Serum lipoprotein (a) associates with a higher risk of reduced renal function: a prospective investigation

Liping Xuan\textsuperscript{1,2}, Tiange Wang\textsuperscript{1,2}, Huajie Dai\textsuperscript{1,2}, Bin Wang\textsuperscript{1,2}, Jiali Xiang\textsuperscript{1,2}, Shuangyuan Wang\textsuperscript{1,2}, Hong Lin\textsuperscript{1,2}, Mian Li\textsuperscript{1,2}, Zhiyun Zhao\textsuperscript{1,2}, Jieli Lu\textsuperscript{1,2}, Yuhong Chen\textsuperscript{1,2}, Yu Xu\textsuperscript{1,2}, Weiqing Wang\textsuperscript{1,2}, Min Xu\textsuperscript{1,2*}, Yufang Bi\textsuperscript{1,2*}, Guang Ning\textsuperscript{1,2}

1. Department of Endocrine and Metabolic Diseases, Shanghai Institute of Endocrine and Metabolic Diseases, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

2. Shanghai National Clinical Research Center for Metabolic Diseases, Key Laboratory for Endocrine and Metabolic Diseases of the National Health Commission of the PR China, Shanghai National Center for Translational Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

*To whom correspondence should be addressed: Yufang Bi, MD & PhD, Min Xu, MD & PhD, Department of Endocrine and Metabolic Diseases, Shanghai Institute of Endocrine and Metabolic Diseases, Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine, 197 Ruijin 2nd Road, Shanghai, 200025, China; Telephone: +86-21-64370045, Ext. 663340; Fax: +86-21-64749885; E-mail: byf10784@rjh.com.cn (Y. Bi) or della.xumin@163.com (M. Xu).
Running title: lipoprotein (a) and reduced renal function

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp (a), lipoprotein (a); OR, odds ratio; SBP, systolic blood pressure; TC, total cholesterol; TG, triacylglycerol; T2D, type 2 diabetes.
Abstract

Lipoprotein (a) (Lp [a]) is a well-known risk factor for cardiovascular disease, but analysis on Lp (a) and renal dysfunction is scarce. We aimed to investigate prospectively the association of serum Lp (a) with the risk of reduced renal function, and further investigated whether diabetic or hypertensive status modified such association. 6,257 Chinese adults aged ≥40 years and free of reduced renal function at baseline were included in the study. Reduced renal function was defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m². During a mean follow-up of 4.4 years, 158 participants developed reduced renal function. Each 1-unit increase in log₁₀-Lp (a) (mg/dl) was associated with 1.99-folds (95% confidence interval [CI] 1.15-3.43) increased risk of incident reduced renal function; multivariable-adjusted odds ratio (OR) for the highest tertile of Lp (a) was 1.61 (95% CI 1.03–2.52) compared to the lowest tertile (P for trend=0.03). The stratified analysis showed the association of serum Lp (a) and incident reduced renal function was more prominent in participants with prevalent diabetes (OR 4.04, 95% CI [1.42-11.54]) or hypertension (OR 2.18, 95% CI [1.22-3.89]). A stronger association was observed among group with diabetes and high Lp (a) (>25 mg/dl), indicating a combined effect of diabetes and high Lp (a) on the reduced renal function risk. Elevated Lp (a) level was independently associated with risk of incident reduced renal function, especially in diabetic or hypertensive patients. 

Supplementary keywords: hypertension, lipids, renal dysfunction, type 2 diabetes, epidemiology.
Introduction

Lipoprotein (a) (Lp [a]) is consisted of apolipoprotein (a) (apo [a]) bound covalently to apolipoprotein B-100 of a low-density lipoprotein (LDL)-like particle (1,2). Plasma Lp (a) mediates proatherogenic effects via LDL moiety, prothrombotic effects by the plasminogen-like apolipoprotein (a) and proinflammatory responses via accumulation of oxidized phospholipids (3-6). Previous epidemiological and genetic studies have demonstrated that Lp (a) was associated with an increased risk of coronary heart disease, stroke, and vascular and nonvascular mortality (7-9).

Chronic kidney disease (CKD) has received increased attention as one of the leading public health problems, affecting 10–16% of the general adult populations in Asia, Europe, and the USA (10-13), and is associated with increased risk of mortality, cardiovascular diseases, and a progression to end-stage renal disease (10,14). Decreased glomerular filtration rate (GFR) is the key kidney markers for definition of CKD (14).

An increase of Lp (a) concentrations was observed in the earliest stage of kidney impairment when GFR was not yet subnormal (15). Moreover, findings of several studies have also shown that increases in plasma Lp (a) levels occurred in patients with non-nephrotic kidney disease and those on hemodialysis (15–17). However, the effect of Lp (a) on the progression of CKD has not been evaluated yet. In fact, CKD frequently coexists with traditional cardiovascular risk factors, such as type 2 diabetes (T2D) and hypertension (18,19). However, comprehensive analysis on the association of circulating Lp (a) levels with risk of reduced renal function in individuals with and without T2D or hypertension is scarce.

This prospective study aimed to prospectively assess the association of elevated serum Lp (a) concentrations with reduced renal function over 4 to 5 years’ follow-up period in well-
defined community study samples; in particular, we investigated whether diabetic or hypertensive status modifies such association.
Materials and Methods

Study population

The study participants were recruited from community residents at Jiading district in Shanghai between March and August 2010. The design of this prospective cohort study has been described in detail earlier (20-22). Briefly, 10,375 of 10,569 registered permanent residents aged ≥40 years participated in the baseline examination for an investigation aimed to explore the effects of risk factors on T2D and related chronic diseases. Participants with missing data on serum creatinine (n=14) or serum Lp (a) (n=9), or eGFR <60 ml/min/1.73m² (n=309) at baseline were excluded and 10,043 participants were eligible for the prospective investigation. From August 2014 to May 2015, these 10,043 participants were invited to complete a follow-up examination. 230 participants died during the follow up period, and 3,396 participants did not attend the follow-up onsite blood sampling and physical examination. Participants with missing data on measurements of serum creatinine (n=14) or serum Lp (a) (n=146) at follow-up were further excluded, which subsequently left a total of 6,257 participants in the final analysis (Supplemental Figure 1).

The Institutional Review Board of Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine approved the study protocol. Written informed consent was obtained from each participant.

