Higher Levels of Lipoprotein-Associated Phospholipase A2 is associated with Increased Prevalence of Cognitive Impairment: the APAC Study

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Lipoprotein-associated phospholipase A\textsubscript{2} (Lp-PLA\textsubscript{2}) is a unique circulating phospholipase with inflammatory and oxidative activities and the limited data regarding the relationship between Lp-PLA\textsubscript{2} and cognitive impairment are conflicted. We conducted a cross-sectional study including 1,374 Chinese adults recruited from 2010 to 2011, aiming to evaluate the relationship between Lp-PLA\textsubscript{2} levels and the prevalence of cognitive impairment in a Chinese community-based population. Participants underwent standardized evaluation. Serum Lp-PLA\textsubscript{2} mass was measured by ELISA. Cognition status was evaluated via the Mini-Mental Status Exam (MMSE) and cognitive impairment was identified as MMSE < 24. Multivariable logistic regression models were used to assess the associations of Lp-PLA\textsubscript{2} mass with cognitive impairment. Lp-PLA\textsubscript{2} mass was significantly associated with the prevalence of cognitive impairment after adjusting for other potential confounding factors (compared with the first quartile, adjusted ORs of the second, third, and fourth quartile were 2.058 (95\% CI, 0.876–4.835), 2.834 (95\% CI, 1.255–6.398), and 4.882 (95\% CI, 2.212–10.777), \(p < 0.0001\)). In conclusion, elevated level of Lp-PLA\textsubscript{2} mass was independently associated with the prevalence of cognitive impairment in Chinese adults.

Cognitive impairment has become a burgeoning public health problem and is predicted to increase dramatically worldwide in the coming decades due to ageing population. This brings a compelling need for the discovery, validation, and standardization of screening instruments that can be used in diagnosis of pre-clinical and symptomatic stages of the disease.

Lipoprotein-associated phospholipase A\textsubscript{2} (Lp-PLA\textsubscript{2}), also known as platelet activating factor acetylhydrolase (PAF-AH), is a unique circulating phospholipase that primarily bound to the low-density lipoprotein (approximately 80\%) with inflammatory and oxidative activities associated with cardiovascular disease and cerebrovascular events independent of traditional risk factors\textsuperscript{1–3}. Since cardiovascular and cerebrovascular risk factors may increase the risk of cognitive impairment, Lp-PLA\textsubscript{2} may also be related with cognitive impairment. The limited data regarding the relationship between Lp-PLA\textsubscript{2} mass or activity and cognitive impairment is conflicted\textsuperscript{4–6}.

The objective of the current study was to evaluate the relationship of serum Lp-PLA\textsubscript{2} mass with the prevalence of cognitive impairment in a Chinese community-based population. We hypothesized that the population with higher levels of Lp-PLA\textsubscript{2} mass would have a higher prevalence of cognitive impairment.

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mass index; FBG (p = 2.219–10.420), respectively, p value for trend third, and fourth quartile were 2.044 (95% CI, 0.883–4.731), 2.940 (95% CI, 1.323–6.534), and 4.808 (95% CI, <0.0001).

Blood glucose, alanine transaminase, and C-reactive protein did not affect the significance, with ORs for the second, third, and fourth quartile 2.058 (95% CI, 0.876–4.835), 2.834 (95% CI, 1.255–6.398), and 4.882 (95% CI, <0.0001).

Working environment with dust, cigarette smoking, past history of hyperlipidemia, hypertension, anti-hypertensive drugs use, diabetes, anti-diabetic drugs use, physical inactivity, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, total cholesterol, body mass index, fasting blood glucose, alanine transaminase, and C-reactive protein cholesterol, and homocysteine among the different quartiles. These variables, with the exception of age and HDL, tended to be decreased in the higher Lp-PLA2 quartile groups, whereas age and HDL levels were higher in the lower Lp-PLA2 quartile groups. We found that there were significant differences in age, body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, total cholesterol, body mass index, fasting blood glucose, alanine transaminase, and C-reactive protein.

