

# Kidney Function Decline in the Elderly: Impact of Lipoprotein-Associated Phospholipase A<sub>2</sub>

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## Key Words

Chronic kidney disease · Elderly · Estimated GFR · Kidney decline · Lipoprotein-associated phospholipase A<sub>2</sub>

## Abstract

**Background:** Whether lipoprotein-associated phospholipase A<sub>2</sub> (Lp-PLA<sub>2</sub>) levels are associated with kidney function decline has not been well studied. **Methods:** We investigated associations of Lp-PLA<sub>2</sub> antigen and activity with kidney function decline and rapid decline over 5.7 years in the Cardiovascular Health Study (n = 4,359). We estimated kidney function by cystatin C (eGFR<sub>cys</sub>) in repeated measures, and defined rapid decline as  $\geq 3$  ml/min/1.73 m<sup>2</sup> per year. We stratified by baseline preserved GFR ( $\geq 60$  ml/min/1.73 m<sup>2</sup>). **Results:** Mean age was  $72 \pm 5$  years. Average eGFR<sub>cys</sub> decline was  $-1.79$  ml/min/1.73 m<sup>2</sup> (SD = 2.60) per year. Among persons with preserved GFR, compared to the lowest quartile of Lp-PLA<sub>2</sub> antigen, eGFR<sub>cys</sub> decline was faster among persons in the second,  $\beta -0.31$  (95% CI  $-0.52, -0.10$ ), third  $-0.19$  ( $-0.41, 0.02$ ) and fourth quartiles  $-0.26$  ( $-0.48, -0.04$ ) after full adjustment. Persons in the highest quartile of Lp-PLA<sub>2</sub> antigen had increased odds of rapid decline 1.34 (1.03, 1.75), com-

pared to the lowest. There was no significant association between levels of Lp-PLA<sub>2</sub> activity and eGFR<sub>cys</sub> decline or rapid decline. Associations were not statistically significant among persons with low eGFR ( $<60$  ml/min/1.73 m<sup>2</sup>) at baseline. **Conclusion:** Higher levels of Lp-PLA<sub>2</sub> antigen but not activity were significantly associated with faster rates of kidney function decline. These findings may suggest a novel vascular pathway for kidney disease progression.

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## Introduction

Chronic kidney disease (CKD) is associated with increased risk for cardiovascular disease (CVD), [1, 2] even at early stages of kidney dysfunction [3]. In addition, clinical and subclinical CVDs are independent predictors of kidney function decline [4]. Proposed mechanisms to explain these associations have included increased inflammation or oxidative stress associated with vascular damage. However, the associations of inflammatory markers and kidney function are modest, and the direction of the association remains unclear [5–7].

Lipoprotein-associated phospholipase A<sub>2</sub> (Lp-PLA<sub>2</sub>) has been independently associated with CVD in several studies [8–11]. Lp-PLA<sub>2</sub> is bound to low-density lipoprotein (LDL) cholesterol in the circulation, it is highly expressed in coronary plaques, and it is thought to have pro-inflammatory properties. Lp-PLA<sub>2</sub> is also thought to promote endothelial dysfunction and increased inflammation within arterial walls [12–15]. Since endothelial dysfunction and increased arterial stiffness [16, 17] have been associated with kidney dysfunction, Lp-PLA<sub>2</sub> may be a plausible pathway associated with kidney dysfunction. The association between Lp-PLA<sub>2</sub> and kidney function decline has not been evaluated.

Understanding whether Lp-PLA<sub>2</sub> is associated with kidney function decline may help elucidate pathways that lead to kidney disease. Therefore, we studied the association of Lp-PLA<sub>2</sub> antigen (mass) and activity with kidney function decline among participants in the Cardiovascular Health Study (CHS). We hypothesized that Lp-PLA<sub>2</sub> would be associated with kidney function decline, independent of serum lipid concentrations.

## Subjects and Methods

### Subjects

We included participants from the CHS, a community-based longitudinal study designed to understand risk factors for development and progression of CVD. Details on design and recruitment have been previously published [18]. Briefly, CHS recruited adults who were 65 years of age or older and living in the community by using Medicare eligibility lists. CHS recruited in four sites: Forsyth County, N.C.; Sacramento County, Calif.; Washington County, Md., and Pittsburgh, Pa. Participants were excluded if they were not expected to remain in the current community for 3 years or longer, were receiving treatment for cancer, or were unable to provide informed consent. The initial 5,201 participants were enrolled from January 1989 to June 1990; an additional 687 black participants (with race self-reported) were recruited and enrolled by June 1993. The institutional review boards at all participating centers approved these studies, and all participants gave informed consent.

