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ORIGINAL ARTICLE

Association Between Cardiovascular-Kidney-Metabolic Health and Early Arterial Injury in Young Adults in the United States: The Future of Families–Cardiovascular Health Among Young Adults Study

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BACKGROUND: The American Heart Association recently introduced the novel construct of Cardiovascular-Kidney-Metabolic (CKM) Syndrome, but it is unclear how the CKM staging construct applies to young adults and how it may correlate with cardiovascular health status and carotid artery health.

METHODS: In the FF-CHAYA study (Future of Families–Cardiovascular Health Among Young Adults), we defined CKM stages using the American Heart Association's framework. Cardiovascular health was measured by Life's Essential 8 scores (a composite metric consisting of dietary quality, physical activity, sleep, nicotine exposure, body mass index, blood glycemia, blood lipids, and blood pressure). We examined cross-sectional associations of CKM stages with Life's Essential 8 scores and carotid ultrasonography measures using multivariable regression models adjusted for age, self-identified gender, and self-identified race/ethnicity.

RESULTS: Among 1283 FF-CHAYA participants (mean [SD] age, 22.9 [0.7] years; 54.4% women), 20.7% of participants were classified as Stage 0 CKM (no risk factors), 40.2% as Stage 1 CKM (excess adiposity), 36.2% as Stage 2 CKM (metabolic risk factors), and 2.8% as Stage 3 CKM (subclinical cardiovascular disease or advanced kidney disease). Compared with Stage 0, participants in Stages 1 to 3 had significantly lower Life's Essential 8 scores (β, −7.6 [95% CI, −9.4 to −5.8] for Stage 1, −13.9 [95% CI, −15.7 to −12.0] for Stage 2, −13.2 [95% CI, −17.4 to −9.0] for Stage 3). In addition, Stages 1 to 3 had significantly higher mean-mean and mean-maximum carotid intima-medial thickness and lower gray scale median compared with Stage 0. For example, mean-maximum carotid intima-medial thickness was 0.014 mm higher (95% CI, 0.005–0.020) for Stage 1, 0.020 mm higher (95% CI, 0.017–0.035) for Stage 2, and 0.100 mm higher (95% CI, 0.085–0.128) for Stage 3, compared with Stage 0.

CONCLUSIONS: Among young adults, a more advanced CKM stage was associated with worse cardiovascular health, including greater evidence of early arterial injury. These findings elucidate the need for earlier preventive efforts and population-level interventions to address upstream drivers of CKM health.

Key Words: blood pressure ■ exercise ■ kidney ■ lipid ■ risk factors

Given the increasing prevalence of cardiovascular disease (CVD) risk factors such as obesity, diabetes, and hypertension in recent years, young adults represent a key population for primary prevention.[1] Between 2020 and 2050, the prevalence of these health conditions among US adults aged 20 to 44 years

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WHAT IS KNOWN

- Cardiovascular disease risk factors are increasing in prevalence among young adults, and strategies are needed to identify and intervene early in the life course.
- The American Heart Association's Cardiovascular-Kidney-Metabolic (CKM) Syndrome staging model provides a framework for specific prevention strategies by CKM stage.
- Data are sparse regarding how CKM stages may be applied among younger adults, including its associations with subclinical disease markers.

WHAT THE STUDY ADDS

- In this sample of young adults across large US cities, CKM Syndrome was highly prevalent, and a more advanced CKM stage was associated with greater evidence of early arterial injury.
- These findings identify opportunities for preventive efforts among young adults and underscore the urgency to address the upstream drivers of CKM health earlier in the life course.

Nonstandard Abbreviations and Acronyms

CARDIA	Coronary Artery Risk Development in Young Adults
cIMT	carotid intima-medial thickness
CKM	Cardiovascular-Kidney-Metabolic
CVD	cardiovascular disease
CVH	cardiovascular health
LE8	Life's Essential 8
FF-CHAYA	Future of Families–Cardiovascular Health Among Young Adults
FFCWS	Future of Families and Child Well-Being Study
IMT	intima-medial thickness

is projected to increase significantly (41.7%–60.0% for obesity, 6.1%–15.5% for diabetes, and 30.3%–40.5% for hypertension), with a disproportionate burden among those from minoritized racial and ethnic groups.[2] Obesity in particular impacts large proportions of individuals in early life and is a major driver of downstream disparities in diabetes, chronic kidney disease, and CVD.[2,3] Therefore, transforming current CVD prevention paradigms is critical for mitigating these projected trends, with a need for efforts to begin earlier in the life course, especially during young adulthood, and a focus on upstream drivers of these inequities.

