UC Irvine
UC Irvine Previously Published Works

Title

Cystatin C, cognition, and brain MRI findings in 90+-year-olds

Permalink

https://escholarship.org/uc/item/2t68s391

Authors

Lau, Wei Ling

Fisher, Mark

Greenia, Dana

et al.

Publication Date

2020-09-01

DOI

10.1016/j.neurobiolaging.2020.04.022

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Neurobiol Aging. Author manuscript; available in PMC 2021 September 01.

Published in final edited form as:

Neurobiol Aging. 2020 September ; 93: 78–84. doi:10.1016/j.neurobiolaging.2020.04.022.

Cystatin C, Cognition and Brain MRI Findings in 90+ Year-olds

Lau Wei Ling, MD[1], **Fisher Mark, MD**[2,3], **Greenia Dana, RN MS**[4], **Floriolli David, MD**[5], **Fletcher Evan, PhD**[6], **Singh Baljeet, PhD**[6], **Sajjadi Seyed, MD PhD**[2,4], **Corrada Maria, ScD**[2,4,7], **Whittle Christina, PhD**[4], **Kawas Claudia, PhD**[2,4,8], **Paganini-Hill Annlia, PhD**[2]

[1]Division of Nephrology and Hypertension, University of California Irvine School of Medicine, Orange, CA

[2]Department of Neurology, University of California Irvine School of Medicine, Irvine, CA

[3]Department of Anatomy & Neurobiology, University of California Irvine School of Medicine, Irvine, CA

[4]Institute for Memory Impairments and Neurological Disorders, University of California, Irvine, CA

[5]Department of Radiological Sciences, University of California Irvine School of Medicine, Irvine, CA

[6]Department of Neurology, Center for Neuroscience, University of California, Davis, CA

[7]Department of Epidemiology, University of California Irvine School of Medicine, Irvine, CA

[8]Department of Neurobiology & Behavior, University of California Irvine School of Medicine, Irvine, CA

Abstract

Chronic kidney disease is emerging as a novel risk factor for cerebrovascular disease but this association remains largely unexplored in older adults. Cystatin C is a more accurate measure than

Corresponding Author: Wei Ling Lau, MD, 333 City Blvd West, Suite 400, Orange, CA 92868, Phone: 714-456-5142, wllau@uci.edu.

CRediT Author Statement

Wei Ling Lau: Conceptualization, Visualization, Roles/Writing - original draft, Writing - review & editing.
Mark Fisher: Conceptualization, Methodology, Project administration, Writing - review & editing.
Dana Greenia: Data curation, Formal analysis, Investigation.
David Floriolli: Formal analysis, Investigation, Software.
Evan Fletcher: Formal analysis, Investigation, Software, Writing - review & editing.
Baljeet Singh: Formal analysis, Investigation, Software.
Seyed Sajjadi: Project administration, Writing - review & editing.
Maria Corrada: Formal analysis, Project administration, Resources.
Christina Whittle: Formal analysis, Investigation, Resources.
Claudia Kawas: Conceptualization, Methodology, Project administration.
Annlia Paganini-Hill: Formal analysis, Methodology, Project administration, Roles/Writing - original draft, Writing - review & editing.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflicts of Interest / Disclosures: None.

Disclosures: None.

Table of Contents for Supplemental Material

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

creatinine of kidney function in the elderly. We evaluated cystatin C, cognitive function and brain imaging in 193 participants from *The 90+ Study* neuroimaging component. Mean age was 93.9 years; 61% were female. Mean cystatin C was 1.62 mg/L with eGFR 39.2 ml/min/1.73 m^2. Performance on measures of global cognition, executive function and visual-spatial ability declined at higher tertiles of cystatin C (lower kidney function). Higher cystatin C was significantly associated with infratentorial microbleeds and lower gray matter volume. Adjusted risk of incident dementia was increased in the middle and high cystatin C tertile groups compared to the low group (hazard ratio in highest tertile 3.81 [95% CI 1.14–12.7]), which appeared to be explained in part by presence of cerebral microbleeds. Overall, cystatin C was associated with cognitive performance, brain imaging pathology and decline to dementia in this oldest-old cohort.

Keywords

Chronic kidney disease; cognition; brain MRI; aging

INTRODUCTION

Vascular cognitive impairment (VCI) is, along with Alzheimer's disease, the most common cause of cognitive decline in the aged (Wu et al., 2019). VCI is generally understood to reflect the effects of cerebral microvascular disease (Rensma et al., 2020). There remain, however, vast gaps in our understanding of mechanisms of VCI (Kalaria, 2018). It is thus imperative to investigate novel processes potentially relevant to the etiology of VCI.

One such novel process is chronic kidney disease (CKD), increasingly recognized as a risk factor for cerebrovascular disease (Chelluboina and Vemuganti, 2019; Masson et al., 2015) and cognitive decline (Kurella et al., 2004; Sarnak et al., 2013). Recent work involving CKD animal and cell culture models, combined with studies emphasizing the association of uremic toxins with multiple elements of cerebrovascular disease, has begun the process of mechanistically linking CKD and cerebral microvascular disease ranging from arteriolar neuropathology to blood-brain barrier injury (Lau et al., 2017; Lau et al., 2020).

Cystatin C is a low molecular weight (13 kDa) protease inhibitor produced by all nucleated cells in the body, freely filtered through the glomeruli and degraded by the proximal tubules (Raman et al., 2017). Equations for kidney function that utilize serum or plasma levels of cystatin C to calculate estimated glomerular filtration rate (eGFR) are more accurate than creatinine-based estimations in the elderly population (Dharnidharka et al., 2002; Fliser and Ritz, 2001) as cystatin C is not affected by muscle mass. A low serum creatinine level in an elderly individual typically reflects low muscle mass and tends to over-estimate GFR, while cystatin C is highly correlated with serial measurements of GFR by iothalamate clearance inclusive of individuals with preserved eGFR above 60–90 ml/min/1.73 m^2 (Perkins et al., 2005).

In the current study, we evaluated cystatin C and its association with indices of cerebral microvascular disease by brain imaging, including cerebral microbleeds and brain atrophy, in community-dwelling individuals of very old age (90 years and older). We also analyzed multiple cognitive domains in this population. While prior work has addressed some of these

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

issues in a younger population (e.g., Finney et al., 1999; Werner et al., 2014; (Darsie et al., 2014; Kurella et al., 2005; Riverol et al., 2015; Seliger et al., 2004; Yaffe et al., 2008), the oldest old have not received comparable study. We hypothesized that kidney function, as measured by cystatin C, has a significant role at the interface between cerebral microvascular disease and cognitive impairment in the very old.

