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Original Article

Cardiovascular-kidney-metabolic syndrome and incidence of dementia among older adults

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ABSTRACT

Background: Cardiovascular-Kidney-Metabolic Syndrome (CKM) has profound impacts on cardiovascular events and mortality, yet its association with dementia risk remains poorly understood.
Objectives: To investigate associations between CKM and dementia risk.
Design: The prospective cohort study is within the Health, Aging, and Body Composition study, which enrolled participants from 1997 to 1998, with a 15-year follow-up for incident dementia.
Setting: The population-based study took place in two US communities in Memphis, Tennessee, and Pittsburgh, Pennsylvania.
Participants: Of the 3,075 participants aged 70 to 79 years initially enrolled, 14 were excluded for lacking baseline cognitive assessment, 308 for baseline cognitive impairment, 4 for missing follow-up, and 108 for missing CKM data, resulting in 2,641 in the analysis.
Measurements: CKM staging, as defined recently by the American Heart Association framework, was based on constructs comprising dysfunctional adiposity, metabolic risk factors, chronic kidney disease (CKD), and cardiovascular disease (CVD). Dementia was identified using hospital records, prescriptions for dementia medication, and a test of global cognition. Adjusted Cox and Fine-Gray proportional hazards models were used to estimate dementia risk and account for competing risk of death.
Results: The 2,641 participants had a mean (SD) age of 74 (2.8) years at baseline; 53 % were female, 36 % were of Black race, and had a range of baseline CKM: 3 % Stage 0 (no CKM), 4 % Stage 1 (excess/dysfunctional adiposity), 26 % Stage 2 (metabolic risk factors), 24 % Stage 3 (subclinical CVD and CKD), and 43 % Stage 4 (clinical CVD and CKD). Compared to participants with CKM Stages 0–2, those with CKM Stages 3–4 had a 50 % increase in dementia risk (hazard ratio 1.50, 95 % CI 1.20 to 1.86) in the fully adjusted model. The association remained significant after additional adjustment for metabolic risk factors, CVD, and CKD, both separately and together. Accounting for competing risk of death yielded similar results.
Conclusions: Among community-dwelling older adults, advanced CKM is associated with an increased risk of dementia. Older adults with CKM may need to be followed closely for adverse cognitive outcomes, and modifiable risk factors should be managed proactively.

1. Introduction

A growing understanding of the systemic interplay among metabolic risk factors, chronic kidney disease (CKD), and cardiovascular disease (CVD) has led to the recognition of Cardiovascular-Kidney-Metabolic Syndrome (CKM). In October 2023, the American Heart Association (AHA) introduced a new clinical framework defining the progression of CKM continuum across five stages: Stage 0 includes individuals with no risk factors; Stage 1 is characterized by excess or dysfunctional adiposity; Stage 2 involves metabolic risk factors and CKD; Stage 3 includes subclinical CVD in CKM; and Stage 4 represents clinical CVD in CKM [1]. In the United States (US), CKM is highly prevalent, with more than 55 % of older adults aged ≥65 having different stage of CKM [2,3]. CKM is strongly linked to premature mortality due to increased risks of CVD [4,5], which contributes to cognitive impairment and dementia among older adults [6–8]. However, the direct role of CKM on the risk of dementia remains to be determined.

Emerging evidence supports the relationship between dementia risk and individual components of CKM, including metabolic syndrome (MetS), diabetes, heart disease, and CKD [6,9–13]. Yet, CKM constructs

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commonly co-occur due to the shared pathophysiological pathways and interactions [3,14]. Recent advances in therapeutic strategies offer multifaceted benefits for CKM, targeting its root causes (e.g., excess adiposity and insulin resistance), and improving CKM health holistically [15–17]. With limited effective treatment for dementia, an opportunity exists to positively impact cognitive outcomes through interventions aimed at improving overall CKM health. Thus, it is critical to understand the full spectrum of CKM health and its role in dementia risk among older adults.