To address the increasing burden of CVD and the interrelatedness of adverse adiposity, metabolic disease, chronic kidney disease, and CVD, the American Heart Association recently introduced the novel construct of Cardiovascular-Kidney-Metabolic (CKM) Syndrome. The CKM staging model provides a framework for specific prevention strategies across CKM stages, with an emphasis on primordial prevention in Stage 0 (representing no CKM risk factors) and increasing intensity of primary prevention across Stages 1 to 3 of CKM Syndrome.[3,4] In particular, Stages 1 and 2 CKM focus on the management of CKM risk factors, while Stage 3 CKM introduces the importance of imaging for earlier detection of subclinical disease. Across all CKM stages, promotion of cardiovascular health (CVH) using the Life's Essential 8 (LE8) score is central to health maintenance and remediation efforts; this focus on health promotion appears particularly useful for younger individuals who may not yet have clinically diagnostic elevations in risk factor levels.[5]

However, at present, data are sparse regarding how the novel CKM construct may be applied among young adults, including how it may intersect with the existing LE8 framework for measuring CVH. Moreover, it is unknown whether CKM stages relate to early markers of carotid arterial injury in young adulthood. Such knowledge could elucidate CKM's prognostic relevance in a primary prevention population. Therefore, we explored the application of the CKM staging model in the FF-CHAYA study (Future of Families–Cardiovascular Health Among Young Adults). We sought to examine the distribution of CKM stages and their correlates with cardiovascular health scores and early arterial injury during young adulthood.

METHODS

Study Sample

FF-CHAYA is an ancillary study of the FFCWS (Future of Families and Child Well-Being Study).[6] FFCWS enrolled ≈5000 mother-baby dyads at the time of birth between 1998 and 2000 in 20 large US cities with oversampling of unmarried mothers, resulting in enriched recruitment of individuals from minoritized racial and ethnic groups and those living below the poverty line. FFCWS has conducted 7 waves of data collection at age 0 (birth) and approximate ages 1, 3, 5, 9, 15, and 22 years of the offspring. The FF-CHAYA substudy consisted of an in-person examination after completion of the year 22 wave of FFCWS in 2021 to 2023, with sample selection and recruitment methods previously described.[6] Of the 1421 participants who completed the FF-CHAYA in-person examination, we excluded 134 participants who were missing data to assess CKM stages, and 3 participants missing additional outcome data for both CVH status and carotid ultrasonography. Finally, we excluded 1 participant with a self-reported history of prevalent CVD given our focus on a primary prevention population. This study was approved by the institutional review board at Princeton University, and all participants provided written informed consent. De-identified data are publicly available through FFCWS for some variables

(https://ffcws.princeton.edu/) or upon reasonable request for all variables from the Coordinating Center.

Study Procedures

During the in-person FF-CHAYA examination, all participants underwent objective assessment of anthropometric measures and blood pressure; phlebotomy for laboratory analysis of blood lipids, hemoglobin A1c, and serum creatinine; and carotid ultrasonography, using standardized protocols that have been previously described.[6] Estimated glomerular filtration rate was calculated using the 2021 chronic kidney disease-EPI creatinine equations.[7] In addition, all participants completed self-administered questionnaires for the assessment of medical history and medications usage, and standardized questionnaires to assess diet (Dietary Screener Questionnaire from the National Health and Nutrition Examination Survey), physical activity (PAQ-K from the National Health and Nutrition Examination Survey), sleep (assessed during wave 22 of the core FFCWS study), and nicotine exposure (tobacco use questionnaire from the CARDIA study [Coronary Artery Risk Development in Young Adults]).[6] Data on childhood social exposures, including parental education levels, parental incarceration, household income and finances at the time of offspring birth, and adverse childhood experiences (ACEs), were collected at the indicated times through interviewer- and self-administered questionnaires during the core FFCWS study.

CKM Health Status

We adapted the staging construct developed by the American Heart Association to assign each FF-CHAYA participant to a CKM stage ranging from 0 to 3, where all CKM stages are mutually exclusive (ie, participants meeting any criteria for a higher stage could not be placed in a lower stage).[3,4] Briefly, Stage 0 CKM represents no CKM risk factors, Stage 1 CKM represents excess or dysfunctional adiposity, Stage 2 CKM represents metabolic or kidney risk factors, and Stage 3 CKM represents subclinical CVD or high-risk equivalents. Detailed methodology for how each CKM stage was defined in the FF-CHAYA cohort is provided in Table S1. Stage 4 CKM was not included in our analysis as participants meeting criteria for clinical CVD were excluded.

Cardiovascular Health Score

CVH was quantified using LE8 scores, with methodology previously described in the FF-CHAYA cohort.[6,8] Briefly, the overall LE8 score ranges from 0 to 100 points, with higher scores reflecting more favorable CVH, and it was calculated as the unweighted average of 8 individual component metric scores: dietary quality, physical activity, sleep, nicotine exposure, body mass index, blood glycemia, blood lipids, and blood pressure. Each individual component metric score also ranges from 0 to 100 points, with higher scores reflecting more favorable metrics. Health behaviors (dietary quality, physical activity, sleep, and nicotine exposure) were assessed using self-reported data collected by questionnaires. Health factors (body mass index, blood glycemia, blood lipids, and blood pressure) were assessed using data from the in-person examination, with medical history and medications usage self-reported. Additional details on scoring of LE8 individual metrics are provided in Table S2. Scores for the LE8 overall score and individual metrics were categorized as low CVH (<50 points), moderate CVH (50–79 points), or high CVH (≥80 points) in accordance with American Heart Association recommendations.[5,9]