METHODS

We report results from a subset of participants of The 90+ Study, an ongoing longitudinal study of aging and dementia in people aged 90 or older (Paganini-Hill et al., 2016). Participants in The 90+ Study were recruited from two groups: (1) survivors of the Leisure World Cohort Study (LWCS) (Paganini-Hill et al., 1986), an epidemiological health study established in the 1980s of the residents of Leisure World, a retirement community in Orange County, California, who were aged 90 or older on or after January 1, 2003, when enrollment into The 90+ Study commenced; and (2) 90+ year-old residents of Orange County, California, who lived within a 2-hour drive of the University of California, Irvine research campus and joined the study through open recruitment (Melikyan et al., 2019). Eligible individuals could participate in The 90+ Study at any of four levels: (1) in-person, (2) over the telephone, (3) through an informant, (4) LWCS participants who died before they themselves could participate in The 90+ Study were included if an informant provided information on medical, family history, and daily functioning.

Cohort construction of The 90+ Study participants who were included in this analysis is illustrated in Figure 1. Of the total 1921 participants, 496 were seen between 2014 (when the neuroimaging component of the study began) and 2018. Between 2014–2018, 258 were able to self-consent to the procedures and were willing to travel to the imaging center. Cystatin C level was determined for 193 and brain MRI was completed in 129 participants. The Institutional Review Board of the University of California Irvine (UCI) approved this study.

Initial and Follow-up Assessments

Participants were given an in-person evaluation, either at the research office or at their home. This evaluation included a neurological examination with mental status testing (Morris, 1993) and assessment of functional abilities (Pfeffer et al., 1982) by a trained physician or nurse practitioner and a neuropsychological test battery (Whittle et al., 2007) that included the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). All participants completed a questionnaire that included demographics and past medical history. Blood samples were collected.

Evaluations were repeated every 6 months. For participants whose poor health, frailty, disability, or unwillingness did not allow an in-person follow-up evaluation, information was obtained by telephone or with an informant. Participants evaluated by telephone completed the short version of the Cognitive Abilities Screening Instrument (CASI-short) (Teng et al., 1994). For participants evaluated through informants, the Dementia Questionnaire (DQ) (Silverman et al., 1986) was completed over the telephone. In addition, informants of all participants were asked about the participant’s cognitive status and functional abilities using a mailed questionnaire. The DQ was completed for all participants shortly after death.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Determination of Cognitive Status

Cognitive status at baseline was determined from an in-person evaluation, either a neurological exam (98%) or MMSE score (2%). Cognitive status at follow-up was also determined from an in-person evaluation for most participants (97%). However, when an in-person evaluation at follow-up was not possible, we used any available information in the following hierarchical order: (1) neurological exam, (2) MMSE, (3) informant questionnaires, and (4) CASI-short. The neurological examiner determined cognitive status applying Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for dementia (APA, 1994). For the MMSE, we used age- and education-specific cutoff scores for dementia derived from this cohort (Whittle et al., 2007). For the CASI-short, we used a score <25 as the cutoff score for dementia. Computer algorithms were used to apply DSM-IV criteria for dementia to the questionnaires obtained from informants. Details about the application of the algorithms and the validity of these methods are published elsewhere (Corrada et al., 2008).

Neuropsychological examination

At each in-person visit, participants were given a standard battery of 10 neuropsychological tests indexing multiple cognitive domains: Mini-Mental State Examination (MMSE) and Modified Mini-Mental State Examination (3MS), fluency for animal names and letter F fluency, Boston Naming Test, California Verbal Learning Test (CVLT-II), Trail Making Test (TMT), Clock Drawing Test, CERAD Construction Test, and WAIS-III Digit Span Test. Details of these tests and modifications made in the administration procedures have been previously presented (Whittle et al., 2007) and are briefly described in the Supplement. The cognitive tests were administered in the order shown in Supplemental Table 1 by trained and certified psychometrists. The visit closest to the blood draw was selected.

Cystatin C and eGFR

A blood sample was measured for cystatin C by the Latex Enhanced Immunoturbidimetric Method by the Pathology & Laboratory Services of the UC Irvine Medical Center. Cystatin C was used to calculate the estimated glomerular filtration rate (eGFR) utilizing the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation which accounts for age and sex (Inker et al., 2012).

Brain MRI

Participants underwent brain magnetic resonance imaging (MRI) using a GE Signa HD 3.0 Tesla MRI system as previously described (Bennett et al., 2017). A high-resolution T1-weighted fast-spoiled gradient recalled echo (TR/TE/IT = 7/3/400 ms, FOV = 256 × 256 mm, 166 sagittal slices, and 1.0 mm^3 spatial resolution), fluid attenuation inversion recovery (FLAIR) sequence and susceptibility-weighted imaging (SWI) were acquired.

We calculated T1-weighted image tissue volumes using in-house methods described previously (Fletcher et al., 2018). Briefly, brain masks to separate brain from whole head were generated using an atlas-based method (Aljabar et al., 2009) followed by human quality control as needed. Stripped brains were further segmented into four tissue types: gray matter (GM), white matter (WM), cerebrospinal fluid (CSF), and white matter

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

hyperintensities (WMH), using a segmentation algorithm designed to enhance accuracy at tissue boundaries (Fletcher et al., 2012) in combination with FLAIR imaging to estimate WMH. Volumes of CSF, GM, WM and WMH were calculated and reported as percent of total brain volume.

MRI scans were also reviewed by a neuroradiologist (DF), who rated definite CMB presence, number and distribution on SWI using the Microbleed Anatomical Rating Scale (MARS) (Gregoire et al., 2009). In MARS, definite CMB were defined as small, rounded or circular, well-defined hypodense lesions within brain parenchyma with clear margins ranging from 2 to 10 mm in size on T2*-weighted images, and locations of CMB were classified into deep, lobar, and infratentorial categories.

Data Analysis

Means and standard deviations (SD) of continuous variables and proportions of categorical variables were derived for the over-all sample and stratified by cystatin C tertile groups. Differences in means were tested using anova and t-tests and in proportions using chi-square and Fisher exact-tests. Stepwise logistic regression analysis was used to examine the cross-sectional association of cystatin C tertiles with demographics and medical history.

For our longitudinal dementia risk analysis, we restricted our analysis to participants who were not demented at baseline and who had at least 1 additional follow-up evaluation. Participants were followed until age at dementia diagnosis, death or last visit, whichever came first. Hazard ratios (HRs) of dementia associated with cystatin C were estimated using Cox regression analysis (Cox, 1972). Age at study entry was recorded at time of cystatin C measurement (delayed entry) and the event of interest was age at dementia diagnosis. HRs were adjusted for age using age (continuous) as the fundamental time scale and for sex, education (not college graduate, college graduate), medical history (no, yes), smoking history (never, past) by including these as covariates in the model. To explore whether the effect of cystatin C on dementia risk was mediated in part by its potential effect on brain structure, we also analyzed these parameters as covariates in the model (CMB, percent gray or white matter, cerebral spinal fluid volume). All statistical analyses were performed using SAS software version 9.4 for Windows (SAS Institute Inc., Cary, NC).

