Serum lipoprotein (a) concentrations are inversely associated with T2D, prediabetes, and insulin resistance in a middle-aged and elderly Chinese population

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Abstract Lipoprotein (a) [Lp(a)], an LDL-like particle, has been proposed as a causal risk factor for CVD among general populations. Meanwhile, both serum Lp(a) and diabetest increase the risk of CVD. However, the relationship between serum Lp(a) and T2D is poorly characterized, especially in the Asian population. Therefore, we conducted a cross-sectional study in 10,122 participants aged 40 years or older in Jiading District, Shanghai, China. Our study found that the prevalence of T2D was decreased from 20.9% to 15.0% from the lowest to the highest quartile of serum Lp(a) concentrations (P for trend <0.0001). Logistic regression analyses showed that the odds ratios and 95% confidence intervals of prevalent T2D for quartiles 2–4 versus quartile 1 were 0.86 (0.73–1.01), 0.88 (0.75–1.04), and 0.76 (0.64–0.90) (P for trend = 0.0002), after adjustment for traditional confounding factors. Moreover, the risks for prevalent prediabetes, insulin resistance, and hyperinsulinemia were also decreased from the lowest to the top quartile. This inverse association between serum Lp(a) and T2D was not appreciably changed after we adjusted hypoglycemic medications or excluded the subjects with hypoglycemic and/or lipid-lowering agents and/or a history of self-reported CVD.—Ding, L. A. Song, M. Dai, M. Xu, W. Sun, B. Xu, J. Sun, T. Wang, Y. Xu, J. Lu, W. Wang, Y. Bi, and G. Ning. Serum lipoprotein (a) concentrations are inversely associated with T2D, prediabetes, and insulin resistance in a middle-aged and elderly Chinese population. J. Lipid Res. 2015. 56: 920–926.

Supplementary key words type 2 diabetes • lipid • epidemiology • cardiovascular risk

Lipoprotein (a) [Lp(a)], synthesized by the liver, is a cholesterol-laden LDL-like particle, consisting of a moiety of apo(a) covalently attached to one molecule of apoB100 via a disulfide bond (1). The concentration of Lp(a) was found to a large extent genetically determined via variations in the LPA gene, especially the LPA kringle IV repeats, which encode apo(a) and exist in multiple copies (2). Both serum Lp(a) levels and LPA gene variants have been reported strongly associated with the risk of CVD (3–5).

Because diabetes predisposes individuals toward CVD, a similar association between circulating Lp(a) levels and

Abbreviations: 2 hPG, 2 h 75 g oral glucose tolerance test plasma glucose; CCHS, Copenhagen City Heart Study; CI, confidence interval; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FSI, fasting serum insulin; HbA1C, hemoglobin A1C; HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; LDL-C, low density lipoprotein cholesterol; log, logarithmically transformed; Lp(a), lipoprotein (a); MET-h/week, metabolic equivalent hours per week; OGT, oral glucose tolerance test; OR, odds ratio; SBP, systolic blood pressure; TC, total cholesterol; WC, waist circumference; WHS, Women’s Health Study.

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risk of T2D was expected. However, among patients with T2D, there are contradictory reports. Early studies have indicated that Lp(a) concentrations were elevated in subjects with T2D (6), especially those with poor metabolic control, and that improved metabolic control resulted in decreases of serum Lp(a) (7). While others found either unchanged (8) or decreased (9) concentrations of serum Lp(a) in patients with T2D versus nondiabetic subjects. These early small case-control or cross-sectional studies provided limited evidence about the association between serum Lp(a) concentrations and risk of T2D. Recently, an inverse association between serum Lp(a) concentrations and risk of T2D in large population studies such as the Women’s Health Study (WHS) and Copenhagen City Heart Study (CCHS) attracted wide attention (10). However, Mendelian randomization analyses identified no causal associations between serum Lp(a) and T2D (11, 12). To date, epidemiologic data regarding the association between T2D and serum Lp(a) concentrations, especially in Asian populations, are rather limited. Additionally, the relationship between serum Lp(a) concentrations and glycemic traits (e.g., glucose, insulin, insulin resistance, and insulin secretion), the hallmark of T2D, remains poorly characterized.

Therefore, our study aimed to investigate the association between serum Lp(a) concentrations and T2D, prediabetes, and insulin resistance, as well as potential modification factors for the association in a middle-aged and elderly Chinese population.