Carotid Ultrasonography

Carotid ultrasonography was performed during the FF-CHAYA in-person examination by 1 of 2 highly experienced sonographers from the University of Wisconsin-Madison Atherosclerosis Imaging Research Program core ultrasound center with the Mindray M9 ultrasound system and L12-4s linear array ultrasound transducer (Mahwah, NJ). The Siemens Arterial Health Package software was used to semi-automatically measure bilateral end-diastolic mean and maximum intima-media thicknesses, from the far walls of the distal 1.0 cm common carotid arteries, the carotid artery bifurcation segments, and the proximal 1.0 cm of the internal carotid arteries, in triplicate, each from 2 complementary angles of approach. Mean-mean common carotid intima-medial thickness (IMT; mm) was calculated as the mean of the right and left mean IMT values. Mean-maximum carotid IMT (mm) was calculated as the mean of the maximum IMT measures from all 3 carotid artery segments. Additional details on ultrasonography and standardized carotid artery measurement procedures have been previously described for the FF-CHAYA study.[6] Intra- and interreader reproducibility for all measures were excellent.[6] The measures analyzed for the present study include markers of early arterial injury (mean-mean and mean-maximum carotid IMT [cIMT], gray scale median, entropy, contrast, and angular second moment [crude and log-transformed]) and arterial stiffness (distensibility coefficient, Young Elastic Modulus).

Statistical Analyses

Participants were stratified by CKM stage (0, 1, 2, or 3) to compare young adult CVH characteristics and carotid ultrasonography measurements. We calculated adjusted mean LE8 scores and carotid ultrasonography measurements by CKM stage and then examined the associations of CKM stages with (1) LE8 scores and (2) carotid ultrasonography measurements using multivariable linear regression models adjusted for age, self-identified gender, and self-identified race/ethnicity. Additional sensitivity analyses were conducted examining LE8 scores for health behaviors only that included the diet, physical activity, sleep, and nicotine exposure individual metrics. All analyses were performed using SAS, version 9.4, and $P<0.05$ was considered statistically significant.

RESULTS

Study Sample Characteristics

Baseline characteristics for the 1283 participants included in the final sample are presented in Table 1, overall and stratified by CKM stage. Overall, mean (SD) age was 22.9 (0.7) years and 54.4% were women, with 51.6% identifying as Black, 27.1% as Hispanic, 16.8% as White, and 4.4% as other race and ethnicity groups. In addition, 51.7% of participants experienced parental incarceration, and 76.4% of participants' mothers

Table 1. Baseline Characteristics of FF-CHAYA Participants

CKM stage	Overall (N=1283)	Stage 0 (n=266)	Stage 1 (n=516)	Stage 2 (n=465)	Stage 3 (n=36)
Mean age, y (SD)	22.9 (0.7)	22.8 (0.6)	22.9 (0.6)	22.9 (0.7)	22.8 (0.6)
Male, n (%)	585 (45.6%)	127 (47.7%)	192 (37.2%)	248 (53.3%)	18 (50.0%)
Race, n (%)					
White	216 (16.8%)	56 (21.1%)	69 (13.4%)	84 (18.1%)	7 (19.4%)
Black	662 (51.6%)	129 (48.5%)	282 (54.7%)	228 (49.0%)	23 (63.9%)
Hispanic	348 (27.1%)	64 (24.1%)	146 (28.3%)	132 (28.4%)	6 (16.7%)
Other	57 (4.4%)	17 (6.4%)	19 (3.7%)	21 (4.5%)	0
Childhood social exposures					
Mother's poverty level at birth, n (%)					
<100%	457 (35.6%)	83 (31.2%)	209 (40.5%)	159 (34.2%)	6 (16.7%)
100–299%	523 (40.8%)	99 (37.2%)	208 (40.3%)	192 (41.3%)	24 (66.7%)
300% +	303 (23.6%)	84 (31.6%)	99 (19.2%)	114 (24.5%)	6 (16.7%)
Parental education ≥ college, n (%)	637 (49.6%)	164 (61.7%)	238 (46.1%)	218 (46.9%)	17 (47.2%)
Raised in a 2-parent home, n (%)	751 (58.5%)	165 (62.0%)	282 (54.7%)	285 (61.3%)	19 (52.8%)
Parental incarceration, n (%)	663 (51.7%)	115 (43.2%)	289 (56.0%)	239 (51.4%)	20 (55.6%)
Cumulative ACEs score to year 5	3.7 (1.3)	3.5 (1.2)	3.7 (1.3)	3.7 (1.3)	4.0 (1.1)
Cardiovascular health characteristics					
Mean body mass index, kg/m²	29.0 (8.2)	21.5 (2.1)	30.1 (6.8)	31.8 (9.2)	30.2 (9.2)
Waist circumference, cm	82.6 (23.6)	68.5 (12.4)	84.1 (21.9)	88.5 (26.9)	89.9 (21.5)
Mean systolic blood pressure, mm Hg (SD)	115.9 (12.0)	111.4 (8.9)	111.8 (9.2)	122.6 (12.7)	120.8 (16.0)
Mean diastolic blood pressure, mm Hg (SD)	69.2 (10.4)	63.1 (7.9)	66.3 (7.3)	75.6 (11.0)	72.7 (13.1)
Mean total cholesterol, mg/dL (SD)	165.0 (32.8)	158.6 (28.3)	160.8 (30.6)	171.9 (33.9)	183.1 (53.5)
Mean HDL cholesterol, mg/dL (SD)	51.4 (15.4)	61.6 (13.4)	49.4 (13.9)	47.7 (15.1)	52.8 (20.0)
Mean trig cholesterol, mg/dL (SD)	94.1 (60.9)	67.0 (26.9)	77.1 (28.3)	127.9 (82.4)	99.4 (60.0)
Mean HbA1c, % (SD)	5.3 (0.5)	5.1 (0.3)	5.2 (0.3)	5.4 (0.8)	5.2 (0.4)
Creatinine, mg/dL	0.8 (0.4)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	1.4 (2.4)
eGFR, mL/min per 1.73 m²	116.4 (15.3)	117.7 (11.8)	118.2 (12.5)	113.9 (17.7)	111.5 (29.8)