RESULTS

The 193 participants were primarily white (97%), female (61%), college graduates (54%), and never smokers (54%) with a mean age of 93.9 years (Table 1). These characteristics reflect those of the entire cohort (99% white, 75% female, 41% college graduates, and 58% never smokers, mean age 93.8 years) but with later enrollment including more non-whites, males, and the less educated. Although participants in this sub-study were more likely than the whole cohort to have high blood pressure (62% vs 49%) and diabetes (12% vs 8%), they were less likely to report having a heart attack (7% vs 10%), congestive heart failure (8% vs 13%), stroke (10% vs 12%), and depression (11% vs 19%).

Figure 2 shows the distributions of cystatin C and stages of CKD as determined by eGFR values. Cystatin C ranged from 0.74 to 3.02 (mean=1.62 mg/L, SD=0.53) with eGFR values

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

of 14 to 92 (mean=39.2 ml/min/1.73 m^2, SD=17.7). The highest cystatin C tertile group included only CKD stage 4–5 subjects. The middle group included 2 subjects with CKD stage 4–5 (eGFR of 28 and 29).

The proportions of participants with/without most medical comorbidities did not differ by cystatin C level (low, medium, high). The proportions differed significantly only for congestive heart failure (CHF) (2%, 5% and 17% for the three levels, p=0.004) and depression (6%, 6% and 20%, p=0.02) (Table 1). Of the demographic and medical history variables, CHF (p=0.001), age (p=0.006), and depression (p=0.01) remained statistically significant in stepwise logistic regression of cystatin C tertiles.

Cystatin C associations with cognitive measures

Table 2 shows the mean+SD of the cognitive test scores for participants by cystatin C tertile groups. The time between the cystatin C measurement and the neuropsychological/ neurological examinations was within 3 months for all but 10 participants. The 3MS (an index of global cognition) showed poorer performance with increasing cystatin C level. Tests of executive function (Trails B – Trails A) and visual-spatial ability (CERAD construction) were also associated with cystatin C level with individuals in the low group performing better. These relationships were essentially unchanged with the elimination of the 10 participants with neuropsychological examination greater than 3 months from cystatin C measurement.

Mean cystatin C level was higher in the 14 participants classified as having dementia compared with 126 individuals with normal cognition and 53 with mild cognitive impairment (1.58 mg/L in normal cognition; 1.62 mg/L in mild cognitive impairment; and 1.96 mg/L in demented, p=0.04) (Table 3).

Cystatin C associations with structural brain measures

Brain MRI was available for 129 participants. Reasons for missing MRI data were bodily presence of hardware (e.g., pacemaker, metal implant) (n=38), other condition (e.g., too weak, could not tolerate time in scanner) (n=16), refused (n=10).

The lowest cystatin C tertile group had a lower proportion of subjects with CMB, especially infratentorial CMB (0% vs 7% and 14%, p=0.04) (Table 4). The mean cystatin C was 2.01 vs 1.59 mg/L in those with vs without infratentorial CMB (p=0.02). Cystatin C level was not related to deep or lobar CMB counts. Mean total gray matter also differed significantly among the 3 cystatin C tertile groups, with the lowest tertile group having a greater mean gray matter (42.2 vs 40.9 and 40.8, p=0.0007).

Longitudinal analysis of incident dementia

The risk of incident dementia among the 171 non-demented participants at baseline who had follow-up visit (average follow-up = 2 years) was 3.06 (95% CI 0.97–9.66) and 3.41 (95% CI 1.11–10.5) for the middle and high cystatin C tertile groups relative to the lowest. With adjustment for sex, education, smoking, and comorbid conditions of hypertension, diabetes, coronary artery disease, heart attack, heart valve disease, congestive heart failure, stroke,

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

TIA, vascular disease, and depression, the hazard ratios were 2.78 (95% CI 0.81–9.54) and 3.81 (95% CI 1.14–12.7) (Figure 3).

To explore whether the risk of dementia for high cystatin C was mediated by brain structure, we repeated the analysis for the 112 non-demented participants at baseline who had CMB and brain matter measurements. Individually the HRs were 2.46 (95% CI 0.74–8.17) and 2.62 (95% CI 0.81–8.47) for the middle and high cystatin C tertile groups relative to the low tertile, 1.96 (95% CI 0.84–4.58) for any CMB vs none, and 0.98 (95% CI 0.78–1.24) for % gray matter of total brain volume. With both cystatin C and CMB in the model, the HR for the high cystatin C group was reduced from 2.62 to 2.35 (95% CI 0.73–7.60) suggesting that cystatin C may be exerting some of its effect via CMB. The other HRs were little changed: from 2.46 to 2.48 (95% CI 0.75–8.24) for the middle cystatin C group and from 1.96 to 1.87 (95% CI 0.79–4.46) for any CMB. The HR for % gray matter was essentially 1.0 (with and without cystatin C and CMB).

DISCUSSION

Our study in 193 community-dwelling adults 90+ year-olds demonstrated a significant association between higher cystatin C (lower kidney function) and cognitive function. Neuropsychological tests for global cognition, executive function and visual-spatial ability demonstrated significantly greater impairment in participants with higher cystatin C levels. After mean follow-up 2 years, persons with lower kidney function had a greater risk of incident dementia than those with higher function. Brain MRI showed positive associations between higher cystatin C and presence of infratentorial CMB and gray matter abnormalities. The increased risk of dementia in those with high cystatin C was reduced when presence of CMB was included in the model suggesting that CMB contribute to the cognitive decline.

The mean serum cystatin C in our sample was 1.62 + 0.53 (range 0.74–3.02 mg/L), with age-dependent increases and no sex differences. Nearly 90% had cystatin C levels > 1.0 consistent with impaired kidney function. Increasing levels of cystatin C with age may reflect physiologic accelerated decline in residual kidney function in the oldest-old; results of prior work on the agecystatin C relationship are mixed (Finney et al., 1999; Werner et al., 2014). The absence of sex differences is consistent with earlier work (Finney et al., 1999).

We show a relationship between increased levels of cystatin C and both CMB and gray matter atrophy. CMB and gray matter atrophy are both highly characteristic of cerebral microvascular disease (Graff-Radford et al., 2017; Kern et al., 2017). Higher cystatin C has been associated with gray matter atrophy in a younger cohort where mean age was 73 years (Riverol et al., 2015). While age, hypertension and cerebral amyloid angiopathy are the best described risk factors for development of CMB (Vernooij et al., 2008), CKD has emerged as an additional independent risk factor for CMB (Lau et al., 2020). We found that cystatin C eGFR was associated with infratentorial CMB regardless of hypertension comorbidity, similar to a report from a Japanese cohort where microalbuminuria (marker of kidney dysfunction) was independently associated with infratentorial CMB (Umemura et al., 2012). Moreover, in mouse CKD models, we found that that the cerebellum was one of the

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

principal sites of microhemorrhage (Lau et al., 2020). Absence of association of strictly lobar CMB with cystatin C is not surprising, given the well-established relationship between lobar CMB and cerebral amyloid angiopathy (Vernooij et al., 2008). WM volume and WMH were not significantly different across cystatin C strata, perhaps due to predominant modulation by advanced age.