RESEARCH DESIGN AND METHODS

Study population and design

The participants in the present study were a general population from a community-based glucose survey in Jiading district, Shanghai, China, from March to August 2010. First, we invited all the permanent residents aged ≥40 years, by using physical examination notice, telephone, or door-to-door visit. A total of 10,569 inhabitants were invited to participate in the survey. From these participants, we sequentially excluded subjects who met the following criteria: 1) those with missing data on their serum Lp(a) concentrations (n = 16) and/or fasting plasma glucose (FPG) and/or 2 h 75 g oral glucose tolerance test (OGTT) plasma glucose (2 hPG) levels and/or fasting serum insulin (FSI) levels (n = 36); 2) those with medical history of self-reported malignant tumors (n = 4); and 3) those with serious hepatic or renal dysfunction (n = 197).

A total of 10,122 eligible individuals were enrolled in the final analysis. The study protocol was approved by the Institutional Review Board of the Rui-jin Hospital affiliated to Shanghai Jiao-Tong University School of Medicine. Each participant signed the written informed consent before data collection.

Questionnaire data collection and clinical measurements

A standard questionnaire was used for collecting information about sociodemographic characteristics, lifestyle, medical history, and family history during face-to-face interviews by trained staff. Family history of diabetes was defined as the existence of diabetes in at least one first-degree relative by asking the participants: “Do any of your first-degree relatives (parent, brother, sister, child) have diabetes (type 1 or type 2)?” Family history of diabetes was considered positive when participants answered “Yes.” Current smokers or drinkers were defined as subjects who smoked cigarettes or consumed alcohol regularly in the past 6 months, respectively. A short form of the International Physical Activity Questionnaire was used, and metabolic equivalent hours per week (MET-h/week) were calculated to evaluate total physical activity (15).

Blood pressure, measured while the participant was seated after resting for at least 10 min, was determined as the average of three measurements on the non-dominant arm, with a 1 min rest period between measurements, using an automated electronic device (OMRON Model HEM-752 FUZZY; Omron Co., Dalian, China). Body height and body weight were recorded to the nearest 0.1 cm and 0.1 kg while participants were wearing lightweight clothing with no shoes. BMI was calculated as body weight (kg) divided by height squared (m²). Waist circumference (WC) was measured at the umbilical level with participants standing properly.

Venous blood samples were obtained from the participants for laboratory tests after at least 10 h of overnight fasting. To evaluate the glucose metabolism status, a two-point (0 and 2 h) OGTT with a 75 g glucose load was performed. Blood glucose from the fasting and 2 h postload blood sampling was measured using the glucose oxidase method on an autoanalyzer (Modular P800; Roche, Basel, Switzerland). Hemoglobin A1C (HbA1C) was detected by HPLC (BIO-RAD D-10). Measurement of FSI, fasting serum TGs, total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), apoA-I, apoB, Lp(a), and fasting serum alanine aminotransferase and γ-glutamyl transpeptidase from fasting plasma samples was undertaken on the autoanalyzer (Modular E170; Roche). In detail, serum LDL-C levels were measured directly by a surfactant active agent, which is specifically LDL-C dissolvable and independent of other lipoproteins. Serum Lp(a) levels were measured by using murine monoclonal antibody (20-0307, 50710-1; Jiemen BIO-TECH, Shanghai, China) by Latex enhanced immune transmittion turbidimetry. For the laboratory test of serum Lp(a), the coefficient of variation (CV) within group was 8%, and the CV between groups was 10%. Additionally, comparisons of serum Lp(a) levels of 41 samples using antibody in our study (Jiemen BIO-TECH) and another antibody (Denka Seiken, Tokyo, Japan) which has been commonly used in previous studies (10, 16), have shown high agreement ([serum Lp(a) concentrations using antibody from Denka Seiken] + 5.47893, r = 0.98116, supplementary Fig. 1).

Definition of T2D and prediabetes

According to the 1999 World Health Organization diagnostic criteria (17), T2D was defined as follows: 1) current usage of insulin or oral hypoglycemic medicine and/or 2) FPG of 7.0 mM or higher and/or 3) 2 hPG of 11.1 mM or higher. Prediabetes was defined as follows: 1) FPG between 6.1 mM and 6.9 mM and/or 2) 2 hPG between 7.8 mM and 11.0 mM.

Definition of insulin resistance and hyperinsulinemia

The index of homeostasis model assessment for insulin resistance (HOMA-IR) was calculated as fasting insulin (μIU/ml) × fasting glucose (mM)/22.5 (18). The top quartile of HOMA-IR, more than 2.5 in the present study, was defined as insulin resistance. Hyperinsulinemia was defined as fasting insulin level in the top quartile (>10 μIU/ml in our study).
Statistical analysis

All analyses were conducted with the use of SAS software, version 9.3 (SAS Institute Inc., Cary, NC). All tests were two-tailed; \( P < 0.05 \) was considered to be statistical significance.