Baseline demographic, childhood social exposures, and clinical characteristics among FF-CHAYA participants. Values represent mean (SD) or n (%), as appropriate, for the overall sample and stratified by CKM syndrome stages. CKM indicates Cardiovascular-Kidney-Metabolic; and FF-CHAYA, Future of Families–Cardiovascular Health Among Young Adults.

indicated that their income was under 300% of the federal poverty level at the time of offspring birth. With regard to CKM staging, 20.7% of participants were classified as Stage 0, 40.2% as Stage 1 CKM, 36.2% as Stage 2 CKM, and 2.8% as Stage 3 CKM—indicating a significant burden (≈80%) of excess adiposity, metabolic risk factors, and subclinical CVD, respectively, in this cohort of young adults. As expected, there were notable differences in measures of adiposity, blood pressure, and lipids across CKM stages, with less marked variation in glycemia and kidney function in these young adults.

CKM Stages and Life's Essential 8 Scores

The Figure presents the distribution of CVH status (low, moderate, high) by CKM stage (additional data in Table S3). With more advanced CKM stages, the prevalence of high CVH (LE8 score ≥80 points) was lower, and the prevalence of low CVH (LE8 score <50 points) was higher. The majority of participants (>50%) had moderate CVH status (LE8 score 50–79 points) across all stages.

Mean LE8 overall and individual metric scores by CKM stage, adjusted for age, gender, and race/ethnicity, are presented in Table 2. Among all FF-CHAYA participants, mean (95% CI) LE8 CVH score was 69.2 (95% CI, 68.4–69.9). Overall LE8 scores differed significantly by CKM stage, from 77.6 (95% CI, 76.1–79.1) in Stage 0 to 64.4 (95% CI, 60.5–68.4) in Stage 3 CKM (P<0.01). Body mass index, glucose, lipids, and blood pressure scores were significantly different across CKM stages, with higher scores in Stage 0 and lower scores in more advanced CKM stages (P<0.01). Mean health behaviors-only LE8 scores and individual health behavior metrics did not differ significantly across CKM stages; mean dietary quality and physical activity scores were low (<50 points), and mean nicotine exposure and sleep scores were moderate (50–79 points) for all CKM stages.

Compared with those in Stage 0, participants in Stage 1 CKM had, on average, 7.6-point lower LE8 scores

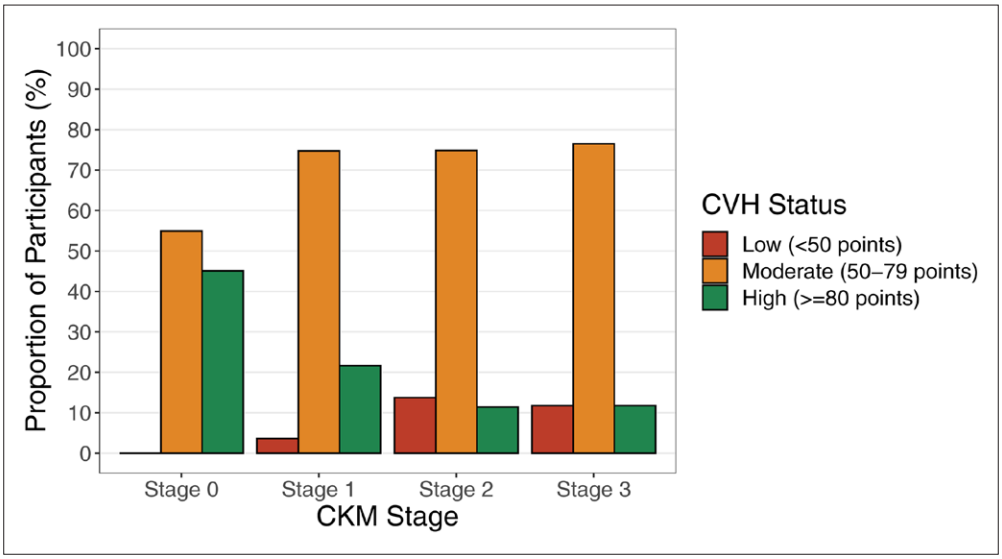

Figure. Cardiovascular health status by cardiovascular-kidney-metabolic (CKM) syndrome stage in the FF-CHAYA (Future of Families–Cardiovascular Health Among Young Adults) cohort.
Joint distribution of cardiovascular health (CVH) scores among FF-CHAYA participants by CKM syndrome stages. CVH was measured using American Heart Association Life's Essential 8, with scores <50 points corresponding to low CVH status, 50 to <80 points corresponding to moderate CVH status, and ≥80 points corresponding to high CVH status.

(95% CI, −9.4 to −5.8]), in Stage 2 CKM had 13.9-point lower scores (95% CI, −15.7 to −12.0), and in Stage 3 CKM had 13.2-point lower scores (95% CI, −17.4 to −9.0).