Data collection and biochemical measurements

A standard questionnaire was used to collect the social demographic information, the history of chronic diseases and medications, and lifestyle factors. The current smoking or drinking
status were defined as ‘yes’ if the subject smoked cigarettes or consumed alcohol regularly in
the past 6 months. Height and weight were measured to the nearest 0.1 kg and 0.1 cm
separately with participants wearing lightweight clothes but without shoes. Body mass index
(BMI) was calculated as weight in kilograms divided by height squared in meters (kg/m²).
Trained investigators measured systolic and diastolic blood pressure (SBP and DBP) in
triplicate on the same day after at least ten-min rest by using an automated electronic device
(OMRON Model HEM-752 FUZZY, Omron Company, Dalian, China), and the average value
of the three measurements was used for analysis.

At baseline and the follow-up visit, all participants received a standard 75-g oral glucose
tolérances tests (OGTT) after an overnight fast of more than 10 hours. Blood samples were
obtained at 0 and 2 hours during the test. Fasting and 2-hour post-loading plasma glucose
(FPG and 2h PG) were measured by the glucose oxidase method using an autoanalyzer
(Modular P800; Roche, Basel, Switzerland). Glycated hemoglobin (HbA1c) levels were
determined by high performance liquid chromatography (Bio-Rad; Hercules, CA, USA).

Fasting serum total cholesterol (TC), triacylglycerol (TG), high-density lipoprotein
cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured by
chemiluminescence method with the auto-analyzer (Modular E170; Roche, Basel,
Switzerland). The fasting serum creatinine (Scr) level was measured by using the picric acid
method on an autoanalyzer (clinical chemistry diagnostic system C16000, Abbott
Laboratories, Otawara-shi, Japan).

**Definitions of diabetes and hypertension**
According to the American Diabetes Association 2010 Criteria, diabetes was defined as FPG $\geq 7.0$ mmol/l (126 mg/dl), 2h-OGTT PG $\geq 11.1$ mmol/l (200 mg/dl), or HbA1c $\geq 6.5\%$, or previously diagnosed diabetes and receiving anti-diabetic therapy (23). The SBP $\geq 140$ mmHg or DBP $\geq 90$ mmHg, or those who were taking anti-hypertension medications were defined as hypertension.

**Measurement of Lp (a)**

Serum Lp (a) levels were determined by murine monoclonal antibody (20-037, S0710-1; Jiemen BIO-TECH, Shanghai, China) by Latex enhanced immune transmission turbidimetry with a normal value of $< 30$ mg/dl. For the laboratory test of serum Lp (a), the coefficient of variation (CV) within group was 8%, and the calibration of Lp (a) concentrations was validated by using a different antibody (Denka Seiken, Tokyo, Japan). More details on serum Lp (a) measurement has shown in our previous study (24).

**Assessment of incident reduced renal function**

The 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (25,26) was used to calculate eGFR (expressed in ml/min per 1.73 m²), where Scr is serum creatinine concentration (in mg/dl) and age in years. The formula was: (1) if female: Scr $\leq 0.7$ mg/dl, $eGFR = 144 \times \frac{Scr}{0.7}^{-0.329} \times (0.993)^{\text{age}}$; Scr $> 0.7$ mg/dl, $eGFR = 144 \times \frac{Scr}{0.7}^{-1.209} \times (0.993)^{\text{age}}$. (2) if male: Scr $\leq 0.9$ mg/dl, $eGFR = 141 \times \frac{Scr}{0.9}^{-0.411} \times (0.993)^{\text{age}}$; Scr $> 0.9$ mg/dl, $eGFR = 141 \times \frac{Scr}{0.9}^{-1.209} \times (0.993)^{\text{age}}$. Reduced renal function was defined as an eGFR of less than 60 ml/min per 1.73m² (11), with mildly decreased GFR defined as eGFR of
60-89 ml/min/1.73 m². Participants without reduced renal function at baseline but defined as reduced renal function at the follow-up visit was categorized as incident reduced renal function.

**Statistical analysis**

Participants were categorized into three groups according to tertiles of serum Lp (a) concentrations: tertile 1 with median of 7 mg/dl (0-11 mg/dl), tertile 2 with median of 18 mg/dl (12-25 mg/dl), and tertile 3 with median of 30 mg/dl (26-162 mg/dl). Data are presented as mean ± standard deviation (SD) or if the distributions were skewed, median (25th–75th percentile) values for continuous variables and frequencies for categorical variables. The comparisons of baseline characteristics among groups were performed by one-way ANOVA for continuous variables, and χ² test for categorical variables. P values for trend was calculated by using linear regression analyses and Cochran-Armitage trend test for continuous and categorical variables across the three groups, respectively. The skewed distribution variables, such as serum TG and Lp (a) data, were logarithmically transformed before statistical analysis.

Multivariable logistic regression analyses were used to assess the risk of incident reduced renal function in relation to serum Lp (a) concentrations in two models: model 1 was adjusted for sex, baseline age (years), and BMI (kg/m²); model 2 was further adjusted for baseline FPG (mmol/l), SBP (mmHg), log₁₀-TG (mmol/l), HDL-C (mmol/l), LDL-C (mmol/l), mildly decreased GFR (yes or no), current smoking and drinking status (yes or no), and use of antihypertensive drugs and antidiabetic drugs (yes or no). Odds ratio (OR) and the
corresponding 95% confidence interval (CI) were calculated in two models. In addition, we performed stratified analysis on the association between serum Lp (a) concentrations and incident reduced renal function according to baseline T2D and hypertension status.

For a more detailed exploration of the effect of combining Lp (a) and T2D, or hypertension status on the risk of reduced renal function, we categorized the participants into four groups according to low [$\leq 25$ mg/dl, equal to combination of Lp (a) tertile 1 and tertile 2] and high Lp (a) level [$>25$ mg/dl, equal to Lp (a) tertile 3], and T2D or hypertension status, respectively: (1) non-T2D with low Lp (a), non-T2D with high Lp (a), T2D with low Lp (a), T2D with high Lp (a); (2) non-hypertension with low Lp (a), non-hypertension with high Lp (a), hypertension with low Lp (a), hypertension with high Lp (a).

The generalized estimating equations were used to examine the regression coefficient ($\beta$) and 95% CIs for association of serum Lp (a) and eGFR. The two time-point (baseline and follow-up visit) measurements of serum Lp (a) were the independent variable, and the two time-point measurements of eGFR as the dependent variables. In this analysis, the multivariable adjustments included sex, age, BMI, FPG, SBP, LDL-C, HDL-C, log10-TG, smoking and drinking status, and use of antihypertensive drugs (not for the non-hypertension strata) and antidiabetic drugs (not for the non-T2D strata). Information on all covariates was updated at follow-up and modelled as repeated measures.