For these analyses, we included all participants who had a measure of kidney function at baseline and at least one follow-up measure of kidney function and who had measures of Lp-PLA<sub>2</sub> at baseline (n = 4,362).

### Primary Predictors

Our two primary predictors of interest were Lp-PLA<sub>2</sub> antigen (mass) and activity. In CHS, phlebotomy was performed after a 12-hour fast, and all assays were performed in frozen serum specimens that were stored at –70°C. Plasma Lp-PLA<sub>2</sub> antigen (mass) was measured at the University of Vermont using a commercially available enzyme-linked immunosorbent assay (ELISA; second generation PLAC Test; diaDexus Inc., South San Francisco, Calif., USA). Plas-

ma Lp-PLA<sub>2</sub> activity was measured at GlaxoSmithKline (Research Triangle, N.C., USA) using a high-throughput radiometric assay, as previously reported. The interassay coefficients of variation were 6.3% for antigen and 7.5% for activity [10]. In CHS, the correlation coefficient between antigen (mass) and activity was 0.51.

### Primary Outcomes

Kidney function measures included serum creatinine and cystatin C. Cystatin C was measured by means of a particle-enhanced immunonephelometric assay (N Latex Cystatin C; Dade Behring) with a nephelometer (BNII; Dade Behring). Serum creatinine was measured by a colorimetric method (Ektachem 700; Eastman Kodak). Kidney function was measured at baseline and at year 3 and 7 visits. Overall, 2,539 persons had 3 measures of kidney function and 1,823 had 2 measures. We estimated the glomerular filtration rate (eGFR) with the use of the CKD-EPI creatinine equation (eGFR<sub>creat</sub>) and the CKD-EPI cystatin C equation (eGFR<sub>cys</sub>) without demographic coefficients:  $eGFR_{cys} = 76.7 \times cys^{-1.19}$ . Both formulae were developed from the pooling of several cohorts with GFR measured from iothalamate clearance [19, 20].

The primary outcome of interest was kidney function decline, assessed by cystatin C using repeated measures of eGFR<sub>cys</sub>. A secondary outcome of interest was rapid kidney function decline, defined as eGFR<sub>cys</sub> decline of  $\geq 3$  ml/min/year, as has been defined in previous studies showing the association of this definition with adverse outcomes [21].

For these two outcomes, we stratified a priori by whether persons had preserved GFR or established CKD, defined as eGFR<sub>creat</sub>  $< 60$  ml/min/1.73 m<sup>2</sup>. In particular, we chose to define CKD at baseline based on creatinine because it is still the clinical standard [22]. We chose to study kidney function decline and rapid decline based on eGFR<sub>cys</sub> rather than eGFR<sub>creat</sub> serial measures for several reasons. First, longitudinal measures of eGFR<sub>cys</sub> have been shown to better correlate with changes in kidney function by direct GFR measurement [23]. Second, we have reported that eGFR<sub>cys</sub> is an important predictor of aging success in the elderly [24] and that eGFR<sub>cys</sub> detects kidney function decline in the elderly better than creatinine across the spectrum of GFR [25]. Third, our group has recently shown that only CKD that is confirmed by eGFR<sub>cys</sub>  $< 60$  ml/min/1.73 m<sup>2</sup> is associated with increased risk for death, CVD events, heart failure and end-stage renal disease, compared to CKD detected by creatinine alone [26].

### Covariates

All CHS participants underwent a comprehensive examination at each visit. Age, gender, race, and medication use were ascertained by questionnaire at the baseline visit. Diabetes was defined as a self-report of diabetes, the use of insulin or oral hypoglycemic agents or a fasting glucose  $\geq 126$  mg/dl. Three blood pressure measurements were obtained 5 min apart in the seated position. The mean of the second two measurements was used for analysis. Prevalent CVD was defined as having a history of coronary heart disease, heart failure or stroke. High-density lipoprotein (HDL) cholesterol was measured using the Olympus Demand System (Olympus, Lake Success, N.Y., USA). LDL cholesterol was calculated by the Friedewald formula after excluding participants with triglycerides  $> 400$  mg/dl. Details on assays have been previously published [27]. C-reactive protein (CRP) was measured with an ELISA and interleukin-6 (IL-6) was measured by ELISA (R&D Systems, Minneapolis, Minn., USA).