In a prospective cohort of Black and White older adults without cognitive impairment, our goal was to investigate the association between CKM stages, defined by the new AHA framework, and the risk of incident dementia over 15 years, adjusting for potential confounders and the competing risk of death. By using the AHA CKM staging, we aimed to assess the CKM continuum from early to advanced stages rather than evaluating each CKM component separately. We hypothesized that older adults with higher CKM stages would have an increased risk of incident dementia.

2. Methods

2.1. Study population

Our study was conducted in the prospective cohort of community-dwelling Black and White participants aged 70 to 79 years from the Health, Aging, and Body Composition (Health ABC) study. At baseline (1997–1998), participants were recruited from a random sample of Medicare-eligible adults living within the designated zip codes in Memphis, Tennessee, or Pittsburgh, Pennsylvania. Older adults who reported no difficulties with activities of daily living and mobility, had no life-threatening cancer diagnoses, and planned to live in the study area for at least three years were eligible. Detailed methods of the Health ABC study have been published previously [18,19].

Among the 3075 participants enrolled, we excluded 14 participants for lacking baseline cognitive assessment, 308 with cognitive impairment at baseline, 4 without follow-up for dementia, and 108 without information for CKM components. The remaining 2641 participants comprised our analytic cohort. Cognitive assessment was conducted using the Modified Mini-Mental State Examination (3MS), a test evaluating orientation, attention, praxis, language, and memory, with scores ranging from 0 to 100 [20]. Cognitive impairment was defined as a 3MS score <80 [21]. The study was approved by the institutional review boards of each site, the coordinating center, and the University of California, San Francisco. All participants provided written informed consent.

2.2. Cardiovascular-kidney-metabolic syndrome

The AHA CKM stage was based on constructs of excess/dysfunctional adiposity, metabolic risk factors, subclinical and clinical CVD, and CKD [1]. We collected all information for CKM stage at baseline. Excess/dysfunctional adiposity was defined as having excess weight (body mass index [BMI] ≥25 kg/m^2), abdominal obesity (waist circumference ≥88 cm in women and ≥102 cm in men), or dysfunctional adipose tissue (fasting glucose ≥100 mg/dL). We calculated BMI as weight in kilograms divided by height in meters squared. Metabolic risk factors included hypertriglyceridemia (triglycerides ≥135 mg/dL), hypertension, MetS, or diabetes. Hypertension was defined as systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥80 mm Hg (using the average of 2 seated measurements), or taking antihypertensive medication. MetS was determined based on the presence of ≥3 of the following: 1) abdominal obesity, 2) high-density lipoprotein (HDL) cholesterol <40 mg/dL for men and <50 mg/dL for women, 3) triglycerides ≥150 mg/dL, 4) hypertension, or 5) fasting glucose ≥100 mg/dL. Diabetes was defined as fasting glucose level ≥126 mg/dL or taking anti-diabetic medication. Since imaging of subclinical CVD was not available for all Health ABC participants, we determined the risk equivalent of subclinical CVD as a high 10-year CVD risk (≥20 %) predicted by the AHA Predict Risk of cardiovascular disease EVENTs (PREVENT) base model, where risk factors values outside the validated ranges were imputed as upper and lower limits of these ranges [22]. The presence of clinical CVD, including coronary artery disease, stroke, congestive heart failure, and peripheral artery disease, at baseline was adjudicated based on standard algorithms [23]. The classification of CKD (low, moderate-high, or very high risk) at baseline was designated using the Kidney Disease Improving Global Outcomes (KDIGO) heat map based on combinations of glomerular filtration rate (GFR) and albuminuria (urine albumin-creatinine ratio) [24]. We used the new, race-free, Chronic Kidney Disease Epidemiology Consortium (CKD-EPI) equation to estimate the GFR based on baseline serum creatinine [25].