Table 1. Baseline characteristics of participants according to Lp-PLA2 quartiles. Data are expressed as mean ± SD or n (%). Abbreviation: MMSE = Mini-Mental Status Exam; LDL = low-density lipoprotein cholesterol; HDL = high-density lipoprotein cholesterol; TG = triglycerides; TC = total cholesterol; BMI = body mass index; FBG = fasting blood glucose; ALT = alanine transaminase; CRP = C-reactive protein.

Table 2. Multivariate analysis of associations between Lp-PLA2 mass and cognitive impairment. A total of 1,374 subjects, 71.8% men and 28.2% women, were analyzed. The baseline characteristics of participants according to quartiles of Lp-PLA2 mass are presented in Table 1. The mean value of Lp-PLA2 mass from the lowest quartile to the highest quartile was 127.66 ± 2.67 ng/ml, 135.58 ± 2.45 ng/ml, 147.06 ± 4.71 ng/ml, and 253.50 ± 202.31 ng/ml, respectively. We found that there were significant differences in age, body mass index, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglycerides, white blood cell count, alanine transaminase, and homocysteine among the different quartiles. These variables, with an exception of age and HDL, tended to be decreased in the higher Lp-PLA2 quartile groups, whereas age and HDL levels were higher in the higher Lp-PLA2 quartile groups. Also, there were significant differences in the proportion of participants who have working environment with dust, cigarette smoking, past history of hyperlipidemia, hypertension, anti-hypertensive drug use, anti-diabetic drug use among the different quartiles.

Higher Lp-PLA2 mass is associated with the increased prevalence of cognitive impairment independent of other potential confounding factors. Cognitive impairment, defined as MMSE score < 24 points, were identified in 107 participants of the total 1,374 participants. Cognitive impairment prevalence from the lowest quartile to the highest quartile of Lp-PLA2 mass were 2.6%, 5.2%, 7.8% and 15.5%, respectively (p < 0.0001). Compared with the first quartile, age-, sex- and education adjusted odd ratios (OR) for the second, third, and fourth quartile were 2.044 (95% CI, 0.883–4.731), 2.940 (95% CI, 1.323–6.534), and 4.808 (95% CI, 2.199–10.420), respectively, p value for trend < 0.0001 (Table 2). Additional adjustments for age, sex, education, working environment with dust, current smoking, current alcohol use, hyperlipidemia, lipid-lowering drugs use, hypertension, anti-hypertensive drugs use, diabetes, anti-diabetic drugs use, physical inactivity, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, total cholesterol, body mass index, fasting blood glucose, alanine transaminase, and C-reactive protein did not affect the significance, with ORs for the second, third, and fourth quartile 2.058 (95% CI, 0.876–4.835), 2.834 (95% CI, 1.255–6.398), and 4.882 (95% CI,
implicated in dementia such as amyloid and tau. Another possible way may be by increasing vascular damage and promoting neural degeneration with loss of cognitive reserve. For its pro-inflammatory role and close association with lipoproteins has been shown to be associated with the presence of advanced lesions leading to plaque instability and clinical events. Besides a few studies, most of the evidence supports inflammation as an important factor in the development of cognitive impairment and supports the idea that inflammatory biomarkers might be useful to help identify the people at higher risk of cognitive impairment. Evidence of an association between Lp-PLA2 and cognitive impairment would back up the hypothesis that inflammation is involved in the pathogenesis of cognitive deficit and decline. Lp-PLA2, may act in the pathogenesis of cognitive impairment by directly and independently affecting the brain or key molecules that are susceptible to lipid peroxidation. It is possible that Lp-PLA2 exhibits a dual action which might provide an opportunity for manipulation of Lp-PLA2 modulation, such as darapladib, an inhibitor of Lp-PLA2. In addition, chronic, low-level inflammation can occur throughout the body in response to various factors, among them a poor diet or exposure to mold and toxins. Nevertheless, some dietary changes, such as including "healthy fats" such as omega-3, may offset the damage from oxidative stress and inflammation and increase chances of higher levels of Lp-PLA2 were almost twice as likely to have Alzheimer's disease (AD) compared with subjects in the highest compared to lowest quartile. In addition, a recent case-control study showed that subjects with increased prevalence of cognitive impairment. The associations found here may support the potential value of inflammation as an important factor in the development of cognitive impairment and supplement the evidence supports inflammation as an important factor in the development of cognitive impairment and supports the idea that inflammatory markers might be useful to help identify the people at higher risk of cognitive impairment. Possible threshold effect is present, although a standardized cut-point for Lp-PLA2 levels below the median. Our results supported the idea that higher Lp-PLA2 is associated with increased prevalence of cognitive impairment. The associations found here may support the potential value of Lp-PLA2 in the development and treatment of cognitive decline. However, the analysis from the Framingham Study failed to replicate these association as Lp-PLA2 mass was not found to be associated with an increased risk of dementia or Alzheimer's disease. The authors proposed that this lack of association could be because of a relatively small number of incident AD cases in the sample and that the participants with dementia were more severe and deceased at follow-up. Also, the lower level of inflammation in Framingham study participants may have been a factor in the lack of associations should there be a threshold in Lp-PLA2 mass for detecting associations with dementia. Another cross-sectional study also found no significant difference in the Lp-PLA2 activity between cognitive impairment group and controls. Though the mean Lp-PLA2 activity observed in their control group (195.4 nmol/min/ml, SD 41.9) was higher than anticipated, the participants with dementia were more severe and deceased at follow-up. Also, the lower level of inflammation in Framingham study participants may have been a factor in the lack of associations should there be a threshold in Lp-PLA2 mass for detecting associations with dementia. Another cross-sectional study also found no significant difference in the Lp-PLA2 activity between cognitive impairment group and controls. Though the mean Lp-PLA2 activity observed in their control group (195.4 nmol/min/ml, SD 41.9) was higher than anticipated, based on levels observed in the Framingham Offspring study (144 nmol/min/ml, SD 36) and the Dallas Heart Study (146 nmol/min/ml, SD 40) possibly a threshold effect is present, although a standardized cut-point for Lp-PLA2 levels is still unclear.