**Table 1.** Baseline characteristics by Lp-PLA<sub>2</sub> antigen

	Quartile 1 (n = 1,136)	Quartile 2 (n = 1,089)	Quartile 3 (n = 1,086)	Quartile 4 (n = 1,048)
Range of Lp-PLA <sub>2</sub> antigen, ng/ml	87.08–257.30	257.31–326.67	326.68–404.88	404.89–944.25
Age, years	72 ± 5	72 ± 5	72 ± 5	72 ± 5
Males	386 (34)	411 (38)	474 (44)	478 (46)
African-Americans	261 (23)	160 (15)	102 (9)	61 (6)
Body mass index	26.8 ± 5.0	26.7 ± 4.6	26.7 ± 4.3	26.5 ± 4.4
Smoking				
Never	557 (49)	531 (49)	494 (46)	461 (44)
Former	465 (41)	453 (42)	474 (44)	453 (43)
Current	112 (10)	104 (10)	117 (11)	133 (13)
Hypertension	476 (42)	463 (43)	453 (42)	447 (43)
Diabetes	170 (15)	157 (14)	140 (13)	150 (14)
Systolic blood pressure, mm Hg	134 ± 20	136 ± 21	135 ± 21	136 ± 22
Diastolic blood pressure, mm Hg	71 ± 11	71 ± 11	70 ± 11	70 ± 11
Hypertension medications	530 (47)	484 (44)	478 (44)	481 (46)
Insulin, IU/ml	12 (9, 17)	12 (9, 17)	13 (10, 17)	13 (10, 18)
Glucose, mg/dl	109 ± 34	110 ± 37	108 ± 28	109 ± 30
LDL cholesterol, mg/dl	118 ± 33	128 ± 34	134 ± 34	141 ± 36
HDL cholesterol, mg/dl	56 ± 16	56 ± 16	54 ± 15	53 ± 15
Triglycerides, mg/dl	114 (87, 161)	122 (91, 160)	126 (95, 170)	119 (95, 163)
Lipid-lowering medications	89 (8)	67 (6)	52 (5)	34 (3)
CRP, mg/ml	2.32 (1.18, 4.36)	2.44 (1.15, 4.25)	2.37 (1.23, 3.75)	2.46 (1.35, 4.32)
IL-6, pg/ml	1.54 (1.03, 2.29)	1.59 (1.10, 2.43)	1.59 (1.12, 2.34)	1.62 (1.16, 2.52)
Prevalent CHF	34 (3)	33 (3)	23 (2)	41 (4)
Prevalent CHD	173 (15)	179 (16)	205 (19)	208 (20)
eGFR-cysC, ml/min/1.73 m <sup>2</sup>	83 ± 18	80 ± 19	79 ± 18	76 ± 19
eGFR-CKD Epi, ml/min/1.73 m <sup>2</sup>	76 ± 17	73 ± 17	73 ± 16	72 ± 17

Results are presented as mean ± SD, median (IQR) or numbers with percentages in parentheses. CHF = Congestive heart failure; CHD = coronary heart disease; eGFR-CKD Epi = CKD-Epi-based eGFR.

### Statistical Analyses

We compared baseline characteristics by quartiles of Lp-PLA<sub>2</sub> antigen (mass) using  $\chi^2$  or ANOVA, as appropriate.

We first evaluated the association between Lp-PLA<sub>2</sub> antigen and activity separately with kidney function decline. We used linear mixed models with random intercepts and slopes to estimate and compare linear trends in mean eGFR. This approach takes into account the correlation of observations by subject. Lp-PLA<sub>2</sub> antigen and activity were modeled linearly per standard deviation (SD) and categorically as quartiles. We used nested models with serial adjustment to understand the role of potential confounders. Model 1 adjusted for age, gender, and race. Model 2 adjusted for model 1 plus diabetes, systolic blood pressure, use of antihypertensive medications, LDL cholesterol, HDL cholesterol, use of lipid lowering medications, and prevalent CVD. Finally, we were interested in understanding whether inflammation may play a role in explaining possible associations. Therefore, model 3 added CRP and IL-6.