Discrete data were presented as frequencies and percentages, and continuous variables as means ± SD or, if the distributions were skewed, as medians (interquartile ranges). One-way ANOVA and Chi-square tests were used to compare differences of continuous and categorical variables among groups, respectively.

Because the frequency distribution of serum Lp(a) was highly skewed (supplementary Table 1 and supplementary Fig. 2), lognormally transformed (lg) Lp(a) levels were used for analyses, and so were other nonnormal distributed measures, such as FSI, TG concentrations, and HOMA-IR. We also divided the distribution of serum Lp(a) values into quartiles: quartile 1 (Q1), 0–8.9 mg/dl; quartile 2 (Q2), 9.0–17.9 mg/dl; quartile 3 (Q3), 18.0–28.9 mg/dl; and quartile 4 (Q4), 29.0–162.0 mg/dl. Anthropometric and laboratory features in each quartile were described and tested for trend across serum Lp(a) quartiles by using linear regression analysis and Cochran-Armitage trend test for continuous and categorical variables, respectively. Simple and multiple linear regression analyses were used to investigate the association between serum Lp(a) and other metabolic risk factors, with serum Lp(a) as an independent variable. Logistic regression analyses were used to compare differences of continuous and categorical variables among groups, respectively. Simple and multiple linear regression analyses were used to investigate the association between serum Lp(a) and other metabolic risk factors, with serum Lp(a) as an independent variable. Logistic regression analyses were conducted to evaluate the risk for prevalent T2D, prediabetes, insulin resistance, and hyperinsulinemia in relation to each quartile increase of serum Lp(a) concentrations. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were calculated in three models. Adjustments were made for the following variables: model 1 was unadjusted; model 2 was adjusted for age, sex, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), smoking status, drinking status, family history of T2D, educational level, and physical activity; and model 3 was further adjusted for serum lipid profiles including TG, TC, LDL-C, HDL-C, apoA-I, and apoB.

In subgroup analyses, relationship between T2D and serum Lp(a) concentrations were further conducted within strata of sex (men/women), age (≥60/<60 years), obesity (BMI ≥30/<30 kg/m^2), current smoker (yes/no), and current drinker (yes/no). Tests for interaction were performed with including simultaneously each strata factor, the quartiles of serum Lp(a) concentrations, and the respective interaction terms [strata factor multiplied by quartiles of serum Lp(a) concentrations] in the models.

RESULTS

In the current analysis, among the 10,122 eligible participants, 37.6% were men and 62.4% were women, with a mean age of 58.5 years. There were 1,775 participants diagnosed as T2D, and the prevalence rate was 17.5%, while the overall prevalence of prediabetes was 27.9%. Among all patients with diabetes, 949 were newly diagnosed diabetics and 826 were previously diagnosed diabetics. Moreover, among these 826 previously diagnosed patients with diabetes, 725 were on antidiabetic agents.

General characteristics according to quartiles of serum Lp(a) concentrations (supplementary Table 1 and supplementary Fig. 2) were summarized in Table 1, and \( P \) for trend was calculated was quartile of serum Lp(a) concentrations taken as a unit. Participants with higher serum Lp(a) concentrations were more likely to be female, less educated, and nonsmoking; to have lower BMI and blood pressure; and to consume alcohol less regularly. Further, serum Lp(a) concentrations were inversely associated with glucose metabolic variables such as FPG, 2 hPG, HbA1C, FSI, and HOMA-IR. Conversely, across the four categories, a significant increased trend was found