We found associations between cystatin C with the global cognitive measure 3MS and tests of executive function (Trails) and visual-spatial ability (CERAD construction). Although we know of no study evaluating cystatin C and cognitive function in those aged 90+ years, several studies have looked at cognition in older adults. These have generally found that cystatin C levels and cognitive function are inversely associated (Darsie et al., 2014; Kurella et al., 2005; Riverol et al., 2015; Seliger et al., 2004; Yaffe et al., 2008). Elders with CKD from an ambulatory clinic setting had poorer performance on executive function and verbal memory compared with published norms (Kurella et al., 2004). Among 3030 community-dwelling adults aged 70–79 years in the Health ABC study, elders with higher cystatin C had worse baseline 3MS score (91.4±8.3 vs 92.4±7.6 for high (>1.25) compared with low (<1.00) cystatin C groups, $p=0.01$) and were more likely to decline in cognitive function over 7 years (2.7 points on the 3MS vs 0.9 points in the low cystatin C group, $p<0.01$) (Yaffe et al., 2008). In the Cardiovascular Health Study (CHS) of 3907 participants aged 65 years and older, low cystatin C-based eGFR was associated with greater decline in cognitive function as measured by the 3MS (Darsie et al., 2014). Consistent with the finding by Seliger et al. that older adults with moderate CKD have an elevated risk of developing dementia (Seliger et al., 2004), we found that higher cystatin C levels are associated with increased risk of incident dementia. Although sample size was much reduced for those with MRI measurements (and no result was statistically significant), the HR for incident dementia was reduced over 10% in the high cystatin C tertile group when adjustment for CMB was included in the model, suggesting that cystatin C may be exerting some of its effect via CMB.

Our study has inherent strengths and limitations. Our major strength is the well-characterized participants who are part of a longitudinal epidemiologic study of aging and dementia. Additionally we used a neuropsychological test battery covering numerous cognitive domains and a structured neurological examination. The ambulatory sample provides a general picture of cystatin C levels and cognitive/imaging metrics in community-dwelling oldest-old. However, our sample was recruited from a highly educated, moderately affluent population, which may limit the generalizability of our findings to populations with less education. Because our sample included relatively high-functioning elderly individuals, we had no participants with end-stage kidney failure on dialysis or nursing home patients. In this regard we likely excluded individuals with more extreme values of cystatin C and with greater cognitive impairment. The cross-sectional design of the brain imaging component does not allow us to determine the temporal direction of the associations or causal inferences between kidney function and imaging metrics. However, our longitudinal analysis of risk of incident dementia provides an analysis of the temporal direction of that association. Finally, we cannot exclude a direct effect of cystatin C on brain function, given its properties that include inhibition of cathepsins, regulation of proteolysis and autophagy, and regulation of cell proliferation and migration (Finckh et al., 2000; Mathews and Levy, 2016).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

In summary, our findings show that cystatin C levels in healthy very old adults >90 years of age ranged 0.74–3.02 (mean=1.62 mg/L) with 87% having CKD (eGFR <60 ml/min/1.73 m^2). In this age group, the association of high serum cystatin C with impaired cognition is global but is especially related to the domains of executive function and visual-spatial ability. Possible mechanisms underlying an association between poor kidney function and cognitive impairment include uremic pathways of brain vascular injury, as evidenced by increased infratentorial microbleeds and loss of gray matter volume on brain MRI. Finally, increased cystatin C levels (more advanced CKD) were associated with increased risk of incident dementia. These findings emphasize the potential significance of maintaining kidney health for improved cognition and quality of life in advanced age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

This work was supported by NIH grants R01AG021055 from NIA and R01NS20989 from NINDS (MF). Part of this work was presented as a Late-Breaking Science poster at the International Stroke Conference, February 2019 (Honolulu, HI).

References

Aljabar P, Heckemann RA, Hammers A, Hajnal JV, Rueckert D, 2009 Multi-atlas based segmentation of brain images: atlas selection and its effect on accuracy. Neuroimage 46(3), 726–738. [PubMed: 19245840]

APA, 1994 Diagnostic and Statistical Manual of Mental Disorders, 4th. ed. American Psychiatric Association, Washington, DC.

Bennett IJ, Greenia DE, Maillard P, Sajjadi SA, DeCarli C, Corrada MM, Kawas CH, 2017 Age-related white matter integrity differences in oldest-old without dementia. Neurobiol Aging 56, 108–114. [PubMed: 28527525]

Chelluboina B, Vemuganti R, 2019 Chronic kidney disease in the pathogenesis of acute ischemic stroke. J Cereb Blood Flow Metab 39(10), 1893–1905. [PubMed: 31366298]

Corrada MM, Brookmeyer R, Berlau D, Paganini-Hill A, Kawas CH, 2008 Prevalence of dementia after age 90: results from the 90+ study. Neurology 71(5), 337–343. [PubMed: 18596243]

Cox DR, 1972 Regression Models and Life-Tables. J R Stat Soc B 34(2), 187–+.

Darsie B, Shlipak MG, Sarnak MJ, Katz R, Fitzpatrick AL, Odden MC, 2014 Kidney function and cognitive health in older adults: the Cardiovascular Health Study. Am J Epidemiol 180(1), 68–75. [PubMed: 24844846]

Dharnidharka VR, Kwon C, Stevens G, 2002 Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. Am J Kidney Dis 40(2), 221–226. [PubMed: 12148093]

Finckh U, von der Kammer H, Velden J, Michel T, Andresen B, Deng A, Zhang J, Müller-Thomsen T, Zuchowski K, Menzer G, Mann U, Papassotiropoulos A, Heun R, Zurdel J, Holst F, Benussi L, Stoppe G, Reiss J, Miserez AR, Staehelin HB, Rebeck GW, Hyman BT, Binetti G, Hock C, Growdon JH, Nitsch RM, 2000 Genetic association of a cystatin C gene polymorphism with late-onset Alzheimer disease. Arch Neurol 57(11), 1579–1583. [PubMed: 11074789]

Finney H, Bates CJ, Price CP, 1999 Plasma cystatin C determinations in a healthy elderly population. Arch Gerontol Geriatr 29(1), 75–94. [PubMed: 15374079]

Fletcher E, Gavett B, Harvey D, Farias ST, Olichney J, Beckett L, DeCarli C, Mungas D, 2018 Brain volume change and cognitive trajectories in aging. Neuropsychology 32(4), 436–449. [PubMed: 29494196]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Fletcher E, Singh B, Harvey D, Carmichael O, DeCarli C, 2012 Adaptive image segmentation for robust measurement of longitudinal brain tissue change. Conf Proc IEEE Eng Med Biol Soc 2012, 5319–5322. [PubMed: 23367130]

Fliser D, Ritz E, 2001 Serum cystatin C concentration as a marker of renal dysfunction in the elderly. Am J Kidney Dis 37(1), 79–83. [PubMed: 11136171]

Folstein MF, Folstein SE, McHugh PR, 1975 “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12(3), 189–198. [PubMed: 1202204]