We used multivariate logistic regression to study the association of Lp-PLA<sub>2</sub> antigen and activity with rapid decline. We adjusted in nested models as above.

Earlier literature has suggested different strengths of association between Lp-PLA<sub>2</sub> and cardiovascular outcomes among per-

sons in different strata of lipids and CRP [10, 28], so we also performed stratified analyses by LDL cholesterol (above and below 130 mg/dl), HDL cholesterol (above and below 40 and 50 mg/dl for men and women, respectively) and CRP (above and below 3 mg/l). All analyses were performed using S-Plus (release 8.0; Insightful, Inc., Seattle, Wash., USA) and SPSS (version 16.0.2; SPSS, Inc., Chicago, Ill., USA).

### Results

Among the 4,359 participants in this study, mean age was 72 ( $\pm 5$  SD) years, 13% were black and 60% female. Mean eGFR<sub>cys</sub> at baseline was 80 ml/min/1.73 m<sup>2</sup> (SD = 19) and mean eGFR<sub>creat</sub> was 74 ml/min/1.73 m<sup>2</sup> (SD = 17). The mean for Lp-PLA<sub>2</sub> antigen level was 341 ng/ml (SD = 118) and activity was 39 nmol/min/l (SD = 13).

Persons in the highest quartile of Lp-PLA<sub>2</sub> antigen levels had higher baseline levels of LDL cholesterol, lower levels of HDL cholesterol, and were less likely to be on a

**Table 2.** Association of Lp-PLA<sub>2</sub> with kidney function decline over 5.7 years among elderly persons by baseline CKD

Models	Lp-PLA <sub>2</sub> antigen <sup>a</sup>				Lp-PLA <sub>2</sub> activity <sup>a</sup>			
	per SD = 118	quartile 2	quartile 3	quartile 4	per SD = 113	quartile 2	quartile 3	quartile 4
<i>eGFR<sub>creat</sub> ≥60 ml/min/1.73 m<sup>2</sup></i>								
Subjects	3,370	838	833	765	3,364	880	803	786
Age, sex, race	-0.10 (-0.18, -0.03)	-0.26 (-0.47, -0.06)	-0.20 (-0.41, 0.001)	-0.26 (-0.47, -0.05)	-0.05 (-0.12, 0.03)	0.05 (-0.15, 0.26)	-0.13 (-0.34, 0.08)	-0.01 (-0.23, 0.20)
+ Risk factors <sup>b</sup>	-0.10 (-0.17, -0.02)	-0.28 (-0.49, -0.07)	-0.22 (-0.43, -0.01)	-0.25 (-0.46, -0.03)	-0.04 (-0.12, 0.03)	0.05 (-0.16, 0.26)	-0.14 (-0.35, 0.08)	-0.005 (-0.22, 0.21)
+ CRP and IL-6	-0.10 (-0.18, -0.02)	-0.31 (-0.52, -0.10)	-0.19 (-0.41, 0.02)	-0.26 (-0.48, -0.04)	-0.04 (-0.12, 0.04)	0.09 (-0.12, 0.31)	-0.10 (-0.32, 0.12)	0.0003 (-0.22, 0.22)
<i>eGFR<sub>creat</sub> &lt;60 ml/min/1.73 m<sup>2</sup></i>								
Subjects	989	251	253	283	987	234	249	288
Age, sex, race	-0.01 (-0.31, 0.28)	0.07 (-0.30, 0.44)	-0.21 (-0.57, 0.16)	0.11 (-0.25, 0.47)	-0.06 (-0.18, 0.05)	-0.12 (-0.49, 0.25)	-0.07 (-0.44, 0.29)	-0.19 (-0.55, 0.17)
+ Risk factors <sup>b</sup>	-0.02 (-0.32, 0.27)	0.05 (-0.32, 0.42)	-0.23 (-0.60, 0.14)	0.10 (-0.26, 0.47)	-0.07 (-0.19, 0.05)	-0.12 (-0.49, 0.25)	-0.07 (-0.44, 0.30)	-0.19 (-0.55, 0.17)
+ CRP and IL-6	-0.02 (-0.37, 0.32)	0.07 (-0.32, 0.45)	-0.29 (-0.68, 0.10)	0.10 (-0.28, 0.48)	-0.03 (-0.15, 0.10)	-0.11 (-0.50, 0.29)	-0.01 (-0.41, 0.38)	-0.06 (-0.45, 0.32)