### TABLE 1. Characteristics of participants stratified by quartiles of Lp(a)

| Quartile | 0–8.9 mg/dl | 9.0–17.9 mg/dl | 18.0–28.9 mg/dl | ≥29.0 mg/dl | \( P \) for trend |
|----------|-------------|----------------|-----------------|-------------|-----------------|
| n (%)    |             |                |                 |             |                 |
| Age (years) | 57.7 ± 9.6  | 58.5 ± 9.5     | 59.1 ± 9.7      | 59.0 ± 9.7  | <0.0001         |
| Male [n (%)] | 1,044 (43.0) | 947 (38.0)     | 907 (36.4)      | 907 (33.6)  | <0.0001         |
| BMI (kg/m²) | 25.5 ± 3.3  | 25.1 ± 3.2     | 25.0 ± 3.3      | 24.9 ± 3.2  | <0.0001         |
| WC (cm) | 84.0 ± 9.1  | 82.6 ± 8.8     | 82.5 ± 9.1      | 81.6 ± 8.7  | <0.0001         |
| SBP (mmHg) | 142.0 ± 20.4 | 140.9 ± 19.6   | 140.1 ± 19.7    | 140.9 ± 20.2 | 0.0375          |
| DBP (mmHg) | 83.5 ± 10.3 | 82.5 ± 10.4    | 82.3 ± 9.9      | 82.6 ± 10.4 | 0.0030          |
| Family history of diabetes [n (%)] | 279 (11.5) | 290 (11.7) | 248 (10.0) | 295 (11.0) | 0.2376 |
| Insulin or oral hypoglycemic agents [n (%)] | 198 (8.1) | 193 (7.7) | 153 (6.1) | 179 (6.6) | 0.0199 |
| Newly diagnosed diabetes [n (%)] | 284 (11.7) | 238 (9.5) | 246 (9.9) | 203 (7.5) | <0.0001 |
| Current smoker [n (%)] | 567 (24.1) | 501 (20.8) | 474 (19.6) | 471 (18.2) | <0.0001 |
| Current drinker [n (%)] | 284 (12.1) | 229 (9.5) | 224 (9.3) | 216 (8.3) | <0.0001 |
| Physical activity (MET-h/week) | 16.0 (0.0–36.0) | 18.0 (0.0–32.0) | 17.7 (0.0–31.5) | 18.0 (0.0–35.0) | 0.8488 |
| ≥9 years of education [n (%)] | 579 (23.9) | 547 (22.0) | 507 (20.5) | 535 (19.9) | 0.0003 |
| FPG (mM) | 5.64 ± 1.59 | 5.52 ± 1.49 | 5.46 ± 1.41 | 5.48 ± 1.35 | <0.0001 |
| 2 hPG (mM) | 8.39 ± 4.46 | 8.22 ± 4.26 | 8.10 ± 4.13 | 7.94 ± 4.07 | <0.0001 |
| HbA1C (%) | 5.86 ± 0.96 | 5.80 ± 0.90 | 5.80 ± 0.90 | 5.78 ± 0.85 | 0.0045 |
| FSI (μIU/ml) | 7.57 (5.05–11.50) | 6.90 (4.60–10.20) | 6.70 (4.70–9.50) | 6.50 (4.44–9.20) | <0.0001 |
| HOMA-IR | 1.78 (1.14–2.86) | 1.61 (1.05–2.49) | 1.54 (1.04–2.37) | 1.52 (1.02–2.25) | <0.0001 |
| TG (mM) | 1.56 (1.04–2.35) | 1.41 (0.98–1.95) | 1.30 (0.94–1.79) | 1.30 (0.90–1.78) | <0.0001 |
| TC (mM) | 5.12 ± 1.05 | 5.24 ± 0.93 | 5.36 ± 0.99 | 5.59 ± 1.00 | <0.0001 |
| HDL-C (mM) | 1.27 ± 0.32 | 1.31 ± 0.31 | 1.34 ± 0.31 | 1.35 ± 0.31 | <0.0001 |
| LDL-C (mM) | 2.91 ± 0.81 | 3.13 ± 0.80 | 3.25 ± 0.83 | 3.44 ± 0.89 | <0.0001 |
| ApoA-I (g/l) | 1.24 ± 0.28 | 1.25 ± 0.26 | 1.27 ± 0.28 | 1.27 ± 0.27 | <0.0001 |
| ApoB (g/l) | 0.92 ± 0.22 | 0.96 ± 0.22 | 0.98 ± 0.23 | 1.03 ± 0.24 | <0.0001 |

Data were means ± SD or medians (interquartile ranges) for skewed variables or numbers (proportions) for categorical variables. \( P \) for trend was calculated using linear regression analyses across the four groups.
regarding the levels of TC, HDL-C, LDL-C, apoA-I, and apoB, but not TG. In addition, family history of diabetes and physical activity (MET-h/week) did not differ between the four quartiles of the serum Lp(a). Additionally, when men and women were analyzed separately, or the patients who were being treated for diabetes were taken out of the analysis, the results did not change significantly (supplementary Tables 2–5).