CKM Stages and Early Carotid Artery Injury

Carotid ultrasonography measurements by CKM stage, adjusted for age, gender, and race/ethnicity, are presented in Table 3. Among FF-CHAYA participants overall, mean-mean cIMT was 0.504 mm (0.501–0.507), mean-maximum cIMT was 0.641 mm (0.637–0.644), and gray scale median was 77.3 (76.5–78.1). With more advanced CKM stage, mean-mean cIMT and mean-maximum cIMT were significantly higher, and gray scale median was significantly lower (P<0.01). Entropy, contrast, distensibility coefficient, and Young Elastic Modulus also differed significantly in statistical analyses, though modestly in absolute terms, with more advanced CKM stage in these young adults.

Table 4 presents the associations of CKM stages with carotid ultrasonography measurements from adjusted models. Compared with Stage 0, mean-maximum cIMT was, on average, 0.014 mm higher (95% CI,

Table 2. Mean Life's Essential 8 Scores by CKM Stage

CKM stage	Adjusted mean (95% CI) LE8 score					
	Overall	Stage 0	Stage 1	Stage 2	Stage 3	*P* value
Overall, points	69.2 (68.4–69.9)	77.6 (76.1–79.1)	70.0 (69.0–71.0)	63.8 (62.6–64.9)	64.4 (60.5–68.4)	<0.001
Health behaviors score, points	56.9 (55.8–58.1)	58.1 (55.6–60.7)	57.0 (55.1–58.8)	56.5 (54.6–58.4)	53.2 (46.3–60.0)	0.527
Individual metric scores, points						
Diet	39.9 (38.2–41.)	42.9 (39.1–46.7)	39.8 (37.1–42.5)	38.5 (35.7–41.4)	36.7 (26.4–46.9)	0.297
Physical activity	42.5 (39.8–45.1)	46.1 (40.3–51.8)	42.0 (37.8–46.1)	41.4 (37.0–45.7)	36.7 (21.2–52.2)	0.506
Nicotine exposure	67.3 (65.1–69.4)	67.0 (62.6–72.1)	66.3 (62.9–69.7)	68.2 (64.6–71.8)	68.1 (55.2–80.9)	0.901
Sleep	77.2 (75.7–78.7)	77.5 (74.1–80.7)	78.3 (75.9–80.7)	76.2 (73.6–78.6)	73.9 (64.8–83.0)	0.571
Body mass index	61.9 (59.9–63.9)	99.6 (95.8–103.)	54.1 (51.4–56.8)	49.5 (46.6–52.3)	56.1 (45.9–66.3)	<0.001
Blood lipids	85.7 (84.5–87.0)	94.4 (91.6–97.1)	87.9 (86.0–89.9)	79.1 (77.0–81.1)	76.9 (69.5–84.2)	<0.001
Blood pressure	83.4 (82.0–84.6)	95.5 (93.2–97.7)	94.1 (92.5–95.7)	65.1 (63.4–66.8)	74.2 (68.0–80.3)	<0.001
Glycemia	94.6 (93.8–95.5)	99.4 (97.6–101.4)	96.3 (94.9–97.5)	90.1 (88.7–91.5)	95.3 (90.4–100.)	<0.001

Values represent mean (95% CI) LE8 scores from multivariable linear regression models adjusted for age, self-identified gender, and self-identified race/ethnicity, with P values representing significance of trends from CKM syndrome Stage 0 to Stage 3. LE8 scores range from 0 to 100 points, with higher values indicating more optimal CVH. The overall LE8 score includes all 8 individual metrics, while the LE8 behaviors score only includes dietary quality, physical activity, sleep health, and nicotine exposure. Participants missing LE8 scores (N=105) were excluded in this analysis. CKM indicates Cardiovascular-Kidney-Metabolic; CVH, cardiovascular health; and LE8, Life's Essential 8.

Table 3. Mean Carotid Measurements by CKM Stage

CKM stage	Adjusted mean (95% CI) carotid measurement					
	Overall	Stage 0	Stage 1	Stage 2	Stage 3	*P* value
Mean-mean cIMT, mm	0.504 (0.501–0.507)	0.486 (0.479–0.493)	0.503 (0.498–0.508)	0.513 (0.508–0.519)	0.528 (0.509–0.547)	<0.001
Mean-maximum cIMT, mm	0.641 (0.637–0.644)	0.622 (0.615–0.630)	0.637 (0.631–0.642)	0.649 (0.643–0.654)	0.72 (0.709–0.749)	<0.001
Gray scale median, units	77.3 (76.5–78.1)	85.1 (83.5–86.8)	76.4 (75.3–77.6)	73.9 (72.6–75.1)	74.8 (70.3–79.3)	<0.001
Entropy	3.73 (3.72–3.74)	3.70 (3.67–3.73)	3.73 (3.71–3.75)	3.74 (3.72–3.77)	3.82 (3.74–3.90)	0.011
Contrast	50.4 (49.7–51.1)	48.3 (46.7–49.8)	50.0 (49.5–51.7)	51.3 (50.1–52.5)	50.8 (46.6–55.0)	0.019
Angular second moment	0.007 (0.007–0.007)	0.007 (0.007–0.008)	0.007 (0.007–0.007)	0.007 (0.007–0.007)	0.006 (0.004–0.007)	0.204
Log-transformed ASM	−5.05 (−5.08 to −5.02)	−5.02 (−5.08 to −4.95)	−5.05 (−5.09 to −5.00)	−5.05 (−5.10 to −5.0)	−5.21 (−5.39 to −5.0)	0.274
Distensibility coefficient	0.007 (0.006–0.007)	0.007 (0.006–0.007)	0.007 (0.007–0.007)	0.006 (0.006–0.006)	0.007 (0.006–0.007)	0.006
Young elastic modulus	929.7 (905.3–954.0)	875.0 (824.9–925.2)	895.0 (858.6–931.4)	1004.8 (966.1–1043.4)	881.4 (741.7–1021.1)	<0.001

