Title

Estimated GFR and Subsequent Higher Left Ventricular Mass in Young and Middle-Aged Adults With Normal Kidney Function: The Coronary Artery Risk Development in Young Adults (CARDIA) Study.

Journal

American journal of kidney diseases : the official journal of the National Kidney Foundation, 67(2)

ISSN

0272-6386

Authors

Bansal, Nisha
Lin, Feng
Vittinghoff, Eric
et al.

Publication Date

2016-02-01

DOI

10.1053/j.ajkd.2015.06.024

Peer reviewed

HHS Public Access

Author manuscript

Am J Kidney Dis. Author manuscript; available in PMC 2017 February 01.

Published in final edited form as:

Am J Kidney Dis. 2016 February ; 67(2): 227–234. doi:10.1053/j.ajkd.2015.06.024.

Estimated GFR and Subsequent Higher Left Ventricular Mass in Young and Middle-Aged Adults With Normal Kidney Function: The Coronary Artery Risk Development in Young Adults (CARDIA) Study

Nisha Bansal, MD MAS[1], **Feng Lin, MS**[2], **Eric Vittinghoff, PhD**[2], **Carmen Peralta, MD**[2], **Joao Lima, MD**[3], **Holly Kramer, MD**[4], **Michael Shlipak, MD**[2], and **Kirsten Bibbins-Domingo, MD PhD**[2]

[1] University of Washington, Kidney Research Institute

[2] University of California, San Francisco

[3] Johns Hopkins University

[4] Loyola University

Abstract

Background—Left ventricular hypertrophy (LVH) is common and is associated with cardiovascular events and death among patients with known chronic kidney disease (CKD). However, the link between reduced glomerular filtration rate (GFR) and left ventricular mass index (LVMI) remains poorly explored among young and middle-aged adults with preserved kidney function. In this study, we examined the association of cystatin C-based estimated GFR (eGFRcys) and rapid decline in eGFR with subsequent LVMI.

Study Design—Observational study

Setting & Participants—We included 2,410 participants from the Coronary Artery Risk Development in Young Adults (CARDIA) cohort with eGFRcys >60 ml/min/1.73 m^2 at Year 15 and who had an echocardiogram performed at Year 25.

Corresponding author: Nisha Bansal MD MAS, Assistant Professor, Kidney Research Institute, University of Washington, 908 Jefferson St, 3rd floor, Seattle, WA 98104, nbansal@nephrology.washington.edu, Facsimile: 206-685-9399, Phone: 206-221-8413.

N SECTION:

Because the Editor-in-Chief recused himself from consideration of this article, the Deputy Editor (Daniel E. Weiner, MD, MS) served as Acting Editor-in-Chief. Details of the journal's procedures for potential editor conflicts are given in the Information for Authors & Editorial Policies.

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

Contributions: Research idea and study design: NB, EV, CP, JL, HK, MS, KB-D; data acquisition: FL, EV; data analysis/ interpretation: NB, CP, JL, HK, MS, KB-D, FL, EV; statistical analysis: FL, EV; supervision or mentorship: MS, KB-D. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. NB takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

Predictor—eGFRcys at Year 15 and rapid decline of eGFRcys (defined as >3% per year over 5 years from Years 15 to 20)

Outcome—LVMI measured at Year 25

Measurements—We adjusted for age, sex, race, diabetes, body mass index, LDL and HDL cholesterol, cumulative systolic blood pressure, and albuminuria.

Results—Mean age was 40 ±4 (SD) years, 58% were female and 43% were Black. After 10 years of follow-up, mean LVMI was 39.6 ±13.4 g/$m^{2.7}$. Compared with eGFRcys >90 ml/min/ 1.73 m^2 (n=2228), eGFRcys 60-75 ml/min/1.73 m^2 (n=29) was associated with 5.63 (95% CI, 0.90-10.36) g/$m^{2.7}$ greater LVMI (p=0.02), but there was no association of eGFR 76-90 ml/min/ 1.73 m^2 (n=153) with LVMI after adjustment for confounders. Rapid decline in eGFRcys was associated with higher LVMI compared to participants without a rapid GFR decline (β-coefficient, 1.48; 95% CI, 0.11-2.83; p=0.03) after adjustment for confounders.

Limitations—There were a limited number of participants with eGFR 60-90 ml/min/1.73 m^2.

Conclusions—Among young and middle-aged adults with preserved kidney function, eGFRcys 60-75 ml/min/1.73 m^2 and rapid decline of eGFRcys were significantly associated with subsequently higher LVMI. Further studies are needed to understand the mechanisms that contribute to elevated LVMI in this range of eGFR.

Keywords

kidney function; estimated glomerular filtration rate (eGFR); cystatin C; renal function decline; left ventricular mass index (LVMI); echocardiogram; left ventricular hypertrophy (LVH); subclinical cardiovascular disease risk factor

Chronic kidney disease (CKD) is a known risk factor for cardiovascular disease.[1, 2] The prevalence of left ventricular hypertrophy (LVH) is estimated to be high among patients with CKD, ranging from 20%-75%,[3-7] and is associated with subsequent cardiovascular events and death.[3-6] The high prevalence of LVH in this high-risk population may be related to risk factors such as hypertension, anemia and altered mineral metabolism.[8]

Previous work has shown that the burden of LVH increases across stages of CKD.[7] Whether left ventricular abnormalities are initiated much earlier in the spectrum of CKD, even prior to development of estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2, is not fully understood Examining the association of early reduced kidney function with higher left ventricular mass (LVM) is important in elucidating the natural history of cardiovascular disease in this high-risk patient population and may identify important areas of opportunity for intervention. Therefore, we examined the association of glomerular filtration rate estimated by cystatin C (eGFRcys) and rapid decline in eGFR with of subsequent LVM index (LVMI) in young and middle aged adults with eGFRcys >60 ml/min/1.73m^2.

