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# Inverse association between serum lipoprotein(a) and cerebral hemorrhage in the Japanese population

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ABSTRACT

*Introduction:* Although lipoprotein(a) (Lp(a)) is involved in cardiometabolic disease processes, the association between serum Lp(a) and stroke and/or its subtypes has not yet been elucidated among Japanese people. This study investigated the association between Lp(a) and the incidence of stroke and/or its subtypes in the general Japanese population.
*Materials and Methods:* This population-based prospective cohort study included 10,494 community-dwelling participants (4,030 males/6,464 females). The incidence of stroke and its subtypes was the primary outcome. The subjects were divided into tertiles based on their Lp(a) levels, and the risk of all stroke and stroke subtypes was examined using Cox's proportional hazard model.
*Results:* A total of 393 subjects (199 males and 194 females) with stroke were identified during a follow-up duration of 10.7 years. The multivariate-adjusted hazard ratios for all stroke events were 0.55 (95% confidence interval: 0.38-0.81) and 0.69 (0.49-0.99) in the 2nd (9–19 mg/dl) and 3rd tertiles (≥20 mg/dl) of Lp(a) in reference to the 1st tertile (<9 mg/dl) in males, and 0.85 (0.59–1.24) and 0.76 (0.52–1.11) in 2nd (10–22 mg/dl) and 3rd tertiles (≥23 mg/dl) of Lp(a) in reference to the 1st tertile (<10 mg/dl) in females. The multivariate-adjusted hazard ratios for cerebral hemorrhage were 0.26 (0.10–0.67) and 0.34 (0.15–0.76) in the 2nd and 3rd tertiles of Lp(a) in reference to the 1st tertile in males, and were 0.48 (0.23–1.04) and 0.44 (0.21–0.96) in the 2nd and 3rd tertiles of Lp(a) in females.
*Conclusions:* Lp(a) was associated with the incidence of cerebral hemorrhage in the general Japanese population, particularly among males, while a similar trend was seen among females. A low Lp(a) level may be a marker of the risk of cerebral hemorrhage in this population.



## Introduction

Lipoprotein(a) (Lp(a)) is a unique lipoprotein particle consisting of a cholesterol-rich low-density lipoprotein (LDL) bound to apolipoprotein(a) (apo(a)) by a disulfide bridge [1]. High circulating Lp(a) levels are thought to be associated with the development of cardiovascular disease, via 1) intimal deposition of cholesterol of Lp(a), 2) the inhibition of thrombolysis and fibrin clearance because of competition between apo(a) (which has homology with plasminogen) with plasminogen for plasminogen receptors on vascular cells, or both [2]. However, the detailed mechanism(s) linking Lp(a) with atherogenesis has not yet been completely characterized [3].

Stroke is a health problem with a high prevalence in aging societies, including Japanese communities [4], which can severely impair the quality of life [5]. It is important to elucidate the pathophysiology of stroke. Therefore, many studies have explored the relationship between stroke and serum Lp(a).

A recent review that summarized prospective studies published prior to March 2009, showed that Lp(a) is a possible predictor of ischemic stroke (the adjusted risk ratio: 1.10 [95% confidential interval [CI]: 1.02–1.18]) [6]. However, conflicting results regarding the association between Lp(a) and stroke have been presented even after this review was published [6], and their association is still debated. One prospective study has shown no significant association between Lp(a) and stroke [7] and several, though not all [8,9], case-control studies have shown

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higher Lp(a) levels in patients with ischemic stroke in comparison to controls [10–14].

In addition, while people with different types of stroke have differing clinical characteristics and prognostic outcomes [5], no prospective studies have so far focused on the association between Lp(a) and stroke subtypes, including cerebral hemorrhage. The review of the Emerging Risk Factors Collaboration only described no significant association between Lp(a) and hemorrhagic stroke (the adjusted risk ratio: 1.06 [95% CI: 0.90–1.26]) [6].

Circulating Lp(a) levels also vary widely by ethnicity [15–17]. This variation of Lp(a) may affect the results of the association between Lp(a) and stroke across ethnic groups. One prospective study suggested Lp(a) as a possible predictor of stroke in the Japanese people, but this result was obtained from Japanese hypercholesterolemic patients enrolled in a clinical trial, a special population that cannot always permit the generalization of the findings [18]. Furthermore, the influence of Lp(a) on stroke subtypes has not yet been characterized among the general Japanese population. Given these backgrounds, the objective of the present study was to investigate the association between the serum Lp(a) levels and the risk of stroke and/or its subtypes in a general Japanese population.

## Materials and Methods

### *Subjects*

The present study used the data of the Jichi Medical School (JMS) cohort study, a population-based prospective cohort study, with baseline data obtained between April 1992 and July 1995 in 12 communities in Japan. The details of the JMS cohort study have been described elsewhere [19]. There were 12,490 participants (4,911 males and 7,579 females; age, 19–93 years) in the JMS cohort study. The follow-up rate of this cohort population was 99.9% (only seven subjects were lost to follow-up). A total of 10,494 subjects (4,030 males and 6,464 females) were eligible for the present study, after excluding subjects without any data regarding serum Lp(a) and those with a past history of stroke.