Elevated levels of inflammatory biomarkers such as IL-6 and C-reactive protein were found in plasma of the patients with AD years before the clinical dementia syndrome developed. Besides a few studies, most of the evidence supports inflammation as an important factor in the development of cognitive impairment and supports the idea that inflammatory markers might be useful to help identify the people at higher risk of cognitive impairment. Evidence of an association between Lp-PLA2 and cognitive impairment would back up the hypothesis that inflammation is involved in the pathogenesis of cognitive deficit and decline. Lp-PLA2, may act in the pathogenesis of cognitive impairment by directly and independently affecting the brain or key molecules that are susceptible to lipid peroxidation. It is possible that Lp-PLA2 exhibits a dual action which might provide an opportunity for manipulation of Lp-PLA2 modulation, such as darapladib, an inhibitor of Lp-PLA2. In addition, a chronic, low-level inflammation can occur throughout the body in response to various factors, among them a poor diet or exposure to mold and toxins. Nevertheless, some dietary changes, such as including "healthy fats" such as omega-3, may offset the damage from oxidative stress and inflammation and increase chances of higher levels of Lp-PLA2 mass were associated with increased prevalence of cognitive impairment (Fig. 1).
maintaining a healthy brain. Whether there is any correlation between increased Lp-PLA2 levels and severity of cognitive impairment can also be further explored to better explain the association. However, this was not feasible in the current study due to the small numbers in each of the severity categories of cognitive impairment. Such relation and its underlying mechanism need to be further studied. To establish the mechanistic links between a single risk factor such as inflammation marker (e.g. Lp-PLA2) and cognitive impairment is difficult. The development of cognitive impairment is complex and complicated by the fact that several diseases often co-exist and share some common risk factors including Lp-PLA2. A better approach to mechanism understanding could be formulating the hypothesis on a “metabolic-cognitive syndrome” to explain the complex relationship between metabolic disorders (i.e. diabetes, hypertension, atherosclerosis, inflammation and other risk factors) and cognitive disturbances and the boundaries between normal and pathological condition.