All analyses were conducted by using SAS version 9.4 (SAS Institute Inc, Cary, NC) and a two-sided $P$ value $<0.05$ was considered statistically significant.
Results

Baseline characteristics of study population

The mean age of the 6,257 participants was 57.7 years (SD 8.6); 2,303 (36.8%) were men. Baseline characteristics of study participants according to tertiles of baseline serum Lp (a) concentrations were showed in Table 1. P for trend was calculated with each tertile of serum Lp (a) concentrations taken as a unit. The participants with the highest tertile of Lp (a) were less frequent men, smoker, alcohol drinker, diabetes, hypertension, and use of antidiabetic drugs; had lower baseline BMI, SBP, DBP, FPG, TG, and eGFR, but higher levels of LDL-C, HDL-C, TC, and higher prevalence of mildly decreased GFR, compared to those with the lowest tertile of Lp (a) (all P for trend <0.05, Table 1).

Associations of Lp (a) concentrations with risk of incident reduced renal function

During follow-up, 158 (2.5%) participants developed reduced renal function. The incidences of reduce renal function were 2.1%, 2.4% and 3.0% from the lowest to the highest serum Lp (a) tertile, respectively. As shown in Table 2, each 1-unit increase in log10-Lp (a) (mg/dl) was associated with 1.81-folds (95% CI 1.08-3.01, *P* = 0.02) increased risk of incident reduced renal function after adjustment for age, sex and BMI (model 1). After further adjustment for baseline FPG, SBP, log10-TG, HDL-C, LDL-C, mildly decreased GFR, smoking and drinking status, and use of antihypertensive drugs and antidiabetic drugs (model 2), the results did not appreciably changed (OR=1.99, 95% CI 1.15–3.43, *P* = 0.01). As compared to tertile 1, ORs for tertile 2 and tertile 3 of serum Lp (a) were 1.11 (95% CI 0.72-1.73), and 1.54 (95% CI 1.01-2.33) in model 1, respectively. In the fully adjusted model 2, the corresponding ORs and
95% CIs were 1.21 (0.76–1.92) and 1.61 (1.03–2.52) (all \( P \) for trend \( \leq 0.03 \); table 2).

Stratified analysis for associations of Lp (a) and incident reduced renal function by baseline diabetes and hypertension status

Furthermore, we conducted stratified analysis for associations of serum Lp (a) concentrations and incident reduced renal function according to baseline diabetes or hypertension status (Figure 1). The incidence of reduced renal function in those with high Lp (a) was consistently higher than those with low Lp (a) within strata. The model was fully adjusted for sex, age, BMI, FPG, SBP, log_{10}-TG, HDL-C, LDL-C, smoking and drinking status, and use of antihypertensive drugs (except for strata of non-hypertension) and antidiabetic drugs (except for strata of non-diabetes). Each 1-unit increase in log_{10}-Lp (a) concentrations were significantly associated with an increased risk of incident reduced renal function in the subgroup of T2D (OR=4.04, 95% CI 1.42-11.54, \( P=0.01 \)) and hypertension (OR=2.18, 95% CI 1.22-3.89, \( P=0.01 \)). There were no significant associations observed in the subgroup of non-T2D (OR=1.51, 95% CI 0.79-2.87, \( P=0.21 \)) and non-hypertension (OR=1.26, 95% CI 0.22-7.25, \( P=0.79 \)). No interactions have been detected in the stratified analysis.

Combined effect of Lp (a), T2D, and hypertension on reduced renal function

The incidence of reduced renal function according to combination of Lp (a) and T2D or hypertension status were summarized in Table 3. Compared to participants with low Lp (a) (\( \leq 25 \) mg/dl) and non-T2D, those with high Lp (a) (>25 mg/dl) and T2D had the highest ORs of 2.44 (95% CI 1.44–4.13, \( P=0.001 \)) in model 1 and 2.14 (95% CI 1.13–4.04, \( P=0.02 \)) in
model 2 for reduced renal function. Similarly, the association between higher Lp (a) concentrations and the incident reduced renal function also achieved the most significant results in the group with high Lp (a) and hypertension with ORs of 4.71 (95% CI 2.19–10.15, \( P < 0.0001 \); model 1) and 3.09 (95% CI 1.31–7.29, \( P = 0.01 \); model 2; Table 3). In order to increase the number of participants with lower blood pressure, we used the upper quartile of blood pressure to re-categorize the participants as the high blood pressure (SBP ≥154 mmHg or DBP ≥90 mmHg). There were 3940 participants who were re-defined as the lower blood pressure groups. The numbers of incident cases (n, %) of decreased renal function in the following groups: low blood pressure with low Lp (a) (36, 1.4%) or high Lp (a) (24, 1.7%), and high blood pressure with low Lp (a) (56, 3.7%) or high Lp (a) (41, 5.3%), were shown in Supplementary Table 1. Similarly, a stronger association was observed in the group with high Lp (a) and high blood pressure with ORs of 2.84 (95% CI 1.75–4.62, \( P < 0.0001 \); model 1) and 2.43 (95% CI 1.46–4.02, \( P = 0.001 \); model 2). The results still indicated a combined effect of Lp (a) concentrations and high blood pressure on the reduced renal function risk.

**Associations of serum Lp (a) concentrations with eGFR**

In addition, we assessed the associations of serum Lp (a) concentrations with eGFR (Table 4). After adjustment for the confounders, each 1-unit increase in \( \log_{10} \)-Lp (a) and each 1-tertile increase in Lp (a) were associated with a 1.04 ml/min/1.73 m\(^2\) (95% CI -1.67, -0.41, \( P = 0.001 \)) and a 0.39 (95% CI -0.66, -0.12, \( P = 0.004 \)) decrease in eGFR in total study participants. We further performed the stratified analysis according to baseline diabetes or hypertension status. The linear associations of \( \log_{10} \)-Lp (a) and eGFR were both found in non-diabetes (\( \beta = -0.77 \)
ml/min/1.73 m², 95% CI -1.47, -0.08, P=0.03), and diabetes patients (β=-2.11, 95% CI -3.56, -0.66, P=0.004). We also observed such association among participants with prevalent hypertension (β=-1.15, 95% CI -1.95, -0.34, P=0.01), but not in those without hypertension (β=-0.88, 95% CI -1.90, 0.12, P=0.08) (Table 4).
Discussion

In this prospective investigation in 6,257 community-dwelling Chinese adults, serum Lp (a) levels were significantly and independently associated with eGFR and risk of incident reduced renal function. Moreover, the association between Lp (a) and reduced renal function was more prominent among patients with diabetes or hypertension.