Graff-Radford J, Simino J, Kantarci K, Mosley TH, Griswold ME, Windham BG, Sharrett AR, Albert MS, Gottesman RF, Jack CR, Vemuri P, Knopman DS, 2017 Neuroimaging Correlates of Cerebral Microbleeds: The ARIC Study (Atherosclerosis Risk in Communities). Stroke 48(11), 2964–2972. [PubMed: 29018129]

Gregoire SM, Chaudhary UJ, Brown MM, Yousry TA, Kallis C, Jäger HR, Werring DJ, 2009 The Microbleed Anatomical Rating Scale (MARS): reliability of a tool to map brain microbleeds. Neurology 73(21), 1759–1766. [PubMed: 19933977]

Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS, Investigators C-E, 2012 Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 367(1), 20–29. [PubMed: 22762315]

Kalaria RN, 2018 The pathology and pathophysiology of vascular dementia. Neuropharmacology 134(Pt B), 226–239. [PubMed: 29273521]

Kern KC, Wright CB, Bergfield KL, Fitzhugh MC, Chen K, Moeller JR, Nabizadeh N, Elkind MSV, Sacco RL, Stern Y, DeCarli CS, Alexander GE, 2017 Blood Pressure Control in Aging Predicts Cerebral Atrophy Related to Small-Vessel White Matter Lesions. Front Aging Neurosci 9, 132. [PubMed: 28555103]

Kurella M, Chertow GM, Fried LF, Cummings SR, Harris T, Simonsick E, Satterfield S, Ayonayon H, Yaffe K, 2005 Chronic kidney disease and cognitive impairment in the elderly: the health, aging, and body composition study. J Am Soc Nephrol 16(7), 2127–2133. [PubMed: 15888561]

Kurella M, Chertow GM, Luan J, Yaffe K, 2004 Cognitive impairment in chronic kidney disease. J Am Geriatr Soc 52(11), 1863–1869. [PubMed: 15507063]

Lau WL, Huisa BN, Fisher M, 2017 The Cerebrovascular-Chronic Kidney Disease Connection: Perspectives and Mechanisms. Transl Stroke Res 8(1), 67–76. [PubMed: 27628245]

Lau WL, Nunes ACF, Vasilevko V, Floriolli D, Lertpanit L, Savoj J, Bangash M, Yao Z, Shah K, Naqvi S, Paganini-Hill A, Vaziri ND, Cribbs DH, Fisher M, 2020 Chronic Kidney Disease Increases Cerebral Microbleeds in Mouse and Man. Transl Stroke Res 11(1), 122–134. [PubMed: 31055735]

Masson P, Kelly PJ, Craig JC, Lindley RI, Webster AC, 2015 Risk of Stroke in Patients with ESRD. Clin J Am Soc Nephrol 10(9), 1585–1592. [PubMed: 26209158]

Mathews PM, Levy E, 2016 Cystatin C in aging and in Alzheimer’s disease. Ageing Res Rev 32, 38–50. [PubMed: 27333827]

Melikyan ZA, Greenia DE, Corrada MM, Hester MM, Kawas CH, Grill JD, 2019 Recruiting the Oldest-old for Clinical Research. Alzheimer Dis Assoc Disord 33(2), 160–162. [PubMed: 29734262]

Morris JC, 1993 The Clinical Dementia Rating (CDR): Current version and scoring rules. Neurology 43, 2412–2414.

Paganini-Hill A, Kawas CH, Corrada MM, 2016 Lifestyle Factors and Dementia in the Oldest-old: The 90+ Study. Alzheimer Dis Assoc Disord 30(1), 21–26. [PubMed: 25710250]

Paganini-Hill A, Ross RK, Henderson BE, 1986 Prevalence of chronic disease and health practices in a retirement community. J Chronic Dis 39(9), 699–707. [PubMed: 3734024]

Perkins BA, Nelson RG, Ostrander BE, Blouch KL, Krolewski AS, Myers BD, Warram JH, 2005 Detection of renal function decline in patients with diabetes and normal or elevated GFR by serial measurements of serum cystatin C concentration: results of a 4-year follow-up study. J Am Soc Nephrol 16(5), 1404–1412. [PubMed: 15788478]

Pfeffer RI, Kurosaki TT, Harrah CH, Chance JM, Filos S, 1982 Measurement of functional activities in older adults in the community. J Gerontol 37(3), 323–329. [PubMed: 7069156]

Raman M, Middleton RJ, Kalra PA, Green D, 2017 Estimating renal function in old people: an in-depth review. Int Urol Nephrol 49(11), 1979–1988. [PubMed: 28913589]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Rensma SP, van Sloten TT, Houben AJHM, Köhler S, van Boxtel MPJ, Berendschot TTJM, Jansen JFA, Verhey FRJ, Kroon AA, Koster A, Backes WH, Schaper N, Dinant GJ, Schalkwijk CG, Henry RMA, Wolfs EML, van Heumen MJA, Schram MT, Stehouwer CDA, 2020 Microvascular Dysfunction Is Associated With Worse Cognitive Performance: The Maastricht Study. Hypertension 75(1), 237–245. [PubMed: 31735081]

Riverol M, Becker JT, López OL, Raji CA, Thompson PM, Carmichael OT, Gach HM, Longstreth WT, Fried L, Tracy RP, Kuller LH, 2015 Relationship between Systemic and Cerebral Vascular Disease and Brain Structure Integrity in Normal Elderly Individuals. J Alzheimers Dis 44(1), 319–328. [PubMed: 25213770]

Sarnak MJ, Tighiouart H, Scott TM, Lou KV, Sorensen EP, Giang LM, Drew DA, Shaffi K, Strom JA, Singh AK, Weiner DE, 2013 Frequency of and risk factors for poor cognitive performance in hemodialysis patients. Neurology 80(5), 471–480. [PubMed: 23303848]

Seliger SL, Siscovick DS, Stehman-Breen CO, Gillen DL, Fitzpatrick A, Bleyer A, Kuller LH, 2004 Moderate renal impairment and risk of dementia among older adults: the Cardiovascular Health Cognition Study. J Am Soc Nephrol 15(7), 1904–1911. [PubMed: 15213280]

Silverman JM, Breitner JC, Mohs RC, Davis KL, 1986 Reliability of the family history method in genetic studies of Alzheimer's disease and related dementias. Am J Psychiatry 143(10), 1279–1282. [PubMed: 3766791]

Teng EL, Hasegawa K, Homma A, Imai Y, Larson E, Graves A, Sugimoto K, Yamaguchi T, Sasaki H, Chiu D, 1994 The Cognitive Abilities Screening Instrument (CASI): a practical test for cross-cultural epidemiological studies of dementia. Int Psychogeriatr 6(1), 45–58; discussion 62. [PubMed: 8054493]

Umemura T, Kawamura T, Sakakibara T, Mashita S, Hotta N, Sobue G, 2012 Microalbuminuria is independently associated with deep or infratentorial brain microbleeds in hypertensive adults. Am J Hypertens 25(4), 430–436. [PubMed: 22237153]