CKM staging scheme, based on the AHA definition, was included in Table S1 in the Supplement. CKM was classified into 5 stages: Stage 0, with no CKM risk factors; Stage 1, with excess/dysfunctional adiposity; Stage 2, with metabolic risk factors and CKD; Stage 3, with subclinical CVD (or high CVD risk) in CKM; Stage 4, with clinical CVD in CKM.

2.3. Dementia incidence

Participants were assessed for global cognition at Years 1, 3, 5, 8, 10, 11, and 16 using the 3MS. During the study follow-up, participants were interviewed about possible hospitalizations every 6 months, and hospital records were requested in case of a hospitalization report. Participants were asked to bring their medications at each annual visit. Over 15 years of follow-up, dementia incidence was determined if any of the following criteria were met for all participants: 1) a hospitalization recorded with dementia listed as a primary or secondary diagnosis, 2) a documented prescription for dementia medication, or 3) ≥1.5 standard deviations (SD) decline in 3MS score from baseline to last visit compared with the mean change in 3MS of their race-matched peers within the cohort [26–28].

2.4. Covariates

Self-reported demographic information (age, sex, and race) and education were obtained at baseline. Participants' race was based on self-identification as either Black or White [18]. The presence of apolipoprotein E (*APOE*) ε4 allele was determined using standard techniques, and participants were categorized as ε4 carriers and non-carriers [29]. Baseline behavior risk factors were also considered, including self-reported alcohol drinking (≤ vs. >1 drink/day) and physical activity (total kcal expended per week walking and exercising) [30]. The 20-item Center for Epidemiologic Studies Depression Scale (CES-D, score ≥16) was used to assess depression.

2.5. Statistical analysis

Descriptive statistics for baseline characteristics and CKM stage were compared among participants by CKM stage or race using χ^2 and Kruskal-Wallis tests. We used Cox proportional hazards models to assess the association between CKM and the risk of incident dementia and adjusted for baseline factors that differ by CKM stage. Time to incident dementia was calculated as the duration between baseline and the date a participant first met the incident dementia criteria with censoring at death or the last study visit (whichever occurred first). We assessed the proportional hazards assumption using the Goodness-of-Fit test based on Schoenfeld residuals and found that it was satisfied for CKM (p = 0.61) and all other covariates, except for age, 3MS, and study site, which were modeled as time-dependent covariates. Sensitivity analyses were conducted using multiple imputation for missing data and excluding participants with cognitive impairment based on an alternative cutoff (3MS <78) [31]. We also assessed the association using Fine-Gray proportional hazards regression, which accounts for the competing risk of death and provides a more conservative estimate of the association. CKM stage was modeled as a categorical variable (e.g.,

Table 1
Baseline Characteristics of the 2641 Health ABC Participants by Cardiovascular-Kidney-Metabolic Syndrome (CKM) Stage.

N (%) or median (IQR)	Stage 0 (*N* = 72)	Stage 1 (*N* = 102)	Stage 2 (*N* = 699)	Stage 3 (*N* = 639)	Stage 4 (*N* = 1129)	p-value[a]
Age, years	73.5 (71.4–75.2)	72 (70.7–74)	72.4 (70.9–74.3)	75.7 (73.3–77.6)	74 (71.8–76.6)	<0.001
Female	34 (47)	61 (60)	508 (73)	259 (41)	526 (47)	<0.001
Black	16 (22)	29 (28)	238 (34)	250 (39)	423 (37)	0.010
Education ≥ high school	64 (89)	87 (85)	569 (81)	491 (77)	889 (79)	0.036
APOE ε4 carrier	23 (33)	36 (38)	199 (30)	168 (27)	281 (26)	0.07
>1 alcohol drink/day	11 (15)	9 (9)	43 (6)	49 (8)	90 (8)	0.08
Depression	3 (4)	5 (5)	26 (4)	24 (4)	58 (5)	0.55
Pittsburgh Study Site	38 (53)	42 (41)	343 (49)	298 (47)	613 (54)	0.006
Exercise, kcal/week	792 (120–1853)	867 (232–1817)	488 (101–1197)	455 (53–1243)	457 (84–1350)	0.038
Baseline 3MS score	96 (89–98)	95 (91–97)	94 (90–97)	92 (88–96)	93 (89–96)	<0.001