Previous studies suggested that an elevated Lp (a) level could be accompanied by renal dysfunction or increased albuminuria in diabetic or non-diabetic patients (15-17,27,28). Lp (a) concentrations increased significantly with decreasing GFR even in the earliest stages of renal impairment (15). A previous study of 217 patients with diabetes showed that patients with co-morbidity of hypertension, coronary heart disease, microalbuminuria or proteinuria had a statistically significant increased level of Lp (a); while the patients with hyperlipoprotein (a) (≥ 30 mg/dL) presented significantly increased levels of urea and total cholesterol (27). Moreover, several studies have demonstrated that Lp (a) was a significant prognostic factor for developing a new onset of CKD in diabetic patients (29-31). In a prospective study including 81 diabetic patients, the creatinine concentrations were significantly higher in patients with Lp (a) level ≥30 mg/dl than those with Lp (a) level <30 mg/dl after 1 year and 2 year of follow-up, respectively (29). Another two cohort studies (30,31), including 862 patients and 581 patients with T2D, both demonstrated that Lp (a) level was an independent prognostic factor for the risk of CKD. In our present prospective investigation, we provided the evidence that an elevated Lp (a) level was an independent risk factor for the progression of reduced renal function in general population and inversely associated with eGFR. This association was independent of hyperglycemia, hypertension, or
lipid profile.

Emerging evidence has indicated that the prevalence of either hypertension or T2D always increases with both decreased GFR (18,19). Since both T2D and hypertension have a highly close relationship with CKD, we assumed that there might be a combined effect of Lp (a) with T2D and hypertension status on CKD, therefore Lp (a) could further help predict the risk of CKD in diabetic and hypertensive patients. In the current study, we not only analyzed the effect of Lp (a) in the general population but also assessed the combined effects of Lp (a) with T2D or hypertension status. Particularly, our results showed that individuals with high Lp (a) were more likely to have stronger effect on reduced renal function when combined with diabetic status. Intriguingly, both the present study and our previous analysis (24) observed that T2D patients tended to have a lower Lp(a) level, indicating an inverse association between Lp (a) concentrations and T2D. Nevertheless, previous studies suggested that diabetes status did not attenuate the robust association between Lp (a) and cardiovascular risk (9, 29), and high glucose metabolism status plus elevated Lp (a) levels even had a higher risk for cardiovascular events (30). In the current analysis, we similarly found that the association between Lp (a) concentrations and reduced renal function risk was more prominent in patients with T2D or hypertension. It has also been demonstrated that Lp (a) was an independent risk factor for diabetic microvascular complications in patients with T2D (31-35), including diabetic nephropathy and retinopathy, which was in the line with our findings. Wen-Jun Tu et al. investigated the association between Lp (a) concentration and diabetic retinopathy (DR) in patients with T2D and found that the patient group with highest concentrations of both Lp (a) and HbA1c (≥7%) had a statistically significant OR for DR compared with the patients with
lower concentrations of both factors, indicating a combined effect of Lp (a) and HbA1c (35). Though a relatively less cases among group with non-hypertension might not have enough power to indicate a combined effect of hypertension and Lp (a), the sensitive analysis still suggested a stronger association among participants with high Lp (a) and high blood pressure. Therefore, on considering the high prevalence of renal dysfunction in hypertensive patients (11, 18), paying more attention to the high Lp (a) levels in patients with hypertension were still recommended.

The mechanisms underlying the relationship between Lp (a) and renal dysfunction remain unclear. The arteriovenous differences in Lp (a) concentrations between arterial and renal veins and apo(a) fragments in urine were observed in previous studies, indicating that the kidney plays a role in the catabolism of Lp (a) (36,37). Lp (a) quantitatively contains the atherogenic risk of LDL particles, which will oxidize after entry into the vessel wall, and then become highly immunogenic and proinflammatory oxidized LDL (ox-LDL) (38). Ox-LDL is known to be toxic to vascular cell and may therefore lead to renal injury. Another main component of apo (a) also potentiates microvascular damage through additional mechanisms, including inflammation through its content of oxidized phospholipids (OxPL) (3). In addition to vascular injury, abnormalities in Lp (a) metabolism might be implicated in glomerular and tubulo-interstitial damage (39,40). Further experimental studies are needed to clarify the causal relationship or pathogenic mechanism of Lp (a) abnormality with renal dysfunction.

Our study has the strengths of the relatively large sample size, well-defined community setting and the highly homogeneous population. To the best of our knowledge, our study was the first to assess the association between Lp (a) and the risk of renal dysfunction and the
combined effect with T2D and hypertension. Several limitations of this study should be acknowledged when interpreting our findings. Firstly, Lp (a) concentrations were not very much influenced by age, sex, and lifestyle factors but were under strict genetic control and highly associated with apo (a) isoforms (41). We did not measure apo (a) phenotypes or Lp (a) genotypes; therefore, the associations of apo (a) isoforms and Lp (a) genotypes with the progression of renal dysfunction remain to be defined. Secondly, the present analysis based on a follow-up prospective design, which could not completely exclude the influence of the potential reverse causation. Previous studies observed an increase of Lp (a) in various kidney dysfunction (15-17), even in the earliest stage of kidney impairment, indicating that renal dysfunction might elevate Lp (a). An elevated Lp (a) was also observed in participants with mildly decreased GFR at baseline in the present study. However, after adjusted for baseline mildly decreased GFR status, the positive association between Lp (a) concentrations and the risk of reduced renal function was still significant. Nevertheless, a prospective investigation with longtime follow-up in a larger sample size cohort, or the Mendelian randomization study that may help to assess the causal link were needed. Thirdly, we used the 2009 CKD-EPI equation to estimate the GFR, rather than the technetium 99m diethylene-triaminepentaacetic acid (99mTc-DTPA) renal dynamic imaging method. However, the accuracy of CKD-EPI equation has already been validated and confirmed in previous studies (42,43). Finally, our study was limited to the Chinese middle aged and elderly population. It was reported that the lower Lp (a) levels were much lower in Chinese than other ethnicity groups (44), so the results might not be generalizable to the younger and other ethnicities.

In conclusion, serum Lp (a) was an independent risk factor of incident reduced renal
function in middle-aged and elderly Chinese. Moreover, the association between Lp (a) and reduced renal function was more prominent among patients with diabetes or hypertension, highlighting the importance of measurements of Lp (a) and treating strategies toward clinical practice and management of Lp (a)-hyperlipoproteinemia.
Data availability

Data are available from the authors on request.

Acknowledgements

We thank all the study participants for their participation and research team who contributed to data collection and laboratory measurement.