From the lowest quartile to the highest quartile of serum Lp(a) concentrations, we detected that the prevalence of T2D dramatically decreased from 20.9% to 15.0% \((P\text{ for trend} <0.0001)\). Furthermore, the prevalence of prediabetes, insulin resistance, and hyperinsulinemia also tended to decrease as serum Lp(a) levels increased (Fig. 1A–D, all \(P\text{ for trend} <0.0001)\). Additionally, the percentages of newly diagnosed diabetes were significantly decreased across the quartiles of Lp(a) from the lowest one to the top one, with a prevalence of 11.7%, 9.5%, 9.9%, and 7.5%, respectively, \(P\text{ for trend} <0.0001\) (Table 1). When men and women were analyzed separately, the results did not change significantly (supplementary Tables 2 and 3).

Analyses of unadjusted and multivariate linear regression demonstrated that serum Lp(a), as an independent variable, was significantly and inversely correlated with all glucose metabolic indexes including FPG, 2 hPG, HbA1C, FSI, and HOMA-IR after incorporating adjustment for potential confounding risk factors covering age, sex, BMI, SBP, DBP, family history of diabetes, drinking status, smoking status, physical activity, educational level, and lipid profiles (Table 2). In simple Pearson’s correlation and unadjusted regression analyses of all parameters with \(\log(Lp(a))\), all parameters including BMI, WC, blood pressure, fasting and postprandial glucose levels, insulin levels, and \(\log(TG)\) were inversely associated with \(\log(Lp(a))\) concentrations. In multivariate linear regression analyses, serum Lp(a), as an independent variable, was significantly and inversely correlated with WC, SBP, FPG, 2 hPG, HbA1C, FSI, \(\log\text{HOMA-IR}\), and \(\log\text{TG}\) but was positively associated with LDL-C, apoA-I, and apoB (supplementary Table 6).

With the first quartile of serum Lp(a) concentrations as the reference group, univariate logistic regression analysis showed significantly decreased ORs for the prevalent T2D, prediabetes, insulin resistance, and hyperinsulinemia across serum Lp(a) categories (Table 3). After adjustment for traditional confounding factors (model 2), the ORs for the prevalent T2D, as compared with the lowest quartile, were 0.83 (95% CI, 0.71–0.97) for Q2, 0.83 (95% CI, 0.71–0.97) for Q3, and 0.73 (95% CI, 0.62–0.85) for Q4, respectively (\(P\text{ for trend} = 0.0002\)). Moreover, following further adjustment for lipid profiles (model 3), a 14%, 12%, and 24% decrease of ORs for the risk of the prevalent T2D was found, respectively, in the second, third, and fourth quartiles, compared with those in the top one (\(P\text{ for trend} = 0.0002\)). Likewise, the ORs for the prevalent prediabetes, insulin resistance, and hyperinsulinemia in model 1 and the multiadjusted models maintained a similar decreased trend across the four quartiles (Table 3).

The associations between T2D and serum Lp(a) concentrations were almost consistently the same in subgroups analyses (supplementary Fig. 3). No statistically significant interaction term between quartiles of serum Lp(a) concentrations and strata factors was found.
TABLE 2. The association of serum Lp(a) with glycometabolism-related traits

| Trait                        | Unadjusted Model | Multivariable Adjusted Model |
|------------------------------|------------------|-------------------------------|
|                              | \( \beta \pm SE \) for 1 Unit | \( P \) | \( \beta \pm SE \) for 1 SD | \( P \) | \( \beta \pm SE \) for 1 SD | \( P \) |
| FPG (mM)                     | -0.203 ± 0.041   | <0.0001                       | -0.072 ± 0.015 | <0.0001 | -0.136 ± 0.042 | 0.0010 |
| 2 hPG (mM)                   | -0.263 ± 0.042   | <0.0001                       | -0.263 ± 0.042 | <0.0001 | -0.136 ± 0.042 | 0.0010 |
| HbA1C (%)                    | 0.000 ± 0.000    | 0.0001                        | 0.000 ± 0.000 | 0.0001 | 0.000 ± 0.000 | 0.0001 |
| LgFSI (µIU/ml)               | -0.071 ± 0.009   | <0.0001                       | -0.025 ± 0.003 | <0.0001 | -0.025 ± 0.008 | 0.0030 |
| LgHOMA-IR                    | -0.083 ± 0.010   | <0.0001                       | -0.029 ± 0.004 | <0.0001 | -0.032 ± 0.009 | 0.0002 |

\( \beta \), regression coefficient. \( P \) value was calculated from unadjusted and multivariable adjusted linear regression analyses. In the multivariable adjusted model, the adjusted variables included age, sex, BMI, WC, SBP, DBP, family history of diabetes, drinking status, smoking status, physical activity, educational level, TC, TG, HDL-C, LDL-C, apoA-I, and apoB.