Abbreviations: IQR=interquartile range; 3MS = Modified Mini-Mental State Examination.
[a] Chi-square test for categorical variables and Kruskal-Wallis test for continuous variables. Participants with missing information: education=5 (0.2 %), APOE=120 (4.5 %), alcohol=8 (0.3 %), depression=20 (0.8 %).

Stage 3–4 vs. 0–2) [2]. We also tested for interactions by race, sex, and *APOE ε4*. Statistical analyses were conducted with SAS 9.4 and R 4.3.2.

3. Results

The mean age of the 2641 participants (36 % Black and 53 % female) was 74 ± 2.8 years. At baseline, participants had a full range of CKM stages: 72 (3 %) at Stage 0 (No CKM risk factors), 102 (4 %) at Stage 1 (Excess/dysfunctional adiposity), 699 (26 %) at Stage 2 (Metabolic risk factors and CKD), 639 (24 %) at Stage 3 (Subclinical CVD in CKM), and 1129 (43 %) Stage 4 (CVD in CKM). Compared to participants with CKM Stages 0–2, those with advanced CKM stages (3–4) were older, more likely to be male and Black older adults, and had lower education and 3MS scores (Table 1). The CKM risk factor profile distribution was also compared by CKM stage in Table S2.

Compared with White participants, Black participants were more likely to have excess/dysfunctional adiposity, metabolic risk factors including elevated blood pressure and diabetes, subclinical CVD, moderate to very high-risk CKD, and CVDs such as stroke and peripheral artery disease; they were less likely to have hypertriglyceridemia and coronary heart disease (Table 2). Black participants were more likely to have advanced CKM stages (3–4, 70 %) than White participants (65 %).

Over up to 15 years of follow-up (mean follow-up time = 9.1 ± 4.1 years), 520 (19.7 %) participants developed incident dementia, and 481 (18.2 %) participants died. Kaplan-Meier curves of dementia-free survival indicate that participants with advanced CKM Stage (3–4) had a higher risk of developing dementia compared to those with CKM Stage 0–2 (22.5 % vs. 14.1 %, $p < 0.001$, Fig. 1). After adjusting for demographics, education, exercise, study site, and baseline 3MS score, participants with advanced CKM stages (3–4) had a 50 % increase in the risk of incident dementia (HR 1.50, 95 % CI 1.20-1.86) compared to those with CKM Stages 0–2. Sensitivity analyses using multiple imputation for missing data and excluding participants with cognitive impairment based on an alternative cutoff (3MS <78) did not change the result. The association between CKM and dementia risk remained significant after additional adjustment for CVD (HR 1.40, 95 % CI 1.08–1.81), metabolic risk factors (HR 1.47, 95 % CI 1.17–1.84), and CKD (HR 1.46, 95 % CI 1.17–1.82) separately, as well as simultaneously adjusting for all three (HR 1.35, 95 % CI 1.03–1.77). When CKM was modeled as a variable with multiple categories, CKM Stages 3 and 4 were associated with a 39 % (HR 1.39, 95 % CI 1.05-1.83) and 53 % (HR 1.53, 95 % CI 1.20-1.95) increased risk of dementia, respectively, compared to Stage 2 (Table 3).

There was no evidence that the effect of CKM was modified by race ($p = 0.62$), sex ($p = 0.56$), or *APOE ε4* ($p = 0.62$), although the association between advanced CKM stages (3–4) and increased dementia risk appeared stronger in White (HR 1.52, 95 % CI 1.14–2.03) than Black participants (HR 1.46, 95 % CI 1.04–2.04), in males (HR 1.66, 95 % CI 1.11–2.49) than females (HR 1.43, 95 % CI 1.1–1.86), and in *APOE ε4* non-carriers (HR 1.67, 95 % CI 1.22–2.27) than carriers (HR 1.47, 95 % CI 1.06–2.04). In sensitivity analyses, models without the adjustment for baseline 3MS or those accounting for the competing risk of death led to similar results (CKM Stages 3–4 vs. 0–2: HR 1.41, 95 % CI 1.13–1.76).