Values represent mean (95% CI) carotid ultrasonography measurements from multivariable linear regression models adjusted for age, self-identified gender, and self-identified race/ethnicity, with *P* values representing significance of trends from CKM syndrome Stage 0 to Stage 3. Participants missing cIMT data (N=5) were excluded in this analysis. ASM indicates angular second moment; cIMT, carotid intima-medial thickness; and CKM, Cardiovascular-Kidney-Metabolic.

0.005–0.020) for Stage 1 CKM, 0.020 mm higher (95% CI, 0.017–0.035) for Stage 2 CKM, and 0.100 mm higher (95% CI, 0.085–0.128) for Stage 3 CKM. Stages 1 to 3 CKM were also associated with significantly higher mean-mean cIMT and lower gray scale median values compared with Stage 0.

DISCUSSION

In this sample of young adults from disadvantaged backgrounds across large US cities, we defined the distribution of CKM stages and their associations with CVH status and carotid artery injury, with several important findings. First, a large majority of FF-CHAYA participants met criteria for CKM Syndrome, with only 20% having no CKM risk factors (eg, Stage 0 CKM). Second, LE8 scores were substantially lower with more advanced CKM stages, although suboptimal CVH status (low or moderate LE8 scores) was present in the majority of participants across all CKM stages. Third, more advanced CKM stage was associated with greater evidence of early arterial injury, even at this young age. These findings provide validation of the novel construct of CKM Syndrome in a demographically diverse sample of young adults and have important implications for CVD prevention.

Our study builds on prior work by extending the CKM staging model to younger adults and demonstrating its intersection with the LE8 framework. Consistent with nationally representative data, we observed a high prevalence of CKM Syndrome and suboptimal CVH in the FF-CHAYA cohort, with a substantially greater burden of Stages 1 to 3 CKM in our cohort compared with US adolescents in the National Health and Nutrition Examination Survey.[9–12] This may be partly explained by the design of FF-CHAYA, which over-sampled individuals

Table 4. Associations of CKM stages with carotid ultrasonography measurements

CKM stage	Beta (95% CI) for carotid measurements			
	Stage 0	Stage 1	Stage 2	Stage 3
Mean-mean cIMT, mm	Reference	0.01 (0.009–0.026)	0.027 (0.019–0.036)	0.042 (0.022–0.062)
Mean-maximum cIMT, mm	Reference	0.014 (0.005–0.02)	0.02 (0.017–0.035)	0.10 (0.085–0.128)
Gray scale median, units	Reference	−8.70 (−10.7 to −6.68)	−11.2 (−13.3 to −9.21)	−10.2 (−15.0 to −5.51)
Entropy	Reference	0.033 (−0.002 to 0.06)	0.045 (0.009 to 0.081)	0.121 (0.037 to 0.205)
Contrast	Reference	2.339 (0.448 to 4.231)	3.029 (1.10 to 4.953)	2.55 (−1.92 to 7.032)
Angular second moment	Reference	−0.0004 (−0.001 to 0.0003)	−0.005 (−0.001 to 0.0003)	−0.002 (−0.003 to −0.0003)
Log-transformed ASM	Reference	−0.02 (−0.11 to 0.054)	−0.03 (−0.11 to 0.048)	−0.19 (−0.38 to 0.002)
Distensibility coefficient	Reference	0.00004 (−0.002 to 0.0004)	−0.0004 (−0.0007 to −0.0001)	−0.0006 (−0.0008 to 0.0007)
Young elastic modulus	Reference	19.98 (−42.0 to 82.02)	129.7 (66.40 to 192.9)	6.357 (−142.1 to 154.7)

Values represent beta coefficient (95% CI) from multivariable linear regression models between carotid ultrasonography measurements and CKM syndrome stages, with CKM Stage 0 as the reference. Models adjusted for age, self-identified gender, and self-identified race/ethnicity. Participants missing cIMT data (N=5) were excluded in this analysis. ASM indicates angular second moment; cIMT, carotid intima-medial thickness; and CKM, Cardiovascular-Kidney-Metabolic.

experiencing greater adversity. Although the associations between CKM stages and LE8 scores that we observed are partly definitional, our findings highlight current gaps in young adulthood to address CVH, as the majority of FF-CHAYA participants in Stage 0 CKM already had moderate LE8 scores, which presents key targets for lifestyle and behavioral modifications. Numerous studies have demonstrated that maintaining optimal CVH status may prevent the development of subclinical and clinical CVD, and even 10-point higher LE8 scores are associated with significantly lower CVD risk.[13–15] While we did not observe differences in LE8 health behavior scores across CKM stages, this may reflect the limited sensitivity of self-reported data for describing these metrics in our study, and the importance of diet, physical activity, smoking cessation, and sleep is well established.[16] Health behaviors are further upstream in the causal pathway for arterial injury and likely require longer than proximal physiological risk factors to manifest associations with subclinical CVD.