Vernooij MW, van der Lugt A, Ikram MA, Wielopolski PA, Niessen WJ, Hofman A, Krestin GP, Breteler MM, 2008 Prevalence and risk factors of cerebral microbleeds: the Rotterdam Scan Study. Neurology 70(14), 1208–1214. [PubMed: 18378884]

Werner KB, Elmståhl S, Christensson A, Pihlsgård M, 2014 Male sex and vascular risk factors affect cystatin C-derived renal function in older people without diabetes or overt vascular disease. Age Ageing 43(3), 411–417. [PubMed: 24321840]

Whittle C, Corrada MM, Dick M, Ziegler R, Kahle-Wrobleski K, Paganini-Hill A, Kawas C, 2007 Neuropsychological data in nondemented oldest old: the 90+ Study. J Clin Exp Neuropsychol 29(3), 290–299. [PubMed: 17454349]

Wu A, Sharrett AR, Gottesman RF, Power MC, Mosley TH, Jack CR, Knopman DS, Windham BG, Gross AL, Coresh J, 2019 Association of Brain Magnetic Resonance Imaging Signs With Cognitive Outcomes in Persons With Nonimpaired Cognition and Mild Cognitive Impairment. JAMA Netw Open 2(5), e193359. [PubMed: 31074810]

Yaffe K, Lindquist K, Shlipak MG, Simonsick E, Fried L, Rosano C, Satterfield S, Atkinson H, Windham BG, Kurella-Tamura M, 2008 Cystatin C as a marker of cognitive function in elders: findings from the health ABC study. Ann Neurol 63(6), 798–802. [PubMed: 18496846]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Highlights

- Lower cystatin C (better kidney function) was associated with better cognition.
- Lower cystatin C was also associated with less brain imaging pathology.
- Preserving kidney function may lower risk of incident dementia in advanced age.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

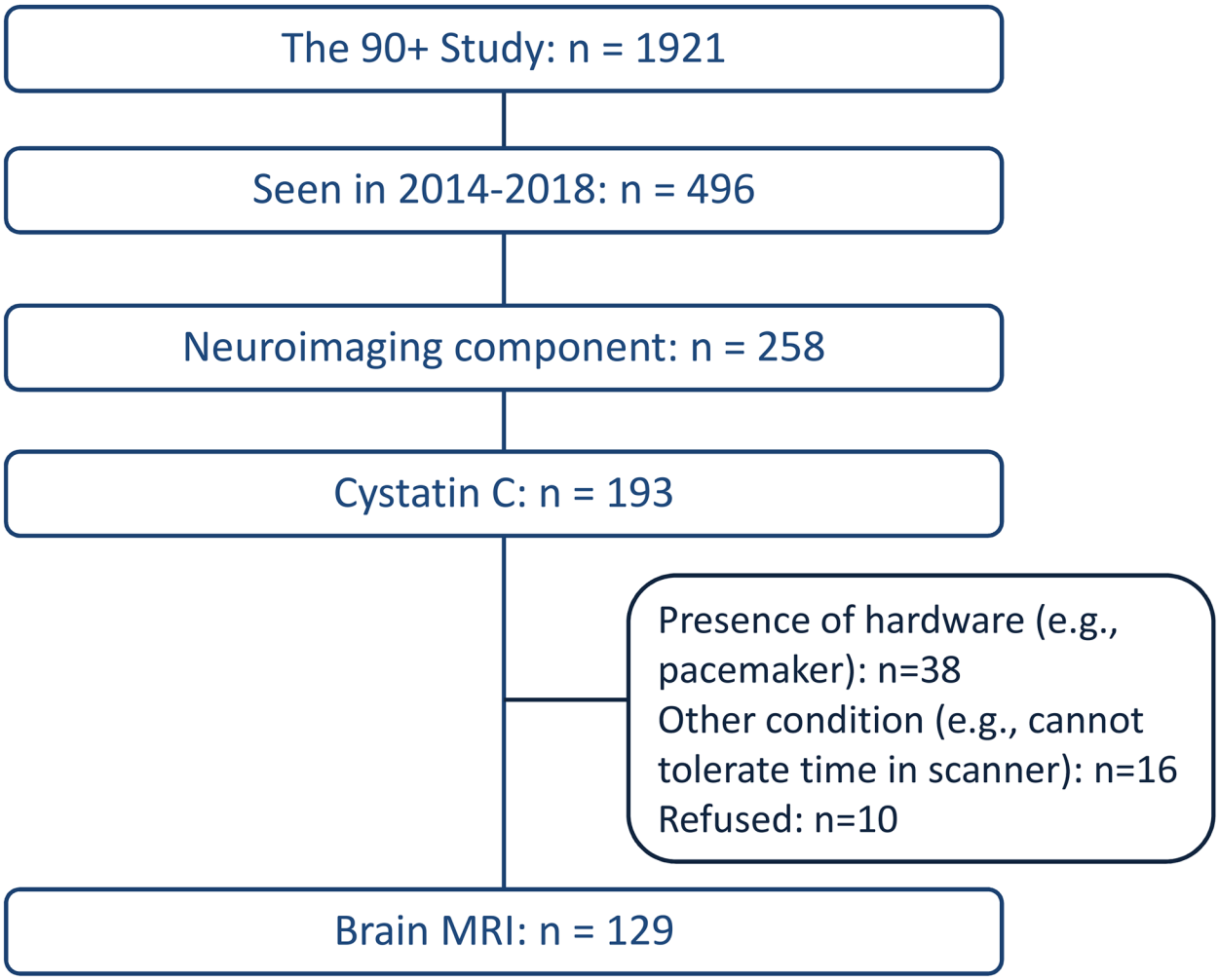

Figure 1.

Cohort construction from The 90+ Study participants. Of the total 1921 participants, 496 were seen between 2014 (when the neuroimaging component of the study began) and 2018. Between 2014–2018, 258 participants gave informed consent to participate in the neuroimaging study. Cystatin C level was determined for 193 and brain MRI was completed in 129 participants.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