METHODS

Study Population

The Coronary Artery Risk Development in Young Adults (CARDIA) Study is a multicenter study of the development and determinants of cardiovascular risk factors in young adults ages 18-30 years at recruitment. The study design has been published previously in detail.[9] In brief, black and white participants were recruited in 1985 and 1986 in four U.S. cities (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California); the cohort was designed to be balanced by age, sex, race, and education. Follow-up examinations were completed at Years 2, 5, 7, 10, 15 and 20. Each examination protocol was approved by institutional review boards at each site, and informed consent was obtained at every examination.

For this analysis we only included participants with: (1) cystatin C measurement at examination Year 15 (2) an echocardiogram at examination Year 25 (3) eGFRcys>60 ml/min/1.73 m^2 at Year 15 and (4) those who did not develop end-stage renal disease (defined as need for dialysis or kidney transplant) at either Year 15 or 20 (**Figure 1**). With these inclusion and exclusion criteria, our final analytic sample was 2,410 participants. Participants who were excluded from the analysis were more likely to be male and Black, to have achieved a lower level of education, and more likely to have hypertension, lower eGFR, higher microalbuminuria, higher systolic blood pressure (BP), lower HDL cholesterol and higher BMI (**Table S1,** available as online supplementary material).

Cystatin C Estimates of GFR

Cystatin C is a kidney filtration biomarker which has been shown to perform well in estimating kidney function in persons at higher ranges of glomerular filtration rate (eGFR) [10-13] and may detect changes in kidney function earlier than creatinine.[14] Therefore, for this analysis of healthy young and middle aged adults with preserved kidney function, we chose to use eGFRcys as our primary measure of kidney function consistent with prior CARDIA analyses.[15-17]

Cystatin C was measured for all CARDIA participants with stored frozen sera from Years 15 and 20 by nephelometer using the N Latex cystatin C kit (Dade Behring, now Siemens). The coefficient of variation was 4.0%. Given the recent advances in standardizing cystatin C assays,[18] we randomly selected 93 samples from participants across all study years with a wide range of eGFR and re-measured the original samples using the Gentian assay. The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) working group for serum cystatin C standardization and the Institute for Reference Materials and Measurements has produced a certified reference material (ERM-DA471/IFCC)[19, 20] which was used to validate the accuracy of the Gentian assay. This recalibration yielded a mean correction factor of 12% from the original assays that was then applied to all cystatin c measurements in the cohort. Kidney function was then determined by cystatin C derived eGFR (eGFRcys) using the 2012 CKD-EPI equation.[13]

For this analysis, we considered the following predictors: (1) baseline eGFRcys at Year 15 and; (2) change in eGFRcys, determined using two eGFR measurements at Year 15 and

Year 20 examinations. Year 20 cystatin C measurements were not available in 48 participants, leaving 2,362 participants for the rapid decline analysis. Rapid decline was defined as >3% per year, which was calculated from annualizing the change in eGFR from Years 15 to 20, which has been used in previous work.[21-23]

Left Ventricular Mass Index

The CARDIA participants at the year 25 examination underwent 2-dimensinoally guided M-mode echocardiography in a parasternal window and 2-dimensional (2D) 4-chamber apical views following American Society of Echocardiography recommendations.[24-26] All studies were recorded in digital format using an Artida cardiac ultrasound scanner (Toshiba Medical Systems, Tokyo, Japan) and interpreted by readers at the Johns Hopkins University Echocardiography Reading Center in Baltimore, Maryland who were blinded. Measurements were made by experienced analysts from digitized images using a standard software off-line image analysis system (Digisonics, Inc., Houston, Texas). The LVMI was acquired after dividing LVM by height raised to the power of 2.7.[27]

Covariates

Covariates were obtained from the Year 15 examination, the baseline for this analysis. A common protocol and quality control procedures were used at all examinations. Participants were asked to fast for 12 hours and to avoid smoking and heavy physical activity for 2 hours before their examination.[28] Age, sex, race, education level and smoking habits were ascertained through questionnaires.

Other covariates included plasma high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, diabetes status (defined as elevated fasting glucose or use of diabetic medications), and body mass index (BMI). The HDL cholesterol was determined using an enzymatic assay by Northwest Lipids Research Laboratory (Seattle, Washington) at all time periods; reanalysis at each examination of stored samples from the previous examination indicated that measurements over the course of time were comparable.[28] The LDL cholesterol was derived by the Friedewald equation.[29] Serum glucose was measured using hexokinase coupled to glucose-6-phosphate dehydrogenase by Linco Research (St. Louis, Missouri). Body weight was measured with light clothing to the nearest 0.2 kilogram, body height without shoes was measured to the nearest 0.5 cm, and BMI was calculated from these measurements (kg/m^2).

As used in prior CARDIA studies, we computed overall BP trajectories and named this variable “cumulative exposure of systolic BP.”[30] Three seated BP measurements were obtained with a random-zero sphygmomanometer; the mean of the second and third readings were used. Mixed models were used to estimate a BP trajectory for each participant to year 15, corresponding to the time of the first eGFR measurement.[30] We assumed that the trajectory for each participant had a constant slope within each decade of life (age 20-30, 30-40 and 40-50 years). Using these individual BP trajectories, we calculated an integrated measurement of years of exposure to BP elevation to the first cystatin C for each participant (mm Hg-years) by calculating the area under the trajectory for each participant.[30] Urine albumin-creatinine ratios were measured as a single, untimed (spot) urine sample was

collected at Years 15 and 20 examinations;[31] Urine albumin concentrations were measured using a nephelometric procedure with a specific anti-albumin monoclonal antibody, and creatinine was assessed using the Jaffé method.[31] All urine albumin-creatinine ratios were standardized to sex and race and expressed in mg/g creatinine.[32] Albuminuria was defined as urine albumin-creatinine ratio ≥30 mg/g.