Grant Support

This study was supported by the Ministry of Science and Technology of China (grant number 2018YFC1311705, 2016YFC1305600 and 2016YFC1304904); the National Natural Science Foundation of China (grant number 81941017, 81930021, 81770842 and 81561128019); the Shanghai Science and Technology Commission (grant number YDZX20173100004881); the Shanghai Municipal Education Commission-Gaofeng Clinical Medicine and Doctoral Innovation Grant (grants 20171901); and Innovative research team of high-level local universities in Shanghai.
References

1. Tsimikas S. 2017. A Test in Context: Lipoprotein(a): Diagnosis, Prognosis, Controversies, and Emerging Therapies. *J Am Coll Cardiol.* 69:692–711.

2. Tsimikas, S., Fazio, S., Ferdinand, K. C., Ginsberg, H. N., Koschinsky, M. L., Marcovina, S. M., Moriarty, P. M., Rader, D. J., Remaley, A. T., Reyes-Soffer, G., Santos, R. D., Thanassoulis, G., Witztum, J. L., Danthi, S., Olive, M., and Liu, L. 2018. NHLBI Working Group Recommendations to Reduce Lipoprotein(a)-Mediated Risk of Cardiovascular Disease and Aortic Stenosis. *J Am Coll Cardiol.* 71:177-192.

3. van der Valk, F. M., Bekkering, S., Kroon, J., Yeang, C., Van den Bosche, J., van Buul, J. D., Ravandi, A., Nederveen, A. J., Verberne, H. J., Scipione, C., Nieuwdorp, M., Joosten, L. A., Netea, M. G., Koschinsky, M. L., Witztum, J. L., Tsimikas, S., Riksen, N. P., and Stroes, E. S. 2016. Oxidized Phospholipids on Lipoprotein(a) Elicit Arterial Wall Inflammation and an Inflammatory Monocyte Response in Humans. *Circulation.* 134:611-624.

4. Wiesner, P., Tafelmeier, M., Chittka, D., Choi, S. H., Zhang, L., Byun, Y. S., Almazan, F., Yang, X., Iqbal, N., Chowdhury, P., Maisel, A., Witztum, J. L., Handel, T. M., Tsimikas, S., and Miller, Y. I. 2013. MCP-1 binds to oxidized LDL and is carried by lipoprotein(a) in human plasma. *J Lipid Res.* 54:1877-1883.

5. Leibundgut, G., Scipione, C., Yin, H., Schneider, M., Boffa, M. B., Green, S., Yang, X., Dennis, E., Witztum, J. L., Koschinsky, M. L., and Tsimikas, S. 2013. Determinants of binding of oxidized phospholipids on apolipoprotein (a) and lipoprotein (a). *J Lipid Res.* 54:2815-2830.

6. Boffa, M. B., and Koschinsky, M. L. 2016. Lipoprotein (a): truly a direct prothrombotic
factor in cardiovascular disease? *J Lipid Res.* **57**:745–757.

7. Emerging Risk Factors Collaboration, Erqou, S., Kaptoge, S., Perry, P. L., Di Angelantonio, E., Thompson, A., White, I. R., Marcovina, S. M., Collins, R., Thompson, S. G., and Danesh, J. 2009. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA*. **302**:412-423.

8. Kamstrup, P. R., Tybjaerg-Hansen, A., Steffensen, R., and Nordestgaard, B. G. 2009. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA*. **301**:2331–2339.

9. Waldeyer, C., Makarova, N., Zeller, T., Schnabel, R. B., Brunner, F. J., Jørgensen, T., Linneberg, A., Niiranen, T., Salomaa, V., Jousilahti, P., Yarnell, J., Ferrario, M. M., Veronesi, G., Brambilla, P., Signorini, S. G., Iacoviello, L., Costanzo, S., Giampaoli, S., Palmieri, L., Meisinger, C., Thorand B., Kee F., Koenig W., Ojeda F., Kontto J., Landmesser U., Kuulasmaa K., and Blankenberg, S. 2017. Lipoprotein(a) and the risk of cardiovascular disease in the European population: results from the BiomarCaRE consortium. *Eur Heart J.* **38**:2490-2498.

10. Eckardt, K. U., Coresh, J., Devuyst, O., Johnson, R. J., Köttgen, A., Levey, A. S., and Levin, A. 2013. Evolving importance of kidney disease: from subspecialty to global health burden. *Lancet*. **382**:158-169.

11. Zhang, L., Wang, F., Wang, L., Wang, W., Liu, B., Liu, J., Chen, M., He, Q., Liao, Y., Yu, X., Chen, N., Zhang, J.E., Hu, Z., Liu, F., Hong, D., Ma, L., Liu, H., Zhou, X., Chen, J., Pan, L., Chen, W., Wang, W., Li, X., and Wang, H. 2012. Prevalence of chronic kidney disease in China: a cross-sectional survey. *Lancet*. **379**: 815–822.
12. Hallan, S. I., Coresh, J., Astor, B. C., Asberg, A., Powe, N. R., Romundstad, S., Hallan, H. A., Lydersen, S., and Holmen, J. 2006. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *J Am Soc Nephrol.* **17:**2275-2284.

13. Coresh, J., Selvin, E., Stevens, L. A., Manzi, J., Kusek, J. W., Eggers, P., Van Lente, F., and Levey, A. S. 2007. Prevalence of chronic kidney disease in the United States. *JAMA.* **298:**2038-2047.

14. Bello, A. K., Nwankwo, E., and El Nahas, A. M. 2005. Prevention of chronic kidney disease: a global challenge. *Kidney Int Suppl.* (98):S11–S17.

15. Kronenberg, F., Kuen, E., Ritz, E., Junker, R., König, P., Kraatz, G., Lhotta, K., Mann, J. F., Müller, G. A., Neyer, U., Riegel, W., Reigler, P., Schwenger, V., and Von Eckardstein, A. 2000. Lipoprotein(a) serum concentrations and apolipoprotein(a) phenotypes in mild and moderate renal failure. *J Am Soc Nephrol.* **11:**105-115.

16. Kronenberg, F., König, P., Neyer, U., Auinger, M., Pribasnig, A., Lang, U., Reitinger, J., Pinter, G., Utermann, G., and Dieplinger, H. 1995. Multicenter study of lipoprotein(a) and apolipoprotein(a) phenotypes in patients with end-stage renal disease treated by hemodialysis or continuous ambulatory peritoneal dialysis. *J Am Soc Nephrol.* **6:**110-120.

17. Stenvinkel, P., Heimbürger, O., Tuck, C. H., and Berglund, L. 1998. Apo(a)-isoform size, nutritional status and inflammatory markers in chronic renal failure. *Kidney Int.* **53:**1336-1342.