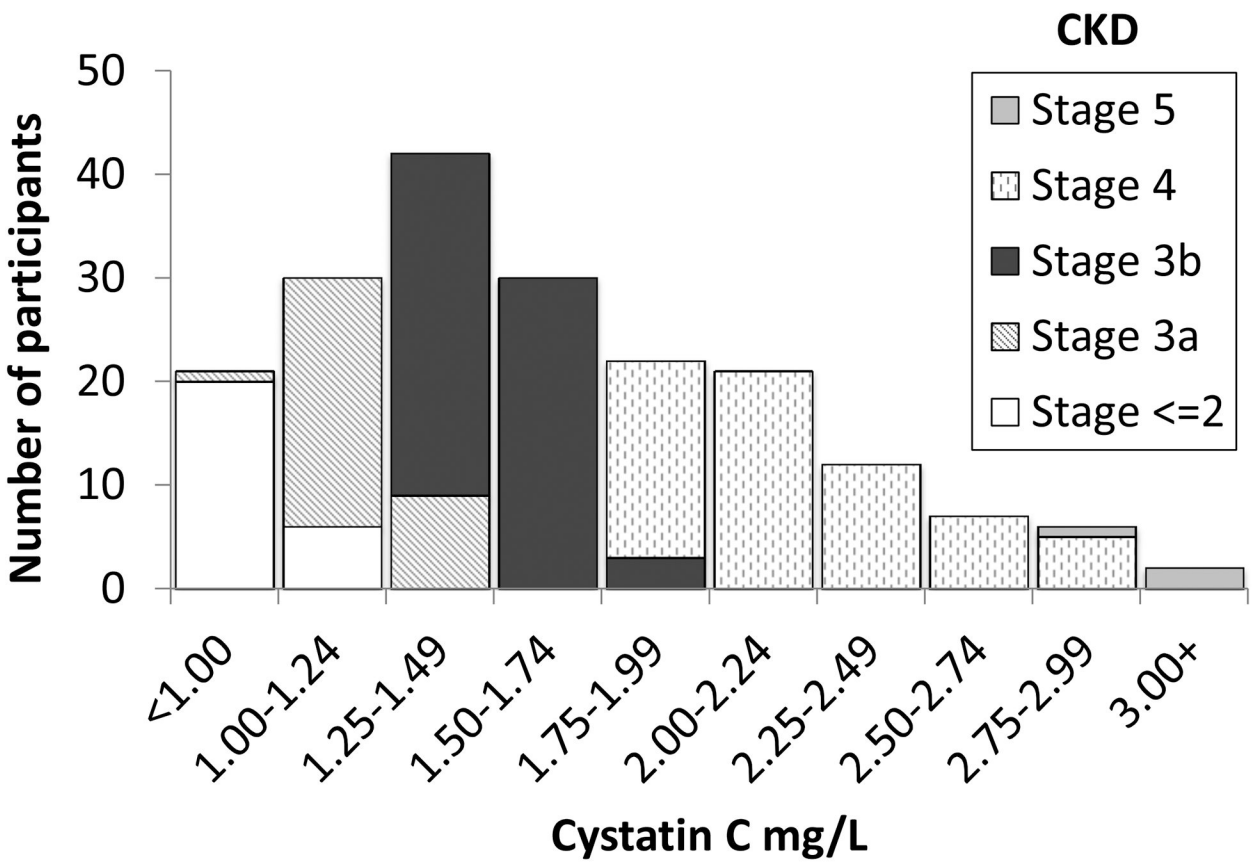

Figure 2.
Distributions of cystatin C and stages of chronic kidney disease (CKD, determined by estimated glomerular filtration rate or eGFR) in 193 individuals aged 90+ years.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

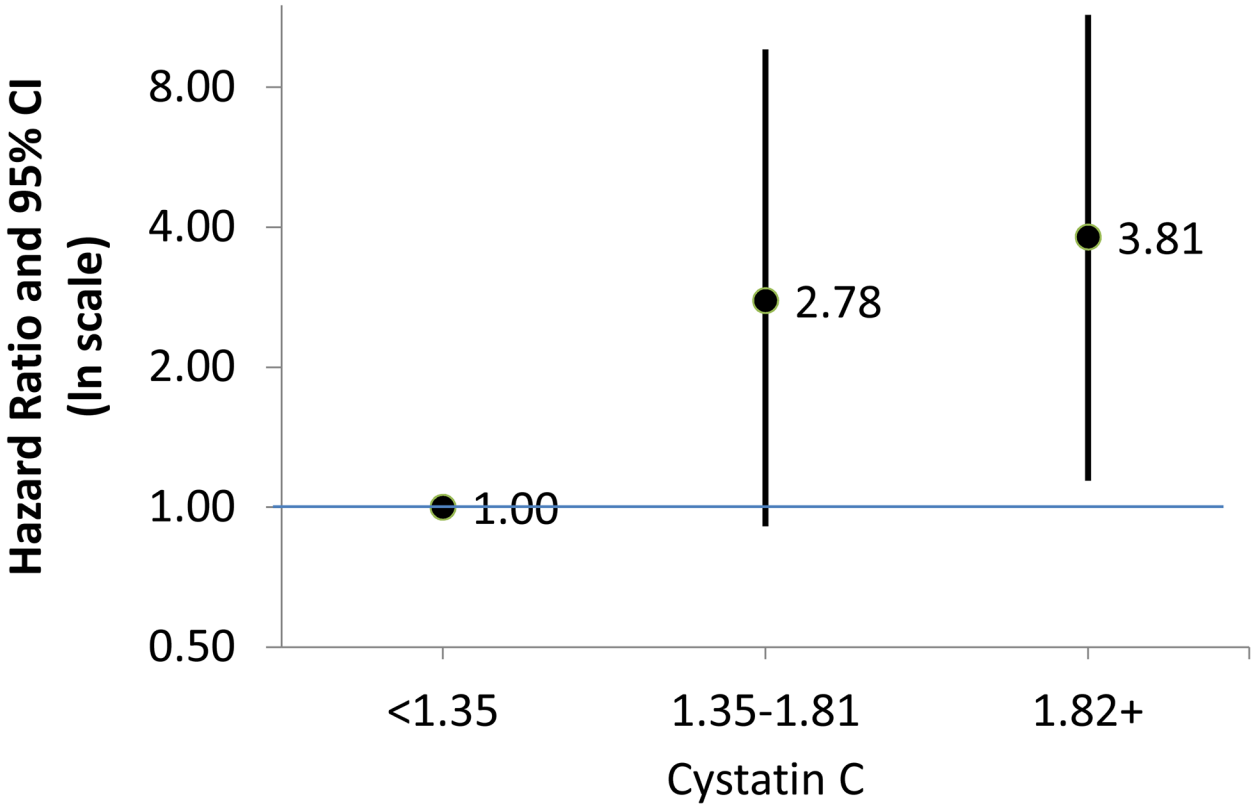

Figure 3.

Increased risk of incident dementia was associated with higher cystatin C tertile groups in 171 individuals aged 90+ years (non-demented at baseline). Hazard ratios and 95% confidence intervals are adjusted for sex, education (not college graduate, college graduate), smoking (never, past), and medical histories (no, yes) of hypertension, diabetes, coronary artery disease, heart attack, heart valve disease, congestive heart failure, stroke, TIA, vascular disease, and depression.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1.