In addition, after excluding those on lipid-lowering and/or hypoglycemic medications and/or with a history of self-reported CVD together, the ORs for prevalent T2D were 0.79 (95% CI, 0.65–0.92) for Q2, 0.91 (95% CI, 0.74–1.11) for Q3, and 0.70 (95% CI, 0.57–0.86) for Q4, respectively (\( P \) for trend = 0.0058) in model 3, as compared with the lowest quartile. The ORs for prevalent insulin resistance were 0.78 (95% CI, 0.66–0.92) for Q2, 0.73 (95% CI, 0.62–0.87) for Q3, and 0.64 (95% CI, 0.54–0.76) for Q4, respectively (\( P \) for trend <0.0001) in model 3, as compared with the lowest quartile. Moreover, when we additionally adjusted the usage of antidiabetic medications among other confounding factors, the ORs for prevalent T2D were 0.81 (95% CI, 0.67–0.99) for Q2, 0.94 (95% CI, 0.77–1.14) for Q3, and 0.69 (95% CI, 0.57–0.85) for Q4, respectively (\( P \) for trend = 0.0002) in model 3, as compared with the lowest quartile, which were consistent with the results when we only excluded subjects with hypoglycemic drugs (\( n = 723 \)). Particularly among participants with self-reported CVD (\( n = 598 \)), the ORs for prevalent T2D were 0.84 (95% CI, 0.71–0.99) for Q2, 0.86 (95% CI, 0.73–1.02) for Q3, and 0.75 (95% CI, 0.63–0.89) for Q4, respectively (\( P \) for trend = 0.0025), after adjustment for conventional risk factors (model 3), as compared with the lowest quartile.

DISCUSSION

In the cross-sectional analysis of 10,122 participants from a middle-aged and elderly Chinese population with a mean age of 58.5 years, we observed a strong inverse association between serum Lp(a) concentrations and prevalence of T2D, prediabetes, and insulin resistance, independent of traditional metabolic risk factors.

The inverse association between serum Lp(a) concentrations and prevalence of T2D observed in our study is consistent with the findings in recent population studies such as WHS and CCHS (10). In WHS, during a 13-year follow-up, 1,670 participants developed diabetes among 26,746 healthy US women recruited at baseline. In their adjusted analyses, the hazard ratios and 95% CIs for

TABLE 3. The risk of T2D, prediabetes, insulin resistance, and hyperinsulinemia in relation to quartiles of serum Lp(a) levels

| Trait                        | Quartile 1 (0–8.9 mg/dl) | Quartile 2 (9.0–17.9 mg/dl) | Quartile 3 (18.0–28.9 mg/dl) | Quartile 4 (≥29.0 mg/dl) | P for trend |
|------------------------------|---------------------------|-----------------------------|-----------------------------|-------------------------|------------|
| T2D                          |                           |                             |                             |                         |            |
| n, cases/participants         | 507/2,431                 | 443/2,498                   | 420/2,495                   | 405/2,698               |            |
| Model 1                       | 1.00                      | 0.82 (0.71–0.94)            | 0.77 (0.67–0.89)            | 0.67 (0.58–0.77)        | <0.0001    |
| Model 2                       | 1.00                      | 0.83 (0.71–0.97)            | 0.83 (0.71–0.97)            | 0.73 (0.62–0.85)        | 0.0002     |
| Model 3                       | 1.00                      | 0.86 (0.73–1.01)            | 0.88 (0.75–1.04)            | 0.76 (0.64–0.89)        | 0.0002     |
| Prediabetes                  |                           |                             |                             |                         |            |
| n, cases/participants         | 602/1,924                 | 572/2,055                   | 558/2,075                   | 578/2,735               |            |
| Model 1                       | 1.00                      | 0.85 (0.74–0.97)            | 0.81 (0.71–0.93)            | 0.78 (0.68–0.89)        | 0.0002     |
| Model 2                       | 1.00                      | 0.83 (0.72–0.96)            | 0.78 (0.67–0.90)            | 0.74 (0.64–0.86)        | <0.0001    |
| Model 3                       | 1.00                      | 0.85 (0.74–0.99)            | 0.81 (0.70–0.94)            | 0.75 (0.65–0.87)        | 0.0002     |
| Insulin resistance            |                           |                             |                             |                         |            |
| n, cases/participants         | 768/2,431                 | 617/2,498                   | 549/2,495                   | 527/2,698               |            |
| Model 1                       | 1.00                      | 0.71 (0.63–0.81)            | 0.61 (0.54–0.69)            | 0.53 (0.46–0.60)        | <0.0001    |
| Model 2                       | 1.00                      | 0.74 (0.64–0.86)            | 0.64 (0.55–0.74)            | 0.55 (0.47–0.64)        | <0.0001    |
| Model 3                       | 1.00                      | 0.80 (0.69–0.93)            | 0.73 (0.63–0.86)            | 0.62 (0.53–0.73)        | <0.0001    |
| Hyperinsulinemia              |                           |                             |                             |                         |            |
| n, cases/participants         | 770/2,431                 | 649/2,498                   | 565/2,495                   | 545/2,698               |            |
| Model 1                       | 1.00                      | 0.76 (0.67–0.86)            | 0.65 (0.56–0.72)            | 0.56 (0.48–0.62)        | <0.0001    |
| Model 2                       | 1.00                      | 0.80 (0.69–0.92)            | 0.65 (0.56–0.75)            | 0.58 (0.50–0.67)        | <0.0001    |
| Model 3                       | 1.00                      | 0.86 (0.74–1.00)            | 0.76 (0.65–0.89)            | 0.67 (0.57–0.78)        | <0.0001    |