To our knowledge, no published articles have assessed this association in Chinese population to date. As cognitive impairment is a major public health problem worldwide, especially to the growing aging population in China, understanding the role of Lp-PLA2 in the development of cognitive impairment may be helpful for the prevention of this disease and its consequences. However, the following limitations should be noted. First, the MMSE was employed to assess cognitive status in this study and this score does not always reflect the cognitive function exactly, as it is sometimes influenced by the subjects’ education level. Although a multitude of potential confounders including education level were considered to minimize their impacts. Ceiling effects may also...
that clinical conditions (e.g. liver dysfunction), drugs (e.g. antiplatelet/antithrombotic drugs) and genotype may
generalizable to other populations. We cannot totally exclude the possibility of selection bias in that relative healthy
individuals may be more likely to refuse to participate in the free medication examination. It should also be noted
that vascular abnormalities in Chinese adults\(^2^7,2^8\). This community-based study cohort was derived from a previously
described population of the Kailuan Study\(^2^7\), which included a total of 101,510 participants (81,110 men) of the
Kailuan community, in Tangshan city, a large modern city Southeast of Beijing. From June 2010 to June 2011, a
sample of 7000 subjects older than 40 years was randomly selected from the Kailuan cohort, using a stratified
random sampling method by age and gender based on the data of the Chinese National Census from 2010. The
sample size was calculated based on detection of 7% of the event rate with 0.7% precision (\(\alpha = 0.05\)). The response
rate was assumed to be >80%. A total of 5,852 subjects signed consent to participate in the APAC study and 5,816
people eventually completed the baseline data collection. Among these 5,816 individuals, 576 subjects were not
included because of not meeting the inclusion criteria as following: (1) no history of stroke, transient ischemic
attack, and coronary disease at baseline as assessed by a validated questionnaire; and (2) absence of neurologic
deficits indicating previous stroke as examined by experienced physicians. At last, a total of 5,440 participants
were included in the APAC Study. The detailed recruitment protocol has previously been reported elsewhere\(^2^9\).

This is a further and in-depth analysis of the APAC study. We excluded 151 participants who died or had a
stroke from recruitment to 2012, and 3,915 participants who had incomplete data on MMSE or Lp-PLA\(_2\) data,
leaving 987 men and 387 women (Fig. 2) available for the analyses. All participants provided written informed
consent and informed of abnormal findings and recommended treatments. The study protocol conformed to the
ethical guidelines of the 1975 Declaration of Helsinki. The study was also approved by the Ethics Committee of
the Kailuan General Hospital and Beijing Tiantan Hospital.

Measurement of Lp-PLA\(_2\). Blood samples were collected from the antecubital veins of participants before
9:00 AM after an overnight fast. Each sample was collected into two tubes, EDTA (Ethylene Diamine Tetraacetic
Acid) tube (to obtain plasma) and serum separator tube (to obtain serum). The samples were centrifuged 10
min by 3000 r/min (serum separator tube was to clot for two hours at room temperature before centrifuge),
plasma and serum were both collected in separate EP tubes. Samples were frozen as rapidly as possible to –80°C
for storage until laboratory determinations were performed. Lp-PLA\(_2\) concentration in the serum (mass) was
measured using enzyme linked immunosorbent assay (CUSABIO company, Human lipoprotein phospholipase
A2 (Lp-PLA\(_2\)) enzyme immunoassay kit, Catalog number CSB-E08319h). The intra-assay and inter-assay coeffi-
cients of variation are 8% and <10%. In order to reduce inter-assay error and measurement error, we assessed
the serum levels of Lp-PLA\(_2\), mass by professional technicians using enzyme linked immunosorbent assay
(CUSABIO company, Human lipoprotein phospholipase A2 (Lp-PLA\(_2\)) enzyme immunoassay kit, Catalog num-
ber CSB-E08319h) at the same time in Beijing Tiantan Hospital affiliated to Capital Medical University, Beijing,
China. Experimental procedures and results of the judging were made according to the kit instructions strictly.