Notably, we observed higher levels of early arterial injury (eg, precursors of atherosclerosis development) with more advanced CKM stage. Although the differences in carotid IMT measurements for Stages 1 to 3 CKM Syndrome compared with Stage 0 seem small in magnitude (≈0.01–0.10 mm), prior work has found that even small absolute differences (≤0.10 mm) are associated with significantly higher risk of myocardial infarction and stroke in older adults, associations that may be further magnified in a younger population like the FF-CHAYA cohort.[6,17] In addition, the levels of carotid IMT observed in our study would be considered more advanced relative to the participants' age.[6] Our finding that carotid IMT measurements were worse with more advanced CKM stage, including the presence of plaque (which defined Stage 3 CKM in this cohort), is generally expected given the known associations of CVD risk factors with atherosclerosis development. Additionally, several studies have linked excess adiposity during early life with higher carotid IMT in adulthood, which may be partly mediated by the development of additional risk factors related to blood pressure, lipids, and glucose.[18–20] However, quantification of the magnitude of arterial injury is uncommon among young adults, and the greater burden we observed may represent a trajectory of higher risk moving through the life course, or accelerated cardiovascular aging. These findings demonstrate that CKM stages are associated with early markers of carotid arterial injury as early as young adulthood and further position the construct as a tool for prognostication and prevention across the life course.

These results should be considered in the context of potential limitations. FF-CHAYA is a unique cohort whose participants are broadly representative of the young adult urban population of the United States.[6] Nonetheless, the participants were over-sampled for individuals from disadvantaged backgrounds, which may not be representative of other groups of young adults with different demographic compositions. Given the cross-sectional design and exploratory aims of this study, causal inference is limited, and multiple outcomes were also evaluated simultaneously, which increases the likelihood of spurious findings. However, the CKM stages and LE8 scores are comprised largely of component metrics for which there is strong evidence for their associations with cardiovascular outcomes, which strengthens our findings. Finally, longitudinal data are needed to understand the prospective associations of the CKM stages among young adults, which can additionally inform risk stratification and prevention efforts in this population.

Taken together, these findings underscore the critical need for preventive efforts to begin earlier in the life course, particularly in the prevention of adverse adiposity and downstream risk factors that may contribute to early arterial injury. Importantly, while the CKM construct aligns with the LE8 framework, it does not replace it, and each offers complementary but distinct approaches for CVD prevention across the life course. CKM Syndrome provides a clinical framework for the management of risk factors and conditions that have shared pathophysiology, with the emergence of novel therapeutics that benefit numerous aspects of cardiovascular, renal, and metabolic health (eg, sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide 1 receptor agonists, and nonsteroidal mineralocorticoid receptor antagonists). The LE8 framework provides specific and actionable targets across its 8 individual metrics to support healthy longevity that can be implemented at the individual and population levels for the primordial prevention of CKM Syndrome, and the primary prevention of additional CKM risk factors and subclinical development of atherosclerosis. Although many young adults may not yet have clinically elevated risk factor levels (and are ineligible because of age for quantitative 10-year risk estimation), many still present opportunities for risk factor optimization through lifestyle and behavioral modification. Therefore, CKM and LE8 are complementary tools for the identification of young adults who may benefit from enhanced preventive efforts and clinical management of adverse risk factors that are increasing in prevalence in the United States.

CONCLUSIONS

Among a diverse sample of young adults from large cities across the United States, the majority met criteria for CKM Syndrome, and more advanced CKM stage was associated with worse CVH metrics, including greater evidence of carotid artery injury. Our findings underscore the urgency of earlier prevention and population-level efforts to address the upstream drivers of CKM health.

Future work should evaluate the application of the CKM stages in clinical practice among younger adults to support risk stratification and preventive efforts.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S3