Statistical Methods

The year 15 examination was considered baseline for this analysis. We first examined the characteristics of the study participants by eGFR category (60-75, 76-90 and >90 ml/min/1.73 m^2). These categories of eGFRcys were chosen based on previous literature that has suggested differential prognosis for outcomes in each of these categories.[33]

We examined the association of year 15 eGFRcys with year 25 LVMI using linear regression in a series of nested models: first adjusting for age, sex, race and then adjusting for other cardiovascular risk factors (smoking, diabetes mellitus, HDL cholesterol, LDL cholesterol, cumulative systolic BP until year 15, BMI and albuminuria at either year 15 or 20). The eGFR was modeled in categories as well as a continuous variable (per 10 ml/min/1.73 m^2 decrease). We also examined the functional form of the association of year 15 eGFRcys with LVMI using a cubic spline. In secondary analyses, we tested for interaction by urine albuminuria as well as race. We performed stratified analyses by race based on a priori hypotheses.

To further understand the association between year 15 eGFRcys and year 25 LVMI, we adjusted for interim cumulative systolic BP as a possible mediator in the analysis. Interim systolic BP was determined by the area under the curve for systolic BP from Year 15 (the baseline eGFRcys measurement) and Year 25 (the time of the LVMI measurement). The rationale for this mediation analysis was that lower year 15 eGFRcys at may be associated with subsequent increased in systolic BP, which may be in the causal pathway linking lower eGFRcys and LVMI. In sensitivity analyses, we repeated our analyses using creatinine-based estimates to calculate eGFR by the combined creatinine-cystatin C equation.[13]

We then examined the association of rapid decline of eGFRcys with year 25 LVMI in multivariable linear regression models. Rapid decline was determined using eGFR measures at Year 15 and Year 20 examinations which were then annualized. Rapid decline was defined as >3% per year.[21-23] We also examined change in eGFRcys as a continuous variable: per 1% decline per year and as a cubic spline analysis. In addition to the aforementioned covariates, we performed several mediation analyses adjusting for: (1) Year 15 eGFRcys; (2) Year 20 eGFRcys; and (3) interim systolic BP between Years 15 and 20.

All analyses were implemented using Stata Version 12 (StataCorp LP, College Station, Texas).

RESULTS

Characteristics of Study Population

Among the 2,410 adults in our population, the mean age was 40 ±4 years, 58% were female and 43% were Black (**Table 1**). Participants with lower eGFRcys at baseline were older, more likely to smoke and have a history of hypertension, and had a higher systolic BP and higher BMI at baseline (**Table 1**).

Association of Year-15 eGFRcys With Year-25 LVMI

After 10 years of follow-up, mean LVMI was 39.6 ±13.4 g/m$^{2.7}$. The LVMI was higher among participants with lower eGFRcys at baseline (**Table 2**). When eGFRcys was examined as a continuous variable, every 10-ml/min/1.73 m^2 decrease in eGFR was associated with 0.85-g/m$^{2.7}$ increase in LVMI in unadjusted models (**Table 2**). With adjustment for possible confounders, this association was attenuated. The functional form of the adjusted association of eGFRcys with LVMI was linear (p-value for non-linearity=0.4) (**Figure 2**)

Participants with eGFR 60-75 (n=29) and 76-90 ml/min/1.73 m^2 (n=153) had 10.12-g/m$^{2.7}$ and 3.48-g/m$^{2.7}$ higher LVMI, respectively, 10 years later (**Table 2**). With adjustment for demographics and cardiovascular risk factors, the association of eGFRcys 76-90 ml/min/1.73 m^2 with higher LVMI was no longer statistically significant. However, eGFRcys 60-75 ml/min/1.73 m^2 was significantly associated with 5.63 g/m$^{2.7}$ higher LVMI 10 years later after multivariable adjustment, including adjustment for albuminuria (**Table 2**). . Interaction by urine albuminuria was not statistically significant (>0.05).

We tested for interaction by race (Black and White), for which there appeared to be a trend, but was not statistically significant (p=0.1). In stratified analyses, among participants with eGFRcys 60-75 (vs. eGFR>90 ml/min/1.73 m^2 for each racial subgroup), LVMI was 10.7-g/m$^{2.7}$ higher in Black participants and 2.5-g/m$^{2.7}$ higher in White participants.

We adjusted for cumulative, interim 10-year systolic BP exposure in multivariable models to test whether systolic BP is a mediator in this association. Adjustment for this potential mediator did not change the association between eGFRcys 60-75 ml/min/1.73 m^2 and higher left ventricular mass 10 years later (**Table 2**).

We repeated our analyses using the combined creatinine-cystatin C eGFR equation (**Table S2**). The association of lower eGFR with LVMI was not as robust when this alternative eGFR equation was used.

Association of eGFR Change From Years 15 to 20 With Year-25 LVMI

Every 1% decline in eGFRcys over 5 years was associated with a 0.40-g/m$^{2.7}$ increase in LVMI at Year 25 (**Table 3**). With adjustment for possible confounders, this association was attenuated and no longer statistically significant. When we examined the functional form of the adjusted association of eGFRcys change with LVMI, it appeared linear (p-value for non-linearity=0.1) (**Figure 3**).

There were 379 participants who had rapid decline of eGFRcys over 5 years, from Years 15 to 20, defined as >3% decline per year. Those with rapid decline of eGFRcys had significantly higher mean LVMI at Year 25 compared to participants without rapid decline of eGFR (**Table 3**).

We examined the effect of adjustment for several possible mediators: eGFRcys at Year 15, eGFRcys at Year 20 and interim systolic BP between year 15 and 20. Adjusting for either starting or ending eGFRcys measurement did not attenuate this association. There was partial attenuation with adjustment for interim systolic BP (**Table 3**).

DISCUSSION

We examined the association between kidney function and subsequent LVMI ten years later among a cohort of healthy young and middle aged adults with eGFR>60 ml/min/1.73 m^2. We found that eGFRcys of 60-75 ml/min/1.73 m^2 as well as rapid decline in eGFRcys was associated with higher LVM 10 years later, independent of known cardiovascular risk factors. This association was not explained by cumulative interim increase in systolic BP between baseline eGFR measurement and ascertainment of LVMI. These results highlight that even mild decreases in kidney function years earlier may be an important risk factor for subsequent development of higher LVMI and that regular monitoring of kidney function may also help identify young adults at high risk for subclinical cardiovascular disease.