18. Wen, C. P., Cheng, T. Y., Tsai, M. K., Chang, Y. C., Chan, H. T., Tsai, S. P., Chiang, P. H., Hsu, C. C., Sung, P. K., Hsu, Y. H., and Wen, S. F. 2008. All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan. *Lancet.*
19. Collins, A. J., Foley, R. N., Chavers, B., Gilbertson, D., Herzog, C., Johansen, K., Kasiske, B., Kutner, N., Liu, J., St Peter, W., Guo, H., Gustafson, S., Heubner, B., Lamb, K., Li, S., Li, S., Peng, Y., Qiu, Y., Roberts, T., Skeans, M., Snyder, J., Solid, C., Thompson, B., Wang, C., Weinhandl, E., Zaun, D., Arko, C., Chen, S.C., Daniels, F., Ebben, J., Frazier, E., Hanzlik, C., Johnson, R., Sheets, D., Wang, X., Forrest, B., Constantini, E., Everson, S., Eggers, P., and Agodoa, L. 2012. 'United States Renal Data System 2011 Annual Data Report: Atlas of chronic kidney disease & end-stage renal disease in the United States. *Am J Kidney Dis.* 59:A7-e420.

20. Lin, L., Peng, K., Du, R., Huang, X., Sun, W., Ding, L., Wang, P., Huang, Y., Xu, Y., Xu, M., Chen, Y., Bi, Y., Wang, W., and Lu, J. 2017. High glomerular filtration rate is associated with arterial stiffness in Chinese population. *J Hypertens.* 35:385-391.

21. Wang, L., Li, M., Zhao, Z., Xu, M., Lu, J., Wang, T., Chen, Y., Wang, S., Dai, M., Hou, Y., Wu, X., Ma, L., Li, L., Liu, S., Wang, W., Xu, Y., Bi, Y., and Ning, G. 2018. Ideal Cardiovascular Health Is Inversely Associated with Nonalcoholic Fatty Liver Disease: A Prospective Analysis. *Am J Med.* 131:1515.e1-1515.e10.

22. Du, R., Wu, X., Peng, K., Lin, L., Li, M., Xu, Y., Xu, M., Chen, Y., Li, D., Lu, J., Bi, Y., Wang, W., and Ning, G. 2019. Serum apolipoprotein B is associated with increased risk of metabolic syndrome among middle-aged and elderly Chinese: A cross-sectional and prospective cohort study. *J Diabetes.* 11:752-760.

23. American Diabetes Association. 2010. Diagnosis and classification of diabetes mellitus. *Diabetes Care.* 33:S62-69.
24. Ding, L., Song, A., Dai, M., Xu, M., Sun, W., Xu, B., Sun, J., Wang, T., Xu, Y., Lu, J., Wang, W., Bi, Y., and Ning, G. 2015. Serum lipoprotein (a) concentrations are inversely associated with T2D, prediabetes, and insulin resistance in a middle-aged and elderly Chinese population. *J Lipid Res.* **56**:920-926.

25. Levey, A. S., Stevens, L. A., Schmid, C. H., Zhang, Y. L., Castro, A. F., 3rd, Feldman, H. I., Kusek, J. W., Eggers, P., Van Lente, F., Greene, T., Coresh, J., and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). 2009. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* **150**:604-612.

26. Inker, L. A., Astor, B. C., Fox, C. H., Isakova, T., Lash, J. P., Peralta, C. A., Kurella Tamura, M., and Feldman, H. I. 2014. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis.* **63**:713-735.

27. Toro, R., Segura, E., Nuñez-Cortes, J. M., Pedro-Botet, J. C., Quezada-Feijoo, M., and Mangas, A. 2015. Relationship between lipoprotein (a) and micro/macro complications in type 2 diabetes mellitus: a forgotten target. *J Geriatr Cardiol.* **12**:93–99.

28. Lin, J., Reilly, M. P., Terembula, K., and Wilson, F. P. 2014. Plasma lipoprotein(a) levels are associated with mild renal impairment in type 2 diabetics independent of albuminuria. *PLoS One.* **9**:e114397.

29. Saeed, A., Sun, W., Agarwala, A., Virani, S. S., Nambi, V., Coresh, J., Selvin, E., Boerwinkle, E., Jones, P. H., Ballantyne, C. M., and Hoogeveen, R. C. 2019. Lipoprotein(a) levels and risk of cardiovascular disease events in individuals with diabetes mellitus or prediabetes: The Atherosclerosis Risk in Communities study. *Atherosclerosis.* **282**:52–56.

30. Jin, J. L., Cao, Y. X., Zhang, H. W., Sun, D., Hua, Q., Li, Y. F., Guo, Y. L., Wu, N. Q.,
Zhu, C. G., Gao, Y., Dong, Q. T., Liu, H. H., Dong, Q., and Li, J. J. 2019. Lipoprotein(a) and Cardiovascular Outcomes in Patients With Coronary Artery Disease and Prediabetes or Diabetes. *Diabetes care.* 42:1312–1318.

31. Song, K. H., Ko, S. H., Kim, H. W., Ahn, Y. B., Lee, J. M., Son, H. S., Yoon, K. H., Cha, B. Y., Lee, K. W., and Son, H. Y. 2005. Prospective study of lipoprotein(a) as a risk factor for deteriorating renal function in type 2 diabetic patients with overt proteinuria. *Diabetes Care.* 28:1718-1723.

32. Yun, J. S., Ahn, Y. B., Song, K. H., Yoo, K. D., Park, Y. M., Kim, H. W., and Ko, S. H. 2016. Lipoprotein(a) predicts a new onset of chronic kidney disease in people with Type 2 diabetes mellitus. *Diabet Med.* 33:639-643.

33. Senba, H., Furukawa, S., Sakai, T., Niiya, T., Miyake, T., Yamamoto, S., Ueda, T., Torisu, M., Minami, H., Miyaoka, H., Onji, M., Tanaka, K., Matsuura, B., Tanigawa, T., Hiasa, Y., and Miyake, Y. 2016. Serum lipoprotein(a) levels and diabetic nephropathy among Japanese patients with type 2 diabetes mellitus. *J Diabetes Complications.* 30:923-927.

34. Jenkins, A. J., Lyons, T. J., Zheng, D., Otvos, J. D., Lackland, D. T., McGee, D., Garvey, W. T., Klein, R. L., and DCCT/EDIC Research Group. 2003. Lipoproteins in the DCCT/EDIC cohort: associations with diabetic nephropathy. *Kidney Int.* 64:817-28.