Table 2
Cardiovascular-Kidney-Metabolic Syndrome (CKM) Risk Factors of 2641 Health ABC Participants by Race.

N (%)	White (*N* = 1685)	Black (*N* = 956)	p-value[a]
Excess/Dysfunctional Adiposity			
BMI ≥25 kg/m^2	1074 (64)	726 (76)	<0.001
Abdominal obesity	1005 (60)	633 (66)	<0.001
Fasting glucose ≥100 mg/dL	523 (31)	381 (40)	<0.001
Metabolic Risk Factors			
Triglyceride ≥135 mg/dL	802 (48)	248 (26)	<0.001
Elevated blood pressure	1267 (75)	824 (86)	<0.001
Diabetes	203 (12)	221 (23)	<0.001
Metabolic syndrome	733 (45)	386 (42)	0.13
Subclinical CVD			
>20 % 10-y CVD risk	790 (47)	523 (55)	<0.001
CVD			
Coronary heart disease	400 (24)	188 (20)	0.016
Congestive heart failure	269 (16)	169 (18)	0.26
Stroke	167 (10)	119 (12)	0.044
Peripheral artery disease	99 (6)	86 (9)	0.003
CKD Classification			
Low risk	1121 (67)	474 (50)	<0.001
Moderate-high risk	530 (31)	427 (45)	
Very high risk	34 (2)	55 (6)	
CKM			
Stage 0	56 (3)	16 (2)	0.010
Stage 1	73 (4)	29 (3)	
Stage 2	461 (27)	238 (25)	
Stage 3	389 (23)	250 (26)	
Stage 4	706 (42)	423 (44)	

Abbreviations: CVD=cardiovascular disease; CKD= chronic kidney disease.
[a] Chi-square tests. Participants with missing information: Metabolic syndrome=69 (2.6 %).

4. Discussion

Our study of a large cohort of cognitively unimpaired older adults investigated the association between CKM stage defined by the new AHA framework and incident dementia over 15 years. We observed a notably high CKM burden among participants in their seventies, with 67 % having advanced-stage CKM (3–4). Advanced CKM stages were associated with an increased risk of dementia, even after accounting for the competing risk of death and potential confounders. The association between advanced CKM and dementia risk was not entirely explained by any single component, whether CVD, metabolic risk factors, or CKD, individually or together. This association was not modified by race, sex, or *APOE ε4*.