Mild decreases in kidney function in the range of eGFRcys 60-75 ml/min/1.73 m^2 were associated with almost 6-g/$m^{2.7}$ higher LVMI 10 years later. While many studies have reported strong associations of known CKD with LVH,[3-7] few have examined these associations among patients with eGFR >60 ml/min/1.73 m^2. A cross-sectional study of participants from the Chronic Renal Insufficiency Cohort (CRIC) study included 789 participants (mean age, 56 years) with eGFRcys >60 ml/min/1.73 m^2.[7] Amongst this group, the mean LVMI was 46.1 g/$m^{2.7}$ (similar to our results) and 32% met criteria for LVH.[7] In another cross-sectional study of 4,971 participants (mean age, 62 years) in the Multi-Ethnic Study of Atherosclerosis (MESA) study, there was a 1.6 higher odds for LVH among participants with eGFRcys of 60-75 ml/min/1.73 m^2.[34] Our study extends these findings to a significantly younger study population with a mean age of 40 years. In our longitudinal analysis, we demonstrated that early decrements in kidney function are associated with subsequent higher LVMI 10 years later. While the absolute change in LVMI was relatively small, previous work has suggested a linear relationship between LVMI and risk of subsequent heart failure. Our study suggests that even early eGFR measurements may help identify individuals at the highest risk of heart failure in middle-age.

We also noted that rapid decline of eGFR, defined as >3% per year over 5 years, was significantly associated with higher LVMI after adjustment for potential confounders. Decrease in kidney function has been a key predictor of adverse outcomes in other studies as well.[21, 23] Rapid eGFR decline was reported to be a strong predictor of cardiovascular events in elderly patients, with and without CKD at baseline.[23] In these studies as well, baseline eGFR was a stronger predictor relative to change in eGFR. [21, 23] We previously reported that among CARDIA participants, rapid decline of eGFR rather than baseline eGFR

was associated with subsequent detectable coronary artery calcium.[15] This study further supports that serial measurements of eGFR, even in the pre-clinical CKD range, may help to identify healthy persons at risk for subsequent subclinical cardiovascular disease.

The association between mild decreased kidney function and subsequent higher LVMI remained significant even after adjustment for well-recognized cardiovascular risk factors. Furthermore, the association of eGFR with higher LVMI was not mediated by interim increases in systolic BP. In patients with established CKD, new, kidney-specific risk factors add to the development of premature and accelerated cardiovascular disease.[35] Perhaps alterations in mineral metabolism can be initiated with early changes in kidney function, even in ranges of "normal" eGFR.[36] For example, alterations of 1,25-hydroxyvitamin D, parathyroid hormone, and fibroblast growth factor 23 are common with decreased kidney function and are associated with higher LVM.[37-41] Other plausible mechanisms include early changes in volume from impaired sodium handling in the setting of mildly decreased kidney function or alterations in the renin-angiotensin-aldosterone system. Further investigation of novel cardiovascular risk factors among adults with mild decreases in kidney function is warranted.

Although we did not find a significant interaction by race (Black versus White participants) in the association of eGFRcys with subsequent LVMI (perhaps due to limited power in the lowest eGFRcys category), there appeared to be a trend of higher LVMI among Black participants with mild reductions in eGFRcys compared with White participants with similar eGFRcys. Prior studies have noted higher LVM in Blacks versus Whites, even with adjustment for known risk factors such as BMI and diabetes.[42, 43] Furthermore, our previous work in CARDIA has shown that incident heart failure is substantially more common in Black vs. White participants and that kidney disease is one of the strongest risk factors for incident heart failure in this patient population.[44] Our data may provide further evidence that there are important racial differences in the burden of subclinical cardiovascular disease.

Our study augments the body of literature that suggests that cardiovascular disease likely is initiated early in the spectrum of clinical decreases in kidney function. Early recognition of risk factors that contribute to pre-clinical reductions in kidney function may be important to decrease the risk of subsequent cardiovascular disease. Furthermore, earlier recognition of pre-clinical decreases in kidney function may also offer opportunities for targeted cardiovascular interventions prior to the development of clinical cardiovascular disease. Our study suggests that it could be beneficial for physicians to be aware of mild CKD and to monitor regularly to identify rapid decline. Whether modification of risk factors such as BP or novel risk factors such as parathyroid hormone improve LVMI in these individuals should be studied.

Our study had several strengths. We based our analyses on a large, racially diverse, well characterized longitudinal cohort of young adults with more than 10 years' follow-up, including data on BP over the duration of follow-up. We utilized serial measurements of cystatin C, a highly sensitive biomarker for kidney function at higher ranges of eGFR and a strong predictor of adverse outcomes.[45-47] Echocardiograms were quantified through a rigorous process in a central laboratory. Our study had some limitations as well. The number

of study participants with eGFR 60-75 ml/min/1.73 m^2 was small. Many participants were missing echocardiograms and could not be included in the analysis, which might limit the generalizability of our findings. We did not have direct measurements of GFR, although eGFR equations have been shown to perform well[13] and eGFRcys is particularly useful in this range of kidney function.[33] There has been concern about the accuracy of serum creatinine measurements in CARDIA, which limits the use of equations for eGFR that use serum creatinine. In evaluating rapid decline, we assumed a linear annual rate of decline due to the availability of two eGFR measurements, 5 years apart. Due to significant changes in the methodology by which LVMI was assessed, we were not able to examine changes in LVMI although an echocardiogram was performed earlier in CARDIA follow-up. Although we adjusted for many of the major risk factors for higher LVM, there is a possibility of residual confounding. Finally, in this observational study, we are not able to determine causality.