35. Tu, W. J., Liu, H., Liu, Q., Cao, J. L., and Guo, M. 2017. Association Between Serum Lipoprotein(a) and Diabetic Retinopathy in Han Chinese Patients With Type 2 Diabetes. *J Clin Endocrinol Metab.* 102:2525-2532.

36. Kronenberg, F., Trenkwalder, E., Lingenhel, A., Friedrich, G., Lhotta, K., Schober, M., Moes, N., König, P., Utermann, G., and Dieplinger, H. 1997. Renovascular arteriovenous
differences in Lp (a) plasma concentrations suggest removal of Lp (a) from the renal circulation. *J Lipid Res.* **38**:1755–1763.

37. Kostner, K. M., Maurer, G., Huber, K., Stefenelli, T., Dieplinger, H., Steyrer, E., and Kostner, G. M. 1996. Urinary excretion of apo(a) fragments. Role in apo(a) catabolism. *Arterioscler Thromb Vasc Biol.* **16**:905–911.

38. Steinberg, D., and Witztum, J. L. 2010. Oxidized low-density lipoprotein and atherosclerosis. *Arterioscler Thromb Vasc Biol.* **30**:2311–2316.

39. Keane W.F. 1994. Lipids and the kidney. *Kidney Int.* **46**:910–920.

40. Greiber, S., Kreusel, M., Pavenstädt, H., Schollmeyer, P., and Wanner, C. 1997. Lipoprotein(a) induces glomerular superoxide anion production. *Nephrol Dial Transplant.* **12**:1330–1335.

41. Kronenberg F. 2016. Human Genetics and the Causal Role of Lipoprotein(a) for Various Diseases. *Cardiovasc Drugs Ther.* **30**:87–100.

42. Stevens, L. A., Schmid, C. H., Greene, T., Zhang, Y. L., Beck, G. J., Froissart, M., Hamm, L. L., Lewis, J. B., Mauer, M., Navis, G. J., Steffes, M. W., Eggers, P. W., Coresh, J., and Levey, A. S. 2010. Comparative performance of the CKD epidemiology collaboration (CKDEPI) and the modification of diet in renal disease (MDRD) study equations for estimating GFR levels above 60 ml/min/1.73 m². *Am J Kidney Dis.* **56**:486–495.

43. Stevens, L. A., Schmid, C. H., Zhang, Y. L., Coresh, J., Manzi, J., Landis, R., Bakoush, O., Contreras, G., Genuth, S., Klintmalm, G. B., Poggio, E., Rossing, P., Rule, A. D., Weir, M. R., Kusek, J., Greene, T., and Levey, A. S. 2010. Development and validation of GFR-estimating equations using diabetes, transplant and weight. *Nephrol Dial Transplant.* **25**:449–
44. Paré, G., Çaku, A., McQueen, M., Anand, S. S., Enas, E., Clarke, R., Boffa, M. B., Koschinsky, M., Wang, X., Yusuf, S., and INTERHEART Investigators. 2019. Lipoprotein(a) Levels and the Risk of Myocardial Infarction Among 7 Ethnic Groups. *Circulation*. **139**: 1472–1482.
Table 1. Baseline characteristics of the study participants stratified by tertiles of serum Lp (a)

| Characteristics                          | Total participants | Tertile 1 | Tertile 2 | Tertile 3 | P for trend |
|------------------------------------------|--------------------|-----------|-----------|-----------|-------------|
| Lp (a), mg/dl                           | 18 (0-162)         | 7 (0-11)  | 18 (12-25)| 30 (26-162)| /           |
| n (%)                                   | 6257               | 2068 (33.1)| 2020 (32.3)| 2169 (34.6)| /           |
| Age, years                              | 57.8±8.6           | 57.1±8.7  | 57.9±8.6  | 58.1±8.5  | 0.001       |
| Men, n (%)                              | 2303 (36.8)        | 865 (41.8)| 736 (36.4)| 702 (32.3)| <0.0001     |
| Body mass index, kg/m²                  | 25.2±3.2           | 25.6±3.3  | 25.1±3.3  | 24.9±3.16 | <0.0001     |
| Systolic blood pressure, mmHg           | 141.3±19.7         | 142.6±19.7| 140.6±19.4| 140.5±19.8| 0.001       |
| Diastolic blood pressure, mmHg          | 83.1±10.3          | 83.8±10.3 | 82.7±10.2 | 82.7±10.3 | 0.0004      |
| Fasting plasma glucose, mmol/l          | 5.5±1.5            | 5.7±1.7   | 5.5±1.5   | 5.4±1.3   | <0.0001     |
| Triacylglycerol, mmol/l                 | 1.4 (0.3-32.8)     | 1.5 (1.0-2.3)| 1.4 (1.0-1.9)| 1.3 (0.9-1.8)| <0.0001     |
| Low-density lipoprotein cholesterol, mmol/l | 3.2±0.9            | 3.0±0.8   | 3.2±0.8   | 3.4±0.9   | <0.0001     |
| High-density lipoprotein cholesterol, mmol/l | 1.3±0.3            | 1.3±0.3   | 1.3±0.3   | 1.4±0.3   | <0.0001     |
| Total cholesterol, mmol/l               | 5.4±1.0            | 5.2±1.0   | 5.3±1.0   | 5.5±1.0   | <0.0001     |
| eGFR, ml/min/1.73 m²                    | 90.9±11.2          | 91.7±11.3 | 90.7±11.2 | 90.3±11.0 | <0.0001     |
| Mildly decreased GFR, n (%)             | 2693 (43.0)        | 831 (40.2)| 882 (43.7)| 980 (45.2)| 0.001       |
| Type 2 diabetes, n (%)                  | 1121 (17.9)        | 457 (22.1)| 326 (16.1)| 338 (15.6)| <0.0001     |
| Hypertension, n (%)                     | 3752 (60.0)        | 1316 (63.6)| 1168 (57.8)| 1268 (58.5)| 0.001       |
| Use of antidiabetic drugs, n (%)        | 465 (7.4)          | 184 (8.9) | 143 (7.1) | 138 (6.4) | 0.002       |
| Use of antihypertensive drugs, n (%)    | 1739 (27.8)        | 591 (28.6)| 538 (26.6)| 610 (28.1)| 0.75        |
| Current smoker, n (%)                   | 1237 (20.0)        | 468 (22.8)| 409 (20.4)| 360 (16.8)| <0.0001     |
| Current drinker, n (%)                  | 630 (10.1)         | 252 (12.3)| 202 (10.1)| 176 (8.2) | <0.0001     |