Ascertainment of Cognitive Impairment. The Mini-Mental Status Exam (MMSE)\(^3^0\) was used as a cog-
nitive screener which contain 18 items that assesses orientation, memory, attention, ability to follow commands,
and copying a geometric figure. Scores range from 0 to 30 points, with a lower score reflecting greater cognitive
impairment. Specially trained physicians or assistants tested all 1,374 participants who met the inclusion criteria
as following: (1) no history of stroke, transient ischemic attack, and coronary disease at baseline as assessed by a
validated questionnaire; and (2) absence of neurologic deficits indicating previous stroke as examined by
experienced physicians. The detailed recruitment protocol has previously been reported elsewhere\(^2^9\).

In conclusion, elevation of Lp-PLA\(_2\) mass levels was significantly associated with higher prevalence of cogni-
tive impairment independent of several vascular, inflammatory and other risk factors.
Assessment of demographic variables and potential covariates. A standardized questionnaire was used for collecting information on subjects’ demographic and socioeconomic data, family and past history. Attained level of education was grouped into those with at most primary education, those with junior education or vocational training, and those with senior vocational or academic education.

All subjects were measured by standing in light clothing without shoes and hats. Height was measured to the nearest 0.1 cm using a portable stadiometer and weight was measured to the nearest 0.1 kg using calibrated platform scales. Then, body mass index (BMI) was calculated as weight (kg)/height (m)².

Information on smoking, alcohol intake and physical activity and past history was collected via questionnaires. History of diseases mainly included hypertension, diabetes mellitus, and hyperlipidemia. Hypertension was defined as presence of a history of hypertension, or using antihypertensive medication, or a SBP ≥140 mm Hg, or a DBP ≥90 mm Hg. Diabetes mellitus was defined as a self-reported history, currently treated with insulin or oral hypoglycemic agents, or fasting blood glucose level ≥7.0 mmol/L (126 mg/dl). Dyslipidemia was defined as a self-reported history, current use of cholesterol lowering medicine, or total cholesterol level ≥5.7 mmol/L (220 mg/dl) or triglyceride ≥1.7 mmol/L (150 mg/dl) or low-density lipoprotein cholesterol (LDL-C) ≥130 mg/dl.

Methods for collecting the fasting blood specimens, measuring glucose and lipids, and the definitions of other vascular risk factor covariates in the APAC study have been described previously34,35.

Statistical Analysis. The participants were classified into 4 groups according to the quartile of Lp-PLA₂ mass. In addition, medians and proportions of potential risk factors for cognitive impairment among these 4 groups were calculated. Continuous variables were presented as mean ± standard deviation and compared using Kraskal-Wallis test. Categorical variables were presented as frequencies (percentage) and compared using the Chi-squared test. Logistic regression was used to evaluate the relationship between Lp-PLA₂ mass and cognitive impairment (MMSE < 24) by calculating the odds ratio (OR) and 95% confidence interval (CI). The possible confounders such as age, sex, education, working environment with dust, current smoking, current alcohol use, hyperlipidemia, lipid-lowering drugs use, hypertension, anti-hypertensive drugs use, diabetes, anti-diabetic drugs use, physical inactivity, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, total cholesterol, body mass index, fasting blood glucose, alanine transaminase, and C-reactive protein.
were adjusted in the statistical analysis. Trend test was performed to examine whether there was a dose-response relationship between Lp-PLA2 levels and cognitive impairment. Statistical analysis was performed using SAS software, version 9.3 (SAS Institute Inc., Cary, NC, USA). All CIs were estimated at the 95% level and significance was set at a P value of <0.05 (2-sided).

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Author Contributions
R.J. and S.C. interpreted the data and drafted the manuscript. X.Z. and S.W. conceived and designed the research. A.W., Y.S. and S.C. acquired the data and analyzed the data. J.W. made critical revision of the manuscript. All authors revised the manuscripts. R.J. and S.C. share the first authorship.

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