In conclusion, among young and middle aged adults with preserved kidney function, early baseline decreases in kidney function as well as rapid decline in eGFR were significantly associated with a higher LVMI 10 years later. Further investigations to study the mechanisms and risk factors that contribute to the development of elevated LVMI with early decreases in kidney function should be pursued.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKOWLEDGEMENTS

Support: This work was supported by the National Institutes of Health (grants K23DK088865 to Dr Bansal and R01DK078124 and K24DK103992 to Dr Bibbins-Domingo). The CARDIA Study is conducted and supported by the National Heart, Lung and Blood Institute (NHLBI) in collaboration with the University of Alabama at Birmingham (HHSN268201300025C and HHSN268201300026C), Northwestern University (HHSN268201300027C), University of Minnesota (HHSN268201300028C), Kaiser Foundation Research Institute (HHSN268201300029C), and Johns Hopkins University School of Medicine (HHSN268200900041C). The CARDIA Study is also partially supported by the Intramural Research Program of the National Institute on Aging (NIA) and an intra-agency agreement between the NIA and NHLBI (AG0005). The manuscript was reviewed by CARDIA for scientific content.

REFERENCES

1. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004; 351:1296–1305. [PubMed: 15385656]
2. Foley RN, Murray AM, Li S, et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. J Am Soc Nephrol. 2005; 16:489–495. [PubMed: 15590763]
3. Eckardt KU, Scherhag A, Macdougall IC, et al. Left ventricular geometry predicts cardiovascular outcomes associated with anemia correction in CKD. J Am Soc Nephrol. 2009; 20:2651–2660. [PubMed: 19850955]
4. Levin A, Thompson CR, Ethier J, et al. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. Am J Kidney Dis. 1999; 34:125–134. [PubMed: 10401026]
5. Paoletti E, Bellino D, Cassottana P, Rolla D, Cannella G. Left ventricular hypertrophy in nondiabetic predialysis CKD. Am J Kidney Dis. 2005; 46:320–327. [PubMed: 16112052]

6. Levin A, Singer J, Thompson CR, Ross H, Lewis M. Prevalent left ventricular hypertrophy in the predialysis population: identifying opportunities for intervention. Am J Kidney Dis. 1996; 27:347–354. [PubMed: 8604703]
7. Park M, Hsu CY, Li Y, et al. Associations between kidney function and subclinical cardiac abnormalities in CKD. J Am Soc Nephrol. 2012; 23:1725–1734. [PubMed: 22935481]
8. Faul C, Amaral AP, Oskouei B, et al. FGF23 induces left ventricular hypertrophy. J Clin Invest. 2011; 121:4393–4408. [PubMed: 21985788]
9. Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. J Clin Epidemiol. 1988; 41:1105–1116. [PubMed: 3204420]
10. Hojs R, Bevc S, Ekart R, Gorenjak M, Puklavec L. Serum cystatin C as an endogenous marker of renal function in patients with mild to moderate impairment of kidney function. Nephrol Dial Transplant. 2006; 21:1855–1862. [PubMed: 16524933]
11. Shlipak MG, Katz R, Sarnak MJ, et al. Cystatin C and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease. Ann Intern Med. 2006; 145:237–246. [PubMed: 16908914]
12. White C, Akbari A, Hussain N, et al. Estimating glomerular filtration rate in kidney transplantation: a comparison between serum creatinine and cystatin C-based methods. J Am Soc Nephrol. 2005; 16:3763–3770. [PubMed: 16236805]
13. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012; 367:20–29. [PubMed: 22762315]
14. Herget-Rosenthal S, Pietruck F, Volbracht L, Philipp T, Kribben A. Serum cystatin C--a superior marker of rapidly reduced glomerular filtration after uninephrectomy in kidney donors compared to creatinine. Clin Nephrol. 2005; 64:41–46. [PubMed: 16047644]
15. Bansal N, Vittinghoff E, Peralta CA, et al. Estimated Kidney Function Based on Serum Cystatin C and Risk of Subsequent Coronary Artery Calcium in Young and Middle-aged Adults With Preserved Kidney Function: Results From the CARDIA Study. Am J Epidemiol. 2013; 178:410–417. [PubMed: 23813702]
16. Peralta CA, Vittinghoff E, Bansal N, et al. Trajectories of kidney function decline in young black and white adults with preserved GFR: results from the Coronary Artery Risk Development in Young Adults (CARDIA) study. Am J Kidney Dis. 2013; 62:261–266. [PubMed: 23473985]
17. Grubbs V, Lin F, Vittinghoff E, et al. Body Mass Index and Early Kidney Function Decline in Young Adults: A Longitudinal Analysis of the CARDIA (Coronary Artery Risk Development in Young Adults) Study. Am J Kidney Dis. 2014; 63:590–597. [PubMed: 24295611]
18. Inker LA, Eckfeldt J, Levey AS, et al. Expressing the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) cystatin C equations for estimating GFR with standardized serum cystatin C values. Am J Kidney Dis. 2011; 58:682–684. [PubMed: 21855190]
19. Grubb A, Blirup-Jensen S, Lindstrom V, et al. First certified reference material for cystatin C in human serum ERM-DA471/IFCC. Clin Chem Lab Med. 2010; 48:1619–1621. [PubMed: 21034257]
20. Blirup-Jensen S, Grubb A, Lindstrom V, Schmidt C, Althaus H. Standardization of Cystatin C: development of primary and secondary reference preparations. Scandinavian journal of clinical and laboratory investigation. Supplementum. 2008; 241:67–70. [PubMed: 18569968]
21. Rifkin DE, Shlipak MG, Katz R, et al. Rapid kidney function decline and mortality risk in older adults. Arch Intern Med. 2008; 168:2212–2218. [PubMed: 19001197]
22. Shlipak MG, Katz R, Kestenbaum B, Fried LF, Siscovick D, Sarnak MJ. Clinical and subclinical cardiovascular disease and kidney function decline in the elderly. Atherosclerosis. 2009; 204:298–303. [PubMed: 18848325]
23. Shlipak MG, Katz R, Kestenbaum B, et al. Rapid decline of kidney function increases cardiovascular risk in the elderly. J Am Soc Nephrol. 2009; 20:2625–2630. [PubMed: 19892934]
24. Gardin JM, Wagenknecht LE, Anton-Culver H, et al. Relationship of cardiovascular risk factors to echocardiographic left ventricular mass in healthy young black and white adult men and women. The CARDIA study. Coronary Artery Risk Development in Young Adults. Circulation. 1995; 92:380–387. [PubMed: 7634452]