Data are ORs, 95% CI. \( P \) values were calculated using logistic regression analyses. Model 1, unadjusted. Model 2, adjusted for age, sex, BMI, WC, SBP, DBP, family history of diabetes, drinking status, smoking status, physical activity, and educational level. Model 3, further adjusted for TC, TG, HDL-C, LDL-C, apoA-I, and apoB.
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quartiles 2–5 versus quintile 1 were 0.87 (0.75–1.01), 0.80 (0.68–0.93), 0.88 (0.76–1.02), and 0.78 (0.67–0.91) (P for trend = 0.002). This inverse association between serum Lp(a) and T2D was then confirmed in a cross-sectional analysis including 9,652 Danish men and women, in which the adjusted OR was 0.58 (95% CI, 0.42–0.79) for serum Lp(a) quintile 5 versus quintile 1 (10). Moreover, data from 77,901 Danes enrolled in the CCHS and the Copenhagen General Population Study (16) also showed that low concentrations of Lp(a) in plasma were associated with risk of T2D, with adjusted ORs of 1.26 (95% CI, 1.09–1.45), 1.17 (95% CI, 1.01–1.36), 1.04 (95% CI, 0.90–1.21), and 1.05 (95% CI, 0.90–1.22), respectively, for Lp(a) quintiles 1–4, compared with quintile 5 (12). Notably, the prevalence of T2D in our study was much higher than that in CCHS and WHS. This may partly be due to the usage of OGTT and antidiabetic agents to detect patients with diabetes, which provided a higher sensitivity.

Moreover, present evidence showed that some antidiabetic drugs, such as metformin (19), troglitazone (20), and insulin (21), might increase the concentrations of serum Lp(a), although findings from studies are inconsistent (22). Meanwhile, among patients with T2D, if glucose levels are normalized after long-term glycaemic control, the serum Lp(a) levels were not significantly changed compared without hypoglycemic treatment (23, 24). In our present study, among 1,775 T2D patients, 46.5% were previously diagnosed diabetes, among which 87.5% were on antidiabetic agents. After we excluded those with hypoglycemic medications, the results were not appreciably changed, with an OR of 0.69 (95% CI, 0.57–0.85) in a comparison of participants in the top quartile versus those in the bottom quartile of the serum Lp(a) distribution in adjusted model. Additionally, when we adjusted the usage of antidiabetic medications, the result was also consistent with our main results [adjusted OR 0.69 (95% CI 0.57–0.85)]. These findings showed no evident effect of hypoglycemic drugs on serum Lp(a) concentrations.

In addition, a possible explanation for this finding could be a survival bias: because both serum Lp(a) and diabetes increase the risk of CVD, in individuals with both risk factors mortality rates might be increased at younger ages. Then the proportion of subjects with low concentrations of Lp(a) among older survivors with diabetes would increase. However, this is not likely to happen. A previous study showed that in younger and older patients with diabetes, Lp(a) levels were both lower compared with age-matched healthy subjects (25). In our analyses, among those with self-reported CVD, the inverse association still existed, with an OR of 0.75 (95% CI, 0.63–0.89) for prevalent T2D after adjustment for conventional risk factors (model 3) for Q4, as compared with the lowest quartile of serum Lp(a) concentrations. Furthermore, after excluding those with a history of self-reported CVD (n = 598), the ORs for prevalent T2D were 0.75 (95% CI, 0.63–0.89) for Q4, in multiajusted model, as compared with the lowest quartile of serum Lp(a) concentrations.