Results represent  $\beta$  (95% CI) ml/min/1.73 m<sup>2</sup> per year, except where otherwise indicated. Baseline CKD defined by CKD-Epi eGFR  $\geq$  or  $<$ 60 ml/min/1.73 m<sup>2</sup>. Quartile 1 is the reference group.

<sup>a</sup> Quartile ranges for Lp-PLA<sub>2</sub> antigen (ng/ml):  $<$ 257.31, 257.31–326.67, 326.68–404.68,  $>$ 404.68; quartile ranges for Lp-PLA<sub>2</sub> activity (nmol/min/ml):  $<$ 30.41, 30.42–37.82, 37.83–46.60,  $>$ 46.60.

<sup>b</sup> Diabetes, systolic blood pressure, antihypertensive medications, LDL and HDL cholesterol, lipid-lowering medications, prevalent coronary heart disease.

lipid-lowering agent. Persons in the highest quartile of Lp-PLA<sub>2</sub> antigen also had lower baseline eGFR by cystatin C and creatinine (table 1).

#### *Lp-PLA<sub>2</sub> and Kidney Function Decline*

The average decline in eGFR<sub>cys</sub> during a median follow up of 5.7 years was  $-1.79$  ml/min/1.73 m<sup>2</sup> (SD = 2.60) per year.

Among persons with eGFR<sub>creat</sub>  $\geq$ 60 ml/min/1.73 m<sup>2</sup>, higher levels of Lp-PLA<sub>2</sub> antigen were significantly associated with faster kidney function decline, and this association was independent of demographics, comorbidities, CRP or IL-6 (table 2). Compared to persons in the lowest quartile of Lp-PLA<sub>2</sub> antigen level, those in quartile 4 had approximately 15% faster rates of kidney function decline. These associations were not present among persons with eGFR<sub>creat</sub>  $<$ 60 ml/min/1.73 m<sup>2</sup> at baseline (table 2).

In contrast to findings with Lp-PLA<sub>2</sub> antigen, Lp-PLA<sub>2</sub> activity level was not significantly associated with kidney function decline (table 2).

#### *Lp-PLA<sub>2</sub> and Rapid Kidney Function Decline*

A total of 1,084 (25%) subjects had a rapid decline in kidney function. Among persons with eGFR<sub>creat</sub>  $\geq$ 60

ml/min/1.73 m<sup>2</sup> at baseline, 855 persons had a rapid decline, and 229 persons in the eGFR<sub>creat</sub>  $<$ 60 ml/min/1.73 m<sup>2</sup> group. Lp-PLA<sub>2</sub> antigen levels were also independently associated with higher odds of rapid kidney function decline among persons with eGFR<sub>creat</sub>  $\geq$ 60 ml/min/1.73 m<sup>2</sup> at baseline. Each SD increase in Lp-PLA<sub>2</sub> antigen was associated with 14% higher odds of rapid decline (table 3). When we categorized Lp-PLA<sub>2</sub> antigen, only the highest quartile was significantly associated with higher odds of rapid decline compared to the lowest quartile (table 3). These associations were not significant among persons with eGFR<sub>creat</sub>  $<$ 60 ml/min/1.73 m<sup>2</sup> at baseline. Lp-PLA<sub>2</sub> activity was not statistically significantly associated with rapid decline (table 3).

#### *Stratified Analyses*

After full adjustment, the association between Lp-PLA<sub>2</sub> antigen and kidney function decline was not significantly different by LDL or HDL level (p value for interaction 0.34 and 0.69, respectively). Moreover, there was no significant effect modification by CRP on the association between Lp-PLA<sub>2</sub> antigen and kidney function decline (p value for interaction 0.79; fig. 1).