REFERENCES

1. Allen N, Wilkins JT. The urgent need to refocus cardiovascular disease prevention efforts on young adults. *JAMA*. 2023;329:886–887. doi: 10.1001/jama.2023.2308
2. Joynt Maddox KE, Elkind MSV, Aparicio HJ, Commodore-Mensah Y, de Ferranti SD, Dowd WN, Hernandez AF, Khavjou O, Michos ED, Palaniappan L, et al; American Heart Association. Forecasting the burden of cardiovascular disease and stroke in the United States through 2050-prevalence of risk factors and disease: a presidential advisory from the American Heart Association. *Circulation*. 2024;150:e65–e88. doi: 10.1161/CIR.0000000000001256
3. Ndumele CE, Rangaswami J, Chow SL, Neeland IJ, Tuttle KR, Khan SS, Coresh J, Mathew RO, Baker-Smith CM, Carnethon MR, et al; American Heart Association. Cardiovascular-kidney-metabolic health: a presidential advisory from the American Heart Association. *Circulation*. 2023;148:1606–1635. doi: 10.1161/CIR.0000000000001184
4. Ndumele CE, Neeland IJ, Tuttle KR, Chow SL, Mathew RO, Khan SS, Coresh J, Baker-Smith CM, Carnethon MR, Després JP, et al; American Heart Association. A synopsis of the evidence for the science and clinical management of Cardiovascular-Kidney-Metabolic (CKM) syndrome: a scientific statement from the American Heart Association. *Circulation*. 2023;148:1636–1664. doi: 10.1161/CIR.0000000000001186
5. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, Grandner MA, Lavretsky H, Perak AM, Sharma G, et al; American Heart Association. Life's essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. *Circulation*. 2022;146:e18–e43. doi: 10.1161/CIR.0000000000001078
6. Lloyd-Jones DM, Allen NB, Stein J, Ning H, Hansen K, Hou L, Katchur NJ, Korcarz C, Kotenko I, Little S, et al. The Future of Families–Cardiovascular Health Among Young Adults (FF-CHAYA) cohort study: rationale, key questions, study design, and participant characteristics. *J Am Heart Assn*. 2025;14:042030. doi: 10.1161/JAHA.125.042030
7. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, Crews DC, Doria A, Estrella MM, Froissart M, et al; Chronic Kidney Disease Epidemiology Collaboration. New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med*. 2021;385:1737–1749. doi: 10.1056/NEJMoa2102953
8. Lam EL, Gauen AM, Kandula NR, Notterman DA, Goldman N, Lloyd-Jones DM, Allen NB, Shah NS. Early childhood food insecurity and cardiovascular health in young adulthood. *JAMA Cardiol*. 2025;10:762–769. doi: 10.1001/jamacardio.2025.1062
9. Lloyd-Jones DM, Ning H, Labarthe D, Brewer LP, Sharma G, Rosamond W, Foraker RE, Black T, Grandner MA, Allen NB, et al. Status of cardiovascular health in US adults and children using the American Heart Association's new "life's essential 8" metrics: prevalence estimates from the National Health and Nutrition Examination Survey (NHANES), 2013 through 2018. *Circulation*. 2022;146:822–835. doi: 10.1161/CIRCULATIONAHA.122.060911
10. Baker-Smith CM, Gauen AM, Petito LC, Khan SS, Allen NB. Prevalence of cardiovascular-kidney-metabolic stages in US adolescents and relationship to social determinants of health. *J Am Heart Assoc*. 2025;14:e040269. doi: 10.1161/JAHA.124.040269
11. Minhas AMK, Mathew RO, Sperling LS, Nambi V, Virani SS, Navaneethan SD, Shapiro MD, Abramov D. Prevalence of the cardiovascular-kidney-metabolic syndrome in the United States. *J Am Coll Cardiol*. 2024;83:1824–1826. doi: 10.1016/j.jacc.2024.03.368
12. Aggarwal R, Ostrominski JW, Vaduganathan M. Prevalence of cardiovascular-kidney-metabolic syndrome stages in US adults, 2011–2020. *JAMA*. 2024;331:1858–1860. doi: 10.1001/jama.2024.6892
13. Ning H, Perak AM, Siddique J, Wilkins JT, Lloyd-Jones DM, Allen NB. Association between life's essential 8 cardiovascular health metrics with cardiovascular events in the cardiovascular disease lifetime risk pooling project. *Circ Cardiovasc Qual Outcomes*. 2024;17:e010568. doi: 10.1161/CIRCOUTCOMES.123.010568
14. Allen NB, Krefman AE, Labarthe D, Greenland P, Juonala M, Kähönen M, Lehtimäki T, Day RS, Bazzano LA, Van Horn LV, et al. Cardiovascular health trajectories from childhood through middle age and their association with subclinical atherosclerosis. *JAMA Cardiol*. 2020;5:557–566. doi: 10.1001/jamacardio.2020.0140
15. Aguayo L, Cotoc C, Guo JW, Labarthe DR, Allen NB, Marino BS, Davis MM, Uttal S, Lloyd-Jones DM, Perak AM. Cardiovascular health, 2010 to 2020: a systematic review of a decade of research on life's simple 7. *J Am Heart Assoc*. 2025;14:e038566. doi: 10.1161/JAHA.124.038566
16. Kaminsky LA, German C, Imboden M, Ozemek C, Peterman JE, Brubaker PH. The importance of healthy lifestyle behaviors in the prevention of cardiovascular disease. *Prog Cardiovasc Dis*. 2022;70:8–15. doi: 10.1016/j.pcad.2021.12.001
17. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation*. 2007;115:459–467. doi: 10.1161/CIRCULATIONAHA.106.628875
18. Zhang T, Fan B, Li S, Wang X, Kong Y, Bazzano L, He J, Chen W, Yan Y. Long-term adiposity and midlife carotid intima-media thickness are linked partly through intermediate risk factors. *Hypertension*. 2023;80:160–168. doi: 10.1161/HYPERTENSIONAHA.122.20217
19. Koskinen J, Kahonen M, Viikari JS, Taittonen L, Laitinen T, Rönnemaa T, Lehtimäki T, Hutri-Kähönen N, Pietikäinen M, Jokinen E, et al. Conventional cardiovascular risk factors and metabolic syndrome in predicting carotid intima-media thickness progression in young adults: the cardiovascular risk in young Finns study. *Circulation*. 2009;120:229–236. doi: 10.1161/CIRCULATIONAHA.108.845065
20. Li S, Chen W, Srinivasan SR, Bond MG, Tang R, Urbina EM, Berenson GS. Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study. *JAMA*. 2003;290:2271–2276. doi: 10.1001/jama.290.17.2271