Characteristics of participants by cystatin C tertile groups

	All Subjects	Cystatin C < 1.35	Cystatin C 1.35–1.81	Cystatin C 1.82+	P-value†
Number of subjects	193	63	65	65	
	Mean + SD Range	**Mean + SD Range**	**Mean + SD Range**	**Mean + SD Range**	
Age (years) at blood draw	93.9 + 3.0 90 to 107	93.2 + 2.9 90 to 104	93.6 + 2.4 90 to 99	94.8 + 3.3 90 to 107	**0.006**
Cystatin C	1.62 + 0.53 0.74 to 3.02	1.07 + 0.17 0.74 to 1.34	1.54 + 0.12 1.35 to 1.81	2.25 + 0.34 1.82 to 3.02	**<0.0001**
eGFR	39.2 + 17.7 14 to 92	59.8 + 13.7 41 to 92	36.1 + 4.3 28 to 45	22.2 + 4.2 14 to 29	**<0.0001**
Days to neuropsychological exam	15 + 44 −102 to 202	12 + 42 −84 to 202	11 + 38 −102 to 132	21 + 50 −99 to 133	0.34
	No. (%)	**No. (%)**	**No. (%)**	**No. (%)**	
Female	118 (61%)	38 (60%)	41 (63%)	39 (60%)	0.95
Education: college grad	104 (54%)	37 (59%)	30 (46%)	37 (57%)	0.31
Never smoked (missing=1)	104 (54%)	31 (50%)	40 (62%)	33 (51%)	0.35
Medical History					
High blood pressure	119 (62%)	34 (54%)	40 (62%)	45 (69%)	0.22
Diabetes	24 (12%)	8 (13%)	6 (9%)	10 (15%)	0.56
Coronary artery disease	24 (12%)	5 (8%)	6 (9%)	13 (20%)	0.10
Heart attack	14 (7%)	2 (3%)	5 (8%)	7 (11%)	0.27
Heart valve disease	9 (5%)	3 (5%)	1 (2%)	5 (8%)	0.25
Congestive heart failure *	15 (8%)	1 (2%)	3 (5%)	11 (17%)	**0.004**
Stroke	19 (10%)	4 (6%)	7 (11%)	8 (12%)	0.56
TIA	35 (18%)	8 (13%)	14 (22%)	13 (20%)	0.38
Any of above	145 (75%)	41 (65%)	51 (78%)	53 (82%)	0.05
Depression **	21 (11%)	4 (6%)	4 (6%)	13 (20%)	**0.02**

† for difference among cystatin C tertile groups

* Mean cystatin C in persons with vs without congestive heart failure: 2.14 + 0.56 vs 1.58 + 0.51 mg/L, p<0.0001

** Mean cystatin C in persons with vs without depression : 1.81 + 0.48 vs 1.60 + 0.54 mg/L, p=0.09

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 2.

Cognitive test scores by cystatin C tertile groups

	Cystatin C < 1.35	Cystatin C 1.35–1.81	Cystatin C 1.82+	P-value†
Cognitive Test	**Mean + SD**	**Mean + SD**	**Mean + SD**	
Global Cognition				
MMSE	27.8 + 1.9	27.0 + 3.3	26.7 + 3.4	0.12
3MS	94.7 + 4.5	91.7 + 9.4	90.9 + 11.3	**0.04**
Language				
Boston Naming Test	13.1 + 2.2	13.0 + 1.9	13.5 + 1.6	0.42
Animal Fluency	15.6 + 4.4	15.3 + 5.4	14.5 + 5.0	0.46
Letter F Fluency	13.2 + 5.2	12.7 + 5.3	13.6 + 4.1	0.60
Recent Memory				
CVLT Trial 1	5.1 + 1.9	5.0 + 2.0	4.8 + 1.8	0.69
CVLT Trial 4	7.7 + 1.2	7.3 + 1.7	7.3 + 1.6	0.26
CVLT Sum 1 to 4	26.9 + 4.9	25.8 + 6.6	25.6 + 5.7	0.44
CVLT Short Delay	7.2 + 1.7	6.8 + 2.2	6.5 + 2.5	0.24
CVLT Long Delay	6.2 + 2.3	6.0 + 2.9	5.7 + 3.1	0.54
CVLT Cued Long Delay	6.6 + 2.1	6.4 + 2.6	6.6 + 2.3	0.92
Executive Function				
Trails A	55 + 24	72 + 34	65 + 34	**0.01**
Trails B	145 + 74	202 + 83	200 + 90	**0.0002**
Trails B - Trails A	91 + 62	130 + 67	135 + 78	**0.002**
Psychomotor Speed				
Trails C	22 + 10	34 + 33	28 + 16	**0.02**
Visual-spatial				
Clock	6.1 + 1.9	5.9 + 2.0	6.3 + 2.0	0.54
CERAD Constructions	9.8 + 1.1	9.1 + 1.3	9.6 + 1.0	**0.007**
Attention/Working Memory				
Digit Span Forward	9.2 + 2.0	8.9 + 1.8	9.1 + 1.8	0.60
Digit Span Backward	5.9 + 2.3	5.6 + 2.1	5.5 + 1.8	0.54
Digit Span Total	15.2 + 3.8	14.5 + 3.4	14.6 + 3.0	0.57

† for difference among cystatin C tertile groups

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 3.

Cognitive status by cystatin C

Cognitive status	No. subjects (%)	Mean + SD[†]
Normal	126 (65%)	1.58 + 0.53
Mild cognitive impairment	53 (27%)	1.65 + 0.52
Demented	14 (7%)	1.96 + 0.52

[†]p=0.04 for difference in mean cystatin C among cognitive status groups

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 4.

MRI findings by cystatin C tertile groups

	All Subjects	Cystatin C < 1.35	Cystatin C 1.35–1.81	Cystatin C 1.82+	P-value†
Cerebral Microbleeds (CMB)	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	
Number of subjects	127	40	44	43	
Any CMB	29 (23%)	7 (17%)	9 (20%)	13 (30%)	0.36
Infratentorial CMB	9 (7%)	0 (0%)	3 (7%)	6 (14%)	0.04
Deep CMB	8 (6%)	2 (5%)	2 (5%)	4 (9%)	0.66
Lobar CMB	18 (14%)	6 (15%)	6 (14%)	6 (14%)	1.00
Lobar CMB only	15 (12%)	5 (12%)	5 (11%)	5 (12%)	1.00
% of total brain volume	**Mean + SD Range**	**Mean + SD Range**	**Mean + SD Range**	**Mean + SD Range**	**P-value†**
Number of subjects	124	40	43	41	
Total cerebral spinal fluid	28.7 + 1.93 25.1 to 34.4	28.1 + 1.70 25.1 to 31.7	28.9 + 2.09 25.4 to 34.4	29.1 + 1.87 25.5 to 33.3	**0.05**
Total gray matter	41.3 + 1.80 36.9 to 46.7	42.2 + 1.81 37.5 to 46.7	40.9 + 1.51 38.1 to 44.3	40.8 + 1.81 36.9 to 44.0	**0.0007**
Total white matter	28.9 + 2.10 24.0 to 34.4	28.8 + 2.01 25.0 to 32.5	29.0s + 2.27 24.0 to 34.4	29.0 + 2.03 24.7 to 33.4	0.88
Total white matter hyperintensities (missing=14)	1.21 + 0.98 0.0004 to 5.06	1.13 + 1.03 0.06 to 3.78	1.39 + 0.94 0.0004 to 3.23	1.11 + 0.97 0.087 to 5.06	0.39

† for difference among cystatin C tertile groups