**Table 3.** Association of Lp-PLA<sub>2</sub> with rapid kidney function decline among elderly persons by baseline CKD

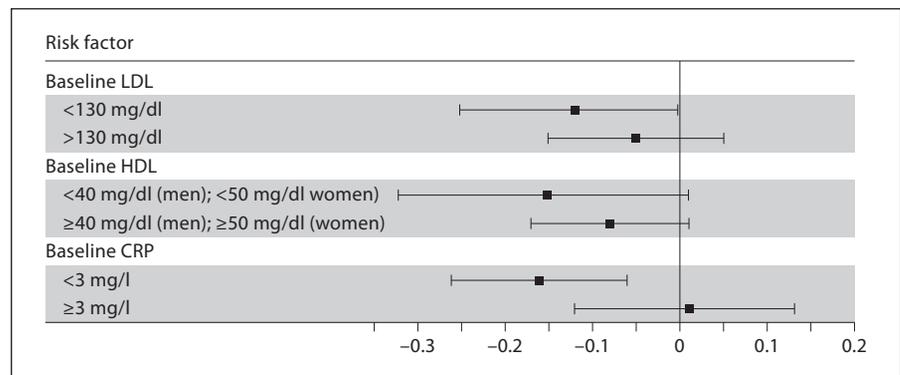
Models	Lp-PLA <sub>2</sub> antigen <sup>a</sup>				Lp-PLA <sub>2</sub> activity <sup>a</sup>			
	per SD = 118	quartile 2	quartile 3	quartile 4	per SD = 13	quartile 2	quartile 3	quartile 4
<i>eGFR ≥60 ml/min/1.73 m<sup>2</sup></i>								
Subjects	3,370	838	833	765	3,364	880	803	786
Age, sex, race, baseline eGFR-cysC	1.14 (1.04, 1.24)	1.23 (0.97, 1.56)	1.04 (0.81, 1.34)	1.37 (1.06, 1.76)	1.08 (0.98, 1.18)	0.96 (0.76, 1.22)	1.00 (0.78, 1.29)	1.17 (0.90, 1.51)
+ Risk factors <sup>b</sup>	1.14 (1.04, 1.26)	1.23 (0.96, 1.56)	1.03 (0.80, 1.33)	1.35 (1.04, 1.76)	1.05 (0.94, 1.17)	0.96 (0.75, 1.23)	0.92 (0.70, 1.20)	1.09 (0.81, 1.46)
+ CRP and IL-6	1.14 (1.04, 1.25)	1.21 (0.95, 1.55)	1.02 (0.79, 1.55)	1.34 (1.03, 1.75)	1.05 (0.95, 1.17)	0.96 (0.75, 1.23)	0.91 (0.69, 1.20)	1.09 (0.82, 1.47)
<i>eGFR &lt;60 ml/min/1.73 m<sup>2</sup></i>								
Subjects	989	251	253	283	987	234	249	288
Age, sex, race, baseline eGFR-cysC	0.73 (0.43, 1.23)	1.06 (0.65, 1.73)	1.56 (0.96, 2.53)	1.03 (0.62, 1.69)	1.15 (0.98, 1.35)	1.13 (0.69, 1.86)	1.03 (0.62, 1.71)	1.36 (0.83, 2.22)
+ Risk factors <sup>b</sup>	0.80 (0.46, 1.40)	0.95 (0.57, 1.58)	1.48 (0.89, 2.44)	0.95 (0.56, 1.61)	1.20 (1.00, 1.44)	1.21 (0.72, 2.02)	1.03 (0.60, 0.79)	1.46 (0.82, 2.60)
+ CRP and IL-6	0.74 (0.42, 1.33)	0.94 (0.56, 1.56)	1.50 (0.91, 2.48)	0.94 (0.55, 1.59)	1.23 (1.02, 1.47)	1.24 (0.74, 2.07)	1.05 (0.61, 1.8)	1.56 (0.87, 2.79)

Figures represent odds ratios (95% CI), except where otherwise indicated. Rapid decline defined as:  $\Delta$ eGFR-cysC >3 ml/min/1.73 m<sup>2</sup> per year. Baseline CKD defined by CKD-Epi eGFR  $\geq$  or <60 ml/min/1.73 m<sup>2</sup>. Quartile 1 is the reference group. eGFR-cysC = Cystatin C-based eGFR.