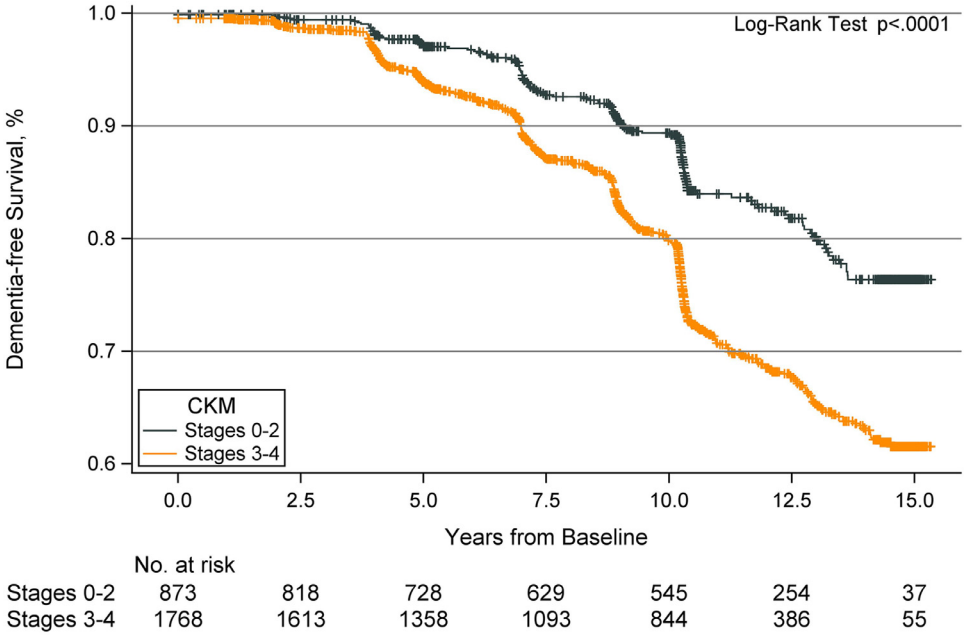

Fig. 1. Kaplan-Meier curves of dementia-free survival of 2641 Health ABC Participants. Participants with advanced CKM Stage (3–4) had a higher risk of dementia compared to those with CKM Stage 0–2 ($p < 0.001$).

Table 3
Association between Cardiovascular-Kidney-Metabolic Syndrome (CKM) stage and Dementia in Cox Proportional Hazards Models.

Model	CKM Stage	Total	Dementia (%)	Hazard Ratio (95 % CI)	p-value
1	0–2	873	123 (14.1)	Reference	
	3–4	1768	397 (22.5)	1.50 (1.20–1.86)	<0.001
2	0–1	174	23 (13.2)	0.96 (0.61–1.52)	0.87
	2	699	100 (14.3)	Reference	
	3	639	145 (22.7)	1.39 (1.05–1.83)	0.020
	4	1129	252 (22.3)	1.53 (1.20–1.95)	0.001

All models were adjusted for age, sex, race, education, exercise, study site, and baseline Modified Mini-Mental State Examination score.

Previous work supporting the contribution of CKM to dementia risk has been limited to isolated CKM constructs, including metabolic risk factors, coronary artery disease, or CKD [6,9–11], and none to date has examined CKM in constellation. Our study addresses a critical gap in the literature by investigating the role of the newly conceptualized CKM health and dementia risk. Applying the latest AHA clinical framework, we were able to examine the impact of CKM across its entire spectrum, from no risk factors to advanced disease stages. Our results align with studies on cardiometabolic multimorbidity [12,13], supporting a combined role of CKM in dementia risk. Furthermore, we found the association remained significant after adjusting for metabolic risk factors, CVD, and CKD separately and together, suggesting that advanced CKM stages may drive dementia risk beyond the additivity of its individual components.

The mechanisms underlying the association between CKM health and dementia remain unclear partly because the intricate pathophysiology behind CKM is not fully understood. A greater cardiometabolic multimorbidity burden, including diabetes, stroke, and myocardial infarction, was found to be associated with lower hippocampal volume, total grey matter volume, and higher white matter hyperintensities, suggesting a combined contribution of both cerebrovascular and neurodegenerative processes [32], independent of genetic risk of dementia. Clinical and subclinical CVD may lead to cerebral small vessel disease by contributing to hypoperfusion and altered brain metabolism, microvascular structure, and permeability [33–35]. CKD increases the risk of cerebrovascular disease and may contribute to vascular dementia via complex alterations involving vascular and endothelial dysfunction [36,37]. The bidirectional association between heart and kidney dysfunction, possibly driven by metabolic abnormalities, could also play a critical role [1,38].