Data are means ± SD, median (interquartile range) for skewed variables, or n (proportion) for categorical variables. P values for trend was calculated by using linear regression analyses and Cochran-Armitage trend test for continuous and categorical variables across the three groups, respectively.
Table 2. Association of serum Lp (a) concentrations with incident risk of reduced renal function.

| Cases, n (%) | Model 1 | | Model 2 | |
|--------------|---------|------------------|---------|------------------|
|              | OR      | 95% CI           | P       | OR      | 95% CI           | P       |
| Continuous   |         |                  |         | Model 1 |                  |         | Model 2 |                  |         |
| Log_{10}-Lp (a) | 158 (2.5) | 1.81 | 1.08-3.01 | 0.02 | 1.99 | 1.15-3.43 | 0.01 |
| Categorical  |         |                  |         | Model 2 |                  |         |         |                  |         |
| Tertile 1    | 43 (2.1) | Ref.             |         | Ref.    | /                | /       |
| Tertile 2    | 49 (2.4) | 1.11 | 0.72-1.73 | 0.62 | 1.21 | 0.76-1.92 | 0.41 |
| Tertile 3    | 66 (3.0) | 1.54 | 1.01-2.33 | 0.04 | 1.61 | 1.03-2.52 | 0.03 |
| P for trend  | 0.03    |                  |         | 0.03    |                  |         |

Data are odds ratio (OR) and 95% confidence interval (CI). Model 1 was adjusted for sex, baseline age, and BMI; Model 2 was further adjusted for baseline FPG, SBP, log_{10}-TG, HDL-C, LDL-C, mildly decreased GFR, smoking and drinking status, and use of antihypertensive drugs and antidiabetic drugs.
Table 3. Combined effect of Lp (a) with type 2 diabetes or hypertension on the risk of incident reduced renal function.

| Cases, n (%) | Model 1 | Model 2 |
|-------------|---------|---------|
| | OR    | 95% CI | P     | OR    | 95% CI | P     |
| Non-type 2 diabetes | | | | | | |
| Low Lp (a) | 68 (2.1) | Ref. | | | | |
| High Lp (a) | 43 (2.4) | 1.21 | 0.80-1.82 | 0.36 | 1.17 | 0.76-1.79 | 0.46 |
| Type 2 diabetes | | | | | | |
| Low Lp (a) | 24 (3.1) | 1.04 | 0.63-1.73 | 0.86 | 0.87 | 0.45-1.70 | 0.69 |
| High Lp (a) | 23 (6.8) | 2.44 | 1.44-4.13 | 0.001 | 2.14 | 1.13-4.04 | 0.02 |
| Non-hypertension | | | | | | |
| Low Lp (a) | 8 (0.5) | Ref. | | | | |
| High Lp (a) | 8 (0.9) | 1.67 | 0.61-4.59 | 0.31 | 1.45 | 0.51-4.13 | 0.48 |
| Hypertension | | | | | | |
| Low Lp (a) | 84 (3.4) | 3.22 | 1.51-6.86 | 0.002 | 2.11 | 0.91-4.91 | 0.08 |
| High Lp (a) | 58 (4.6) | 4.71 | 2.19-10.15 | <0.0001 | 3.09 | 1.31-7.29 | 0.01 |

Data are odds ratio (OR) and 95% confidence interval (CI). Participants were categorized into four groups by combining low and high Lp (a) with T2D or hypertension status, respectively. Low Lp (a) was defined as the combination of Lp (a) tertile 1 and tertile 2 (≤25 mg/dl), and high Lp (a) was otherwise defined as Lp (a) tertile 3 (>25 mg/dl). Model 1 adjusted for sex, baseline age, and BMI; Model 2 further adjusted for baseline FPG, SBP, log10-TG, HDL-C, LDL-C, mildly decreased GFR, smoking and drinking status, and use of antihypertensive drugs and antidiabetic drugs.
Table 4. Association of Lp (a) concentrations with eGFR.

|                          | Each 1-unit increase in log_{10} Lp (a) |          |          | Each 1-tertile increase in Lp (a) |          |
|--------------------------|----------------------------------------|---------|---------|----------------------------------|---------|
|                          | β (95% CI)                             | P       | β (95% CI) | P       |
| **Total participants**   | -1.04 (-1.67, -0.41)                   | 0.001   | -0.39 (-0.66, -0.12)               | 0.004   |
| **Type 2 diabetes**      |                                        |         |          |                                        |         |
| No                       | -0.77 (-1.47, -0.08)                   | 0.03    | -0.32 (-0.61, -0.02)               | 0.03    |
| Yes                      | -2.11 (-3.56, -0.66)                   | 0.004   | -0.72 (-1.37, -0.06)               | 0.03    |
| **Hypertension**         |                                        |         |          |                                        |         |
| No                       | -0.88 (-1.90, 0.12)                    | 0.08    | -0.32 (-0.74, 0.10)                | 0.14    |
| Yes                      | -1.15 (-1.95, -0.34)                   | 0.01    | -0.46 (-0.81, -0.11)               | 0.01    |

The regression coefficient (β) and 95% confidence interval (CI) were examined by linear regression models with generalized estimating equations, with the repeated measures of serum Lp (a) as the independent variable and the corresponding repeated measures of eGFR as the dependent variable. The adjustments included sex, age, BMI, FPG, SBP, log_{10} TG, HDL-C, LDL-C, smoking and drinking status, and use of antihypertensive drugs (not for the non-hypertension strata) and antidiabetic drugs (not for the non-type 2 diabetes strata). Information on all covariates was updated at follow-up and modelled as repeated measures.
Figure and figure legend

Figure 1 Association of baseline Lp (a) levels with incident reduced renal function stratified by diabetes and hypertension status. Data are odd ratios (95% confidence interval) for of each one unit increase in log_{10}-Lp (a). The model was adjusted for sex, baseline age, BMI, FPG, SBP, log_{10}-TG, HDL-C, LDL-C, mildly decreased GFR, smoking and drinking status, and use of antihypertensive drugs (not for the non-hypertension strata) and antidiabetic drugs (not for the non-diabetes strata).

| Type 2 diabetes | Cases, n (%) | OR (95% CI) | P value |
|-----------------|--------------|-------------|---------|
| No              | 111 (2.2)    | 1.51 (0.79-2.87) | 0.21    |
| Yes             | 47 (4.2)     | 4.04 (1.42-11.54) | 0.01    |

| Hypertension | Cases, n (%) | OR (95% CI) | P value |
|--------------|--------------|-------------|---------|
| No           | 16 (0.6)     | 1.26 (0.22-7.25) | 0.79    |
| Yes          | 142 (3.8)    | 2.18 (1.22-3.89) | 0.01    |