<sup>a</sup> Quartile ranges for Lp-PLA<sub>2</sub> antigen: <257.31, 257.31–326.67, 326.68–404.68, >404.68; quartile ranges for Lp-PLA<sub>2</sub> activity: <30.41, 30.42–37.82, 37.83–46.60, >46.60.

<sup>b</sup> Diabetes, systolic blood pressure, antihypertensive medications, LDL and HDL cholesterol, lipid-lowering medications, prevalent coronary heart disease.

**Fig. 1.** Association of Lp-PLA<sub>2</sub> antigen with kidney function decline (in ml/min/1.73 m<sup>2</sup> per year) among elderly persons by LDL, HDL and CRP levels at baseline.



## Discussion

In this study, we found that Lp-PLA<sub>2</sub> antigen, not activity, was significantly associated with kidney function decline and rapid kidney function decline among elderly persons without CKD (eGFR  $\geq$ 60 ml/min/1.73 m<sup>2</sup>), independent of lipids, CRP and IL-6. Our findings have important implications for the understanding of potential pathways that may link CVD and kidney disease. Lp-

PLA<sub>2</sub> has emerged as an independent risk factor for heart failure, stroke, coronary heart disease and cardiovascular death [8–10]. Lp-PLA<sub>2</sub> appears to be associated with the development of endothelial dysfunction and inflammation and disruption of the arterial intima by hydrolyzing oxidized phospholipids and oxidating LDL [12–15]. Since several studies have shown that subclinical CVD [4], endothelial dysfunction [29], and reduced arterial elasticity [30] are associated with faster rates of kidney function

decline, it is possible that Lp-PLA<sub>2</sub> is a novel common pathway of vascular injury in CKD and CVD.

Moreover, Lp-PLA<sub>2</sub> may be involved in an important pathway for development of CKD. In particular, our findings may shed light on why previous literature on the association of serum concentration of lipids and inflammatory markers with kidney disease has been inconsistent [31, 32]. Lp-PLA<sub>2</sub> travels bound preferentially to small LDL, and it hydrolyzes phospholipids, thus promoting atherogenic activity of LDL. Studying total LDL cholesterol and kidney disease may not fully capture these associations. In fact, in a study from the Multi-Ethnic Study of Atherosclerosis, levels of small LDL particles, but not conventional LDL levels were associated with early kidney dysfunction [33]. We found that inflammation did not attenuate our findings. Since the direction of the association between inflammation and kidney disease remains unclear [5, 6], future studies on the interplay between Lp-PLA<sub>2</sub>, inflammation, and kidney function decline are warranted.

We are the first to report an independent association between Lp-PLA<sub>2</sub> antigen (mass) and kidney function decline. Strengths of this study include the well-characterized population, repeated measures of kidney function and the prospective design. Moreover, the use of cystatin C as a kidney function marker improves prediction of kidney decline in the elderly. However, we are limited by no direct measure of GFR. The small observed changes in eGFR may have reduced our ability to detect anything less than large associations. Future studies should include persons with large changes in eGFR over time [34].

However, no large, community-based epidemiological studies include iothalamate GFR. Our findings that Lp-PLA<sub>2</sub> antigen but not activity are associated with kidney function decline are in accordance with prior reports from CHS and a report on differing associations between antigen and activity and calcified coronary plaque in a young cohort [10, 35]. These differences in associations between antigen and activity may be due to differences in

assay design or variability. Alternatively, it is possible that the Lp-PLA<sub>2</sub> antigen assay can better capture the complexity of the atherogenic process, particularly in this elderly cohort. Future studies are needed to elucidate these mechanisms. Our findings that the association of Lp-PLA<sub>2</sub> and kidney function decline was not observed among persons with eGFR <60 ml/min/1.73 m<sup>2</sup> should be interpreted with caution, as it is possible that survival bias and regression to the mean may account for these findings. Alternatively, it is possible that certain pathways may have different relative importance in the development versus progression of CKD. We are unable to account for any possible associations with albuminuria, as CHS did not measure albuminuria at baseline.

In summary, we found that Lp-PLA<sub>2</sub> antigen (mass) is independently associated with kidney function decline and rapid kidney function decline among elderly persons with preserved GFR. Future studies should evaluate this novel pathway in other populations. Moreover, more studies are needed to elucidate causal pathways.

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