25. Kishi S, Armstrong AC, Gidding SS, et al. Relation of left ventricular mass at age 23 to 35 years to global left ventricular systolic function 20 years later (from the Coronary Artery Risk Development in Young Adults study). Am J Cardiol. 2014; 113:377–383. [PubMed: 24176073]
26. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol. 1986; 57:450–458. [PubMed: 2936235]
27. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005; 18:1440–1463. [PubMed: 16376782]
28. Loria CM, Liu K, Lewis CE, et al. Early adult risk factor levels and subsequent coronary artery calcification: the CARDIA Study. J Am Coll Cardiol. 2007; 49:2013–2020. [PubMed: 17512357]
29. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972; 18:499–502. [PubMed: 4337382]
30. Pletcher MJ, Bibbins-Domingo K, Lewis CE, et al. Prehypertension during young adulthood and coronary calcium later in life. Ann Intern Med. 2008; 149:91–99. [PubMed: 18626048]
31. Murtaugh MA, Jacobs DR Jr. Yu X, Gross MD, Steffes M. Correlates of urinary albumin excretion in young adult blacks and whites: the Coronary Artery Risk Development in Young Adults Study. Am J Epidemiol. 2003; 158:676–686. [PubMed: 14507604]
32. Jacobs DR Jr. Murtaugh MA, Steffes M, Yu X, Roseman J, Goetz FC. Gender- and race-specific determination of albumin excretion rate using albumin-to-creatinine ratio in single, untimed urine specimens: the Coronary Artery Risk Development in Young Adults Study. Am J Epidemiol. 2002; 155:1114–1119. [PubMed: 12048225]
33. Shlipak MG, Matsushita K, Arnlov J, et al. Cystatin C versus creatinine in determining risk based on kidney function. N Engl J Med. 2013; 369:932–943. [PubMed: 24004120]
34. Moran A, Katz R, Jenny NS, et al. Left ventricular hypertrophy in mild and moderate reduction in kidney function determined using cardiac magnetic resonance imaging and cystatin C: the multi-ethnic study of atherosclerosis (MESA). Am J Kidney Dis. 2008; 52:839–848. [PubMed: 18845370]
35. Sarnak MJ. Cardiovascular complications in chronic kidney disease. Am J Kidney Dis. 2003; 41:11–17. [PubMed: 12776309]
36. Isakova T, Wahl P, Vargas GS, et al. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. Kidney Int. 2011; 79:1370–1378. [PubMed: 21389978]
37. Yamamoto KT, Robinson-Cohen C, de Oliveira MC, et al. Dietary phosphorus is associated with greater left ventricular mass. Kidney Int. 2013; 83:707–714. [PubMed: 23283134]
38. Assalin HB, Rafacho BP, dos Santos PP, et al. Impact of the length of vitamin D deficiency on cardiac remodeling. Circ Heart Fail. 2013; 6:809–816. [PubMed: 23709660]
39. Gutierrez OM, Januzzi JL, Isakova T, et al. Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. Circulation. 2009; 119:2545–2552. [PubMed: 19414634]
40. van Ballegooijen AJ, Visser M, Cotch MF, et al. Serum vitamin D and parathyroid hormone in relation to cardiac structure and function: the ICELAND-MI substudy of AGES-Reykjavik. J Clin Endocrinol Metab. 2013; 98:2544–2552. [PubMed: 23585664]
41. van Ballegooijen AJ, Visser M, Kestenbaum B, et al. Relation of vitamin D and parathyroid hormone to cardiac biomarkers and to left ventricular mass (from the Cardiovascular Health Study). Am J Cardiol. 2013; 111:418–424. [PubMed: 23168286]
42. Glasser SP, Lynch AI, Devereux RB, Hopkins P, Arnett DK. Hemodynamic and echocardiographic profiles in African American compared with White offspring of hypertensive parents: the HyperGEN study. Am J Hypertens. 2014; 27:21–26. [PubMed: 24242823]
43. Natori S, Lai S, Finn JP, et al. Cardiovascular function in multi-ethnic study of atherosclerosis: normal values by age, sex, and ethnicity. AJR. American journal of roentgenology. 2006; 186:S357–365. [PubMed: 16714609]

44. Bibbins-Domingo K, Pletcher MJ, Lin F, et al. Racial differences in incident heart failure among young adults. N Engl J Med. 2009; 360:1179–1190. [PubMed: 19297571]

45. Shlipak MG, Sarnak MJ, Katz R, et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. N Engl J Med. 2005; 352:2049–2060. [PubMed: 15901858]

46. Bibbins-Domingo K, Chertow GM, Fried LF, et al. Renal function and heart failure risk in older black and white individuals: the Health, Aging, and Body Composition Study. Arch Intern Med. 2006; 166:1396–1402. [PubMed: 16832005]

47. Huang SH, Macnab JJ, Sontrop JM, et al. Performance of the creatinine-based and the cystatin C-based glomerular filtration rate (GFR) estimating equations in a heterogenous sample of patients referred for nuclear GFR testing. Transl Res. 2011; 157:357–367. [PubMed: 21575920]