This research has important implications amid the strikingly high and increasing prevalence of CKM and dementia in the US [2,3,39,40]. As the risk of CKM progression increases with age, our findings revealed a similar to higher proportion of advanced-stage CKM in this older cohort than others [2,3,41]. Our findings on the association between advanced CKM stages and dementia risk beyond the additivity of individual CKM components underscores the need for a proactive, integrated approach to CKM management that addresses metabolic, cardiovascular, and kidney components simultaneously. Early identification and targeted intervention may help reduce CKM progression to advanced stages and, in turn, modify dementia risk in the aging population. The availability of effective therapies, such as sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide 1 receptor agonists, and renin-angiotensin-aldosterone system inhibitors, have multiple benefits on CKM health by targeting metabolic risk factors, kidney function, and cardiovascular health in confluence [15–17]. While statins have proven benefits in reducing CVD risk, findings on their impact on dementia risk remain mixed [42,43], emphasizing the need for further research to evaluate whether medications targeting CKM may help reduce dementia risk. Integrating CKM screening and treatment into routine clinical care, particularly for high-risk individuals, could be a potential strategy for dementia prevention. Given the association of ad-

vanced CKM stages with dementia risk, disability, and mortality [44], it may be imperative to identify and manage CKM at earlier stages and within younger populations. Substantial opportunities exist to enhance CKM screening by incorporating measures such as albumin-creatinine ratio alongside estimated GFR, especially in individuals with diabetes, hypertension, and MetS, to assess CKM health more thoroughly. More importantly, these efforts may help prevent CKM from advancing to later stages and its associated health risks, including dementia.

In one of the largest cohorts of community-based older adults, our study fills a critical gap in understanding the risk of dementia in relationship with CKM stage. The strengths of our study include the prospective study design and up to 15 years of follow-up for incident dementia. Tapping into a more comprehensive CKM measurement with the recent AHA staging approach, we were able to detect the associations between advanced CKM stages and long-term dementia risk among older adults, independent of the competing risk of death and potential confounders. Our study also has some limitations. Given the observational nature of this study, we established an association between advanced CKM stages and dementia risk but did not determine causality. Compared to a dementia diagnosis using comprehensive clinical evaluation, our definition may be less sensitive and does not account for depressive symptoms or other comorbid conditions, although dementia misclassification should not differ by CKM stage. Although we had adjudicated CVDs, including coronary artery disease, stroke, congestive heart failure, and peripheral artery disease, the Health ABC study did not adjudicate atrial fibrillation, which may introduce the potential for misclassification for CKM stage and bias the observed association towards the null. Thus, future studies with more comprehensive data on CVD and dementia adjudication are needed to confirm our findings. While the new AHA framework allows us to assess the CKM continuum, its superiority over other classification systems has yet to be established. With the small number of participants in CKM Stages 0 ($n = 72$) and 1 ($n = 102$), our study was underpowered to detect risk differences, which should be evaluated in larger studies with younger cohorts. Additionally, the lack of repeated measurements for all CKM components throughout follow-up limited our ability to assess within-person stage changes, highlighting the need for longitudinal studies to evaluate CKM progression and its causal impact on dementia risk. We also lacked data on the etiology of dementia, even though the current understanding of the pathophysiology underlying CKM points to both vascular and neurodegenerative pathways. Finally, unmeasured confounding from sociocultural and structural factors, risk factors earlier in life, and other comorbid conditions may also contribute to the association between CKM and dementia risk. Our findings may not be generalizable to other age or racial/ethnic groups, as our cohort included only geographically limited Black and White older adults.

In conclusion, worse CKM health is associated with a high risk of dementia over 15 years among community-dwelling older adults without cognitive impairment. With the emergence of a high burden of CKM in the population, older adults with advanced-stage CKM may need to be closely followed for long-term cognitive outcomes. Our findings also underscore the importance of maintaining optimal CKM health in cognitive aging, particularly among older adults.

Declaration of generative AI and AI-assisted technologies in the writing process

No generative AI and AI-assisted technologies were used in the writing process of this work.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Xiaqing Jiang: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Amber L. Bahorik:** Writing – review & editing. **Christina S. Dintica:** Writing – review & editing. **Kristine Yaffe:** Writing – review & editing, Supervision, Funding acquisition, Data curation, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100112.

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