63)
eGFR>45				
N	1481	629	491	361
Events	173	64	60	49
Total years FUP	13331	5658	4472	3201
Event rate per 1000py	12.98	11.31	13.42	15.31
Unadjusted HR (95%CI)	1.08 (0.96, 1.23)	1.00	1.18 (0.83, 1.68)	1.34 (0.92, 1.95)
Model 1 HR (95%CI)	1.09 (0.96, 1.24)	1.00	0.96 (0.67, 1.38)	1.18 (0.80, 1.74)
Model 2 HR (95%CI)	1.12 (0.98. 1.28)	1.00	1.00 (0.69. 1.45)	1.33 (0.88. 2.01)

[#]Indicates number of participants with two or more 3MS assessments for evaluation of decline with baseline 3MS >83

Model 1: Adjusted for baseline 3MS, age, sex, race and education

Model 2: Model 1 + cardiovascular disease, stroke, current smoking, BMI, DM2, eGFR and UACR

Abbreviations: CRIC, Chronic Renal Insufficiency Cohort; DBP, diastolic blood pressure; 3MS, Modified Mini-Mental State exam; BMI, body mass index; DM2, type 2 diabetes mellitus; eGFR, estimated glomerular filtration rate; UACR, urine albumin to creatinine ratio; py, patient-years