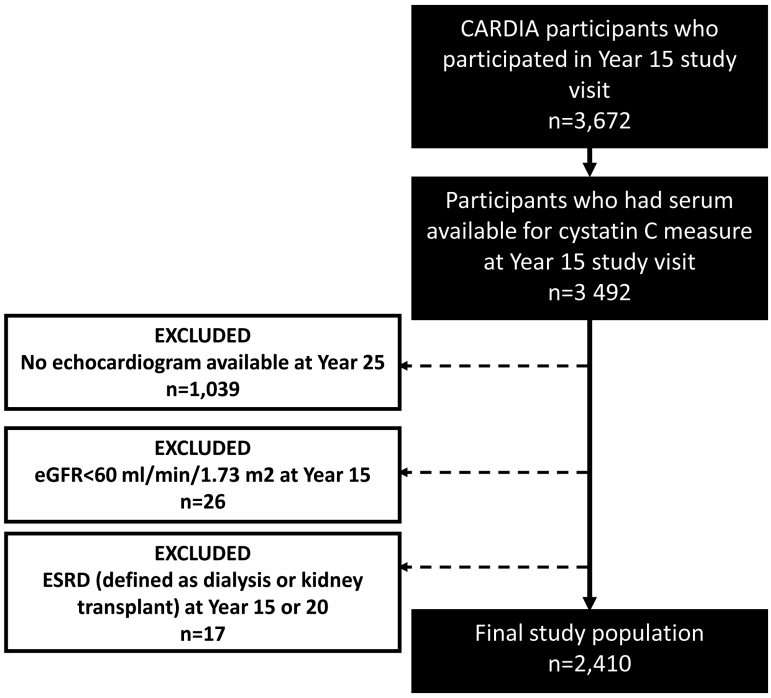

Figure 1. Derivation of study sample

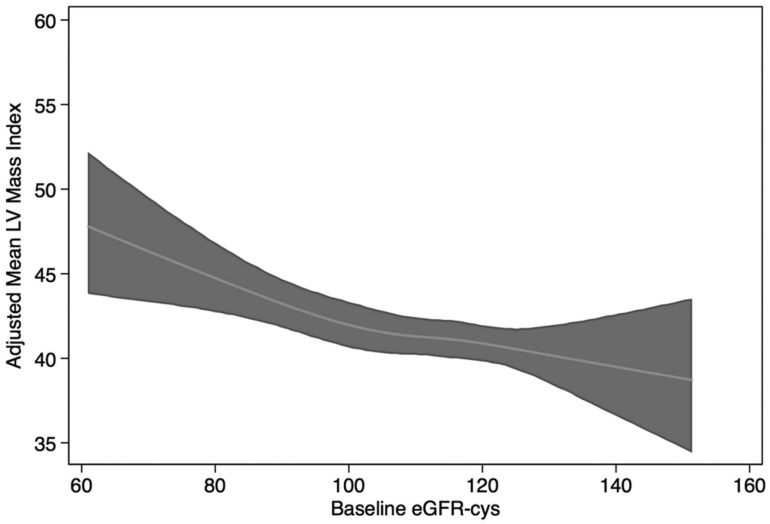

Figure 2. Cubic spline of adjusted* association of eGFRcys at Year 15 with left ventricular mass index. Nonlinearity P = 0.4

***** adjusted for age, sex, race, smoking, diabetes mellitus, LDL cholesterol, HDL cholesterol, systolic blood pressure, BMI, microalbuminuria

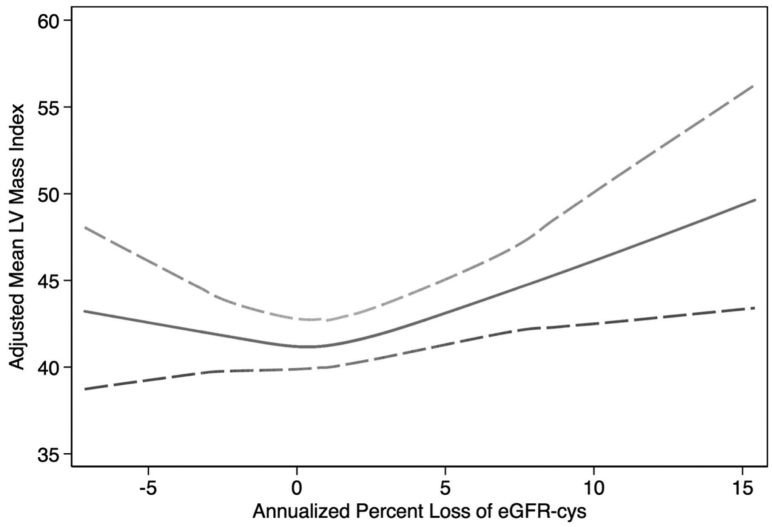

Figure 3. Cubic spline of adjusted* association of eGFRcys change from Year 15 to Year 20 with left ventricular mass index. Nonlinearity P = 0.1

* adjusted for age, sex, race, smoking, diabetes mellitus, LDL and HDL cholesterol, systolic blood pressure, BMI, microalbuminuria, eGFR at Year 15

Table 1

Baseline characteristics of participants by $eGFR_{cys}$ category

Characteristic	Total (N=2410)	eGFRcys			p value
		60-75 (n= 29)	76-90 (n= 153)	>90 (n=2228)	
Age, years	40.2 ± 3.6	41.5 ± 3.7	41.2 ± 3.5	40.2 ± 3.6	<0.001
Female sex	1398 (58.0%)	16 (55%)	79 (51.6%)	1303 (58.5%)	0.2
Black race	1045 (43.4%)	11 (38%)	73 (47.7%)	961 (43.1%)	0.5
<12 years of education	99 (4.1%)	5 (17%)	8 (5.2%)	86 (3.9%)	0.007
Current tobacco use	467 (19.4%)	8 (28%)	47 (30.7%)	412 (18.5%)	<0.001
History of diabetes	216 (9.0%)	4 (14%)	15 (9.8%)	197 (8.8%)	0.5
History of hypertension	674 (28.0%)	16 (55%)	55 (35.9%)	603 (27.1%)	<0.001
eGFRcys, ml/min/1.73 m2	109.4 ± 11.9	69.6 ± 3.9	84.4 ± 3.8	111.7 ± 9.2	<0.001
Urine albuminuria > 30 mg/g*	78 (3%)	6 (21%)	10 (6.9%)	62 (3.0%)	<0.001
Systolic BP, mm Hg	112.0 ± 14.1	117.9 ± 18.5	115.6 ± 17.8	111.6 ± 13.7	<0.001
LDL cholesterol, mg/dL	113.4 ± 31.9	112.0 ± 42.6	116.5 ± 29.5	113.2 ± 31.9	0.5
HDL cholesterol, mg/dL	51.3 ± 14.6	41.9 ± 13.5	43.4 ± 11.8	51.9 ± 14.6	<0.001
BMI, kg/m^2	28.1 ± 6.5	33.5 ± 8.3	32.8 ± 7.8	27.8 ± 6.2	<0.001
eGFRcys change from Year 15 to 20	−6.8 ± 9.4	2.0 ± 11.1	−0.4 ± 11.2	−7.4 ± 9.0	<0.001