The mechanism of this inverse relationship between serum Lp(a) and T2D, as well as insulin resistance, is not well elucidated. The available evidence at present suggests that hormones have pronounced effects on serum Lp(a) levels (26). For example, testosterone (27) and insulin-like growth factor 1 (28) may lower serum Lp(a) concentrations; meanwhile, growth hormone might stimulate it (29). Then these hormonal regulations may be involved in the glucose and lipid metabolism together. Regrettably, we did not have a specific measure of these hormones. Therefore, these potential effects of hormones cannot be analyzed in our study. Second, bile acids had an Lp(a)-lowering effect via downregulated LPA gene expression (30). Meanwhile, fibroblast growth factor 19 (FGF19) was reportedly decreased in Chinese subjects with impaired fasting plasma glucose and inversely associated with fasting glucose levels (31). Therefore, one possible explanation might be that low levels of FGF19 in diabetic patients and the consequently high levels of bile acids may together influence the expression of LPA negatively. Furthermore, a high level of insulin could decrease apo(a) synthesis by suppression of mRNA levels in cynomolgus monkey hepatocytes (32), which may account for lower concentrations of serum Lp(a) found in T2D.

To our knowledge, this is the first study exploring the relationship between serum Lp(a) and T2D, prediabetes, insulin resistance, and with hyperinsulinemia at the same time in a large Chinese population. Serum Lp(a) concentrations are reported to be genetically determined (2) and different in various races (33). Although related large population studies have been performed in individuals of European or American origin, it is worth exploring this subject in Asians. The large sample size of the middle-aged and elderly Chinese population in our study provided a persuasive statistical power to detect the inverse association. Beyond that, the use of OGTT for unbiased ascertainment of T2D in our study avoided the diagnostic bias that hormones have pronounced effects on serum Lp(a) levels (26). For example, testosterone (27) and insulin-like growth factor 1 (28) may lower serum Lp(a) concentrations; meanwhile, growth hormone might stimulate it (29). Then these hormonal regulations may be involved in the glucose and lipid metabolism together. Regrettably, we did not have a specific measure of these hormones. Therefore, these potential effects of hormones cannot be analyzed in our study. Second, bile acids had an Lp(a)-lowering effect via downregulated LPA gene expression (30). Meanwhile, fibroblast growth factor 19 (FGF19) was reportedly decreased in Chinese subjects with impaired fasting plasma glucose and inversely associated with fasting glucose levels (31). Therefore, one possible explanation might be that low levels of FGF19 in diabetic patients and the consequently high levels of bile acids may together influence the expression of LPA negatively. Furthermore, a high level of insulin could decrease apo(a) synthesis by suppression of mRNA levels in cynomolgus monkey hepatocytes (32), which may account for lower concentrations of serum Lp(a) found in T2D.

Our study has some limitations. First, we found that in our study (supplementary Table 6) serum Lp(a) was extensively associated with age, WC, SBP, insulin resistance, blood glucose, and other metabolic traits. Given that our study is an observational cross-sectional investigation in nature, therefore, we were unable to reach a causal association between serum Lp(a) levels and the risk of T2D and related metabolic traits. Second, we did not perform LPA genotyping studies to undertake the Mendelian randomization analyses necessary for establishing the causality between serum Lp(a) levels and T2D. Third, the participants in our study are from a middle-aged and elderly Chinese population. Caution should be used in generalizing the findings to other age and ethnicity groups. Fourth, we directly measured LDL-C by a surfactant active agent, which inevitably included Lp(a)-C. This might have contributed some bias to our LDL-C levels. Finally, in the measurement of serum Lp(a), the exact epitope against which the monoclonal antibody used in our study was directed was not identified. However, given the high agreement of serum Lp(a) levels detected using our antibody and another commonly used one, as well as the large sample...
size in our study, it should not appreciably influence the main results. Studies on the cellular or molecular level are warranted to explore the effect of Lp(a) on T2D.

In conclusion, our findings indicated an inverse association between serum Lp(a) concentrations and the prevalence of T2D, prediabetes, insulin resistance, and hyperinsulinemia in a middle-aged and elderly Chinese population, with a mean age of 58.5 years. This inverse association that we have uncovered provides evidence for better understanding of Lp(a) in patients with diabetes. It is important that more prospective studies and Mendelian randomization analyses are warranted and would shed light on the roles of Lp(a) in T2D pathogenesis.

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