### *Follow-up and Diagnosis of Stroke*

A routine mass screening examination system for cardiovascular disease was held in Japan by the Health and Medical Law Service in Japan and the system was utilized to collect the baseline data of the cohort study [19]. Most subjects were followed-up in repeated routine mass examinations every year. Subjects who did not come to the repeated examinations were directly contacted by mail and/or phone. All subjects were asked whether or not they had a history of new-onset stroke after participating in this cohort study, and those with a history of stroke were required to provide the information of hospital to which they were referred. The medical records at hospitals were checked to determine whether these subjects had been diagnosed and/or hospitalized for stroke. Public health nurses also visited these subjects to supplement information. The forms specific for recording the information of stroke were filled out by the investigators of this study, and computed tomography films and/or magnetic resonance imaging films for diagnosing a stroke were obtained from hospitals.

### *Diagnosis of Stroke*

The diagnosis of stroke, including transient ischemic attack or mini-stroke, was carried out independently by a diagnosis committee, of one radiologist, one neurologist and two cardiologists. The diagnosis was determined by the presence of a focal and nonconvulsive neurological deficit lasting for 24 hours and longer with a clear onset. Neuroimaging, such as computed tomography and/or magnetic resonance imaging, was used for 98% of all stroke cases, while only 2% of all stroke cases were diagnosed mainly based on the detailed information of the medical records at hospitals and by public health nurses. Stroke was classified into major subtypes according to the criteria of the National Institute of Neurological Disorder and Stroke [20].

### *Laboratory Examination*

The systolic blood pressure (SBP) and diastolic blood pressure were measured using an automated sphygmomanometer (BP203RV-II; Nippon Colin Co. Ltd., Komaki, Japan) placed on the right arm of a seated subject who had rested in the sitting position for 5 minutes before the measurement. The body mass index (BMI) was calculated as weight (kg)/height (m)$^2$. The serum total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) levels were measured by enzymatic methods (Wako Co. Ltd., Osaka, Japan). Blood glucose was measured by an enzymatic method (Kanto Chemistry Co. Ltd., Tokyo, Japan). The serum Lp(a) levels were measured using an enzyme-linked immunosorbent assay kit (Biopool Co. Ltd., Uppsala, Sweden; intra- and inter-assay coefficients of variation <5%). The minimum detectable Lp(a) level was 1 mg/dl and if such levels are obtained, the undetectable Lp(a) value was recorded as 0.5 mg/dl. In addition, the medical history and lifestyle-related factors (smoking status: current-, ex- and non-smoking; alcohol drinking status: current-, ex- and non-drinking) were obtained by self-reported questionnaires.

### *Statistical Analysis*

Data are expressed as the means ± standard deviation (SD). The distribution of Lp(a) was skewed, and the data are expressed as the geometric means ± SD. Proportional data are expressed as percentages. Unpaired *t*-test for variables, Mann-Whitney U test for Lp(a) and chi-square test for categorical data were used to detect the difference in data between males and females. The crude incidence ratios were expressed as per 1000 person-years. Hazard ratios (HRs) and 95% CI for stroke and its subtypes were calculated using Cox's proportional hazard model with the 1st tertile of Lp(a) levels as a reference. Adjustment for age was used in calculating HRs, and full adjustment for age, smoking status and drinking status, BMI, SBP, TC, HDL-C and blood glucose was also used. These analyses were done using the SAS software package (version 8.2; SAS Institute, Inc., Cary, North Carolina, USA). A p-value $<0.05$ was considered to be significant.

## Results

A total of 393 subjects (199 males and 194 females) with new-onset stroke were identified over a mean follow-up duration of 10.7 years. The baseline characteristics of the cohort subjects are shown in Table 1. Males had significantly higher levels of blood pressure and blood glucose, and significantly a higher prevalence of current smokers and drinkers than females. Females had significantly higher levels of BMI, TC, HDL-C and Lp(a) than males.

The geometric mean Lp(a) level was 12.4 mg/dl in males and 14.6 mg/dl in females, and thus the cut-off levels of Lp(a) were 9 and 20 mg/dl in males and 10 and 23 mg/dl in females in tertiles of Lp(a). Table 2 shows that the crude annual incidence rates of all stroke events were 4.05 per 1,000 person-years in the 1st tertile of Lp(a) levels, 3.14 in the 2nd tertile and 3.46 in the 3rd tertile among all subjects. There was a significantly lower risk of all stroke events in the 2nd and the 3rd tertiles than that in the 1st tertile by an age-adjusted model (2nd tertile; HR: 0.72, 95% CI: 0.56–0.91, 3rd tertile; 0.71, 0.56–0.89) or a fully adjusted model (2nd tertile; HR: 0.74, 95% CI: 0.57–0.96, 3rd tertile; 0.76, 0.58–0.98). A lower risk of all stroke events with increased Lp(a) tertile levels was clearly observed in males (2nd tertile: 0.55, 0.38–0.81, 3rd tertile: 0.70, 0.49–0.99 in a fully adjusted model), while this was similarly but insignificantly