Note: N=2,410. eGFRcys values expressed in ml/min/1.73 m2. Values for categorical variables are given as number (percentage); for continuous variables, as mean ± standard deviation.

BMI, body mass index; BP, blood pressure; $eGFR_{cys}$, cystatin C-based estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein

*182 participants were missing urine albuminuria measurements

Table 2

Association of baseline eGFRcys and subsequent LVMI 10 years later

	LVMI	Unadjusted		Model 1		Model 2		Model 3		Model 4 (mediation)	
		Coefficient (95%CI)	p value	Coefficient (95%CI)	p value	Coefficient (95%CI)	p value	Coefficient (95%CI)	p value	Coefficient (95%CI)	p value
Per 10-ml/min/1.73 m2 lower baseline eGFRcys	N/A	0.85 (0.36, 1.33)	<0.001	1.06 (0.58, 1.55)	<0.001	0.25 (−0.22, 0.73)	0.4	0.26 (−0.22, 0.74)	0.3	0.23 (−0.24, 0.71)	0.3
Baseline eGFRcys category											
>90 (n=2228)	39.26 ± 13.36	(reference)		(reference)		(reference)		(reference)		(reference)	
76-90 (n= 153)	42.74 ± 12.96	3.48 (1.29, 5.68)	0.002	2.77 (0.63, 4.91)	0.01	−1.55 (−3.59, 0.52)	0.1	−1.52 (−3.59, 0.55)	0.1	−1.64 (−3.70, 0.42)	0.1
60-75 (n= 29)	49.38 ±16.43	10.12 (5.22, 15.02)	<0.001	10.01 (5.24, 14.79)	<0.001	5.78 (1.09, 10.47)	0.02	5.63 (0.90, 10.36)	0.02	5.52 (0.81, 10.22)	0.02

Note: Values are mean ± standard deviation, or difference in LVMI in $g/m^{2.7}$ (95% CI) at Year 25 relative to reference group. eGFRcys values expressed in ml/min/1.73 m2. Model 1: adjusted for age, sex and race; Model 2: adjusted for age, sex, race, smoking, diabetes mellitus, LDL and HDL cholesterol, systolic BP, BMI; Model 3: adjusted for age, sex, race, smoking, diabetes mellitus, LDL and HDL cholesterol, systolic BP, BMI, microalbuminuria; Model 4: adjusted for age, sex, race, smoking, diabetes mellitus, LDL and HDL cholesterol, systolic BP, BMI, microalbuminuria and interim systolic BP between Years 15 and 25.

BMI, body mass index; BP, blood pressure; CI, confidence interval; $eGFR_{Cys}$, cystatin C-based estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVMI, left ventricular mass index; N/A, not applicable

Table 3

Association of eGFRcys change between Years 15 and 20 and subsequent LVMI at Year 25

	Unadjusted		Model 1		Model 2		Model 3 (mediation)		Model 4 (mediation)		Model 5 (mediation)	
eGFR change	**Coefficient (95%CI)**	**p value**	**Coefficient (95%CI)**	**p value**	**Coefficient (95%CI)**	**P value**	**Coefficient (95%CI)**	**p value**	**Coefficient (95%CI)**	**p value**	**Coefficient (95%CI)**	**p value**
Per 1% decline per y over 5 y	0.40 (0.13, 0.67)	0.004	0.29 (0.03, 0.56)	0.03	0.14 (−0.11, 0.39)	0.3	0.13 (−0.13, 0.38)	0.3	0.19 (−0.11, 0.50)	0.2	0.11 (−0.14, 0.36)	0.4
Rapid decline* (n= 379)	3.26 (1.79, 4.74)	<0.001	2.87 (1.42, 4.31)	<0.001	1.48 (0.12, 2.84)	0.03	1.47 (0.11, 2.83)	0.03	1.95 (0.36, 3.54)	0.02	1.26 (−0.10, 2.62)	0.07
No rapid decline (n=1983)	(reference)		(reference)		(reference)		(reference)		(reference)		(reference)	

Note: Values given as difference in LVMI in $g/m^{2.7}$ (95% CI) at Year 25 relative to reference group. Model 1: adjusted for age, sex and race; Model 2: adjusted for age, sex, race, smoking, diabetes mellitus, LDL and HDL cholesterol, systolic BP, BMI, microalbuminuria; Model 3: adjusted for age, sex, race, smoking, diabetes mellitus, LDL and HDL cholesterol, systolic BP, BMI, microalbuminuria, eGFR at Year 15; Model 4: adjusted for age, sex, race, smoking, diabetes mellitus, LDL and HDL cholesterol, systolic BP, BMI, microalbuminuria, eGFR at Year 20; Model 4: adjusted for age, sex, race, smoking, diabetes mellitus, LDL and HDL cholesterol, systolic BP, BMI, microalbuminuria, and interim systolic BP between Years 15 and Year 20.

BMI, body mass index; BP, blood pressure; CI, confidence interval; $eGFR_{Cys}$, cystatin C-based estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVMI, left ventricular mass index

*Defined as >3% per year over 5 years.