# Serum alkaline phosphatase levels and the risk of new-onset diabetes in hypertensive adults

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# Abstract

**Background:** The association between alkaline phosphatase (ALP) and incident diabetes remains uncertain. Our study aimed to investigate the prospective relation of serum ALP with the risk of new-onset diabetes, and explore possible effect modifiers, in hypertensive adults.

**Methods:** A total 14,393 hypertensive patients with available ALP measurements and without diabetes and liver disease at baseline were included from the China Stroke Primary Prevention Trial (CSPPT). The primary outcome was new-onset diabetes, defined as physician-diagnosed diabetes or use of glucose-lowering drugs during follow-up, or fasting glucose ≥7.0mmol/L at the exit visit. The secondary study outcome was new-onset impaired fasting glucose (IFG), defined as FG <6.1mmol/L at baseline and ≥6.1 but <7.0mmol/L at the exit visit.

**Results:** Over a median of 4.5 years follow-up, 1,549 (10.8%) participants developed diabetes. Overall, there was a positive relation of serum ALP and the risk of new-onset diabetes (per SD increment, adjusted OR, 1.07; 95%CI: 1.01, 1.14) and new-onset IFG (per SD increment, adjusted OR, 1.07; 95%CI: 1.02, 1.14). Moreover, a stronger positive association between baseline ALP (per SD increment) with new-onset diabetes was found in participants with total homocysteine (tHcy) <10μmol/L (adjusted OR, 1.24; 95%CI: 1.10, 1.40 *vs.* ≥10μmol/L: adjusted OR, 1.03; 95%CI: 0.96, 1.10; *P*-interaction=0.007) or FG ≥5.9mmol/L (adjusted OR, 1.16; 95%CI: 1.07, 1.27 *vs.* <5.9mmol/L: adjusted OR, 1.00; 95%CI: 0.93, 1.08; *P*-interaction =0.009)

**Conclusions:** In this non-diabetic, hypertensive population, higher serum ALP was significantly associated with the increased risk of new-onset diabetes, especially in those with lower tHcy or higher FG levels.

**Clinical Trial Registration-URL:** Trial registration: NCT00794885 (clinicaltrials.gov). Retrospectively registered November 20, 2008.


# Background

Diabetes mellitus has been a public issue with increasing prevalence worldwide [1, 2]. The global diabetes prevalence in 2019 is estimated to be 9.3% (463 million people), projected to reach 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 [1]. Diabetes result in many complications, including cardiovascular disease (CVD) and chronic kidney diseases (CKD), amputation and vision problems [3, 4]. The identification of more modifiable risk factors may possibly reduce the huge burden of diabetes and its associated complications by leading to early detection and prevention.

Prior studies have reported that liver function may be associated with diabetes [5, 6]. Alkaline phosphatase (ALP) is a generally accepted clinical marker of hepatic or bone disease [7]. However, only a few previous prospective studies [8–11] have been carried out to evaluate the relation of ALP and incident diabetes, and reported inconsistent results. In addition, although hypertension is one of the important risk factors for diabetes [3, 12, 13], few related studies has been conducted in hypertensive

patients. More importantly, potential modifiers on the association between ALP and incident diabetes have not been comprehensively examined in previous studies.

This study was motivated by the limited and inconclusive evidence regarding the ALP levels and incident diabetes, and a special opportunity to address this question in a large, randomized controlled trial with regular antihypertensive treatments, BP measurements and diabetes status reports. Specifically, using data from China Stroke Primary Prevention Trial (CSPPT) [14], we aimed to investigate the prospective association between serum ALP and new-onset diabetes among hypertensive adults, and to examine possible modifiers on the association.

# Methods

### Study design and participants

The study design, methods and major results of the CSPPT (ClinicalTrials.gov identifier NCT00794885) have been reported elsewhere in detail [14–16]. Briefly, the CSPPT was a multi-community, randomized, double-blind, controlled trial conducted from May 19, 2008 to August 24, 2013 in 32 communities in Anhui and Jiangsu provinces in China. Eligible participants were men and women aged 45–75 years who had hypertension, defined as seated, resting systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg at both the screening and recruitment visit, or who were on anti-hypertensive medication. The major exclusion criteria included history of physician-diagnosed stroke, myocardial infarction (MI), heart failure, post-coronary revascularization, and/or congenital heart disease, and/or current supplementation by folic acid, vitamin B12 or vitamin B6.

In the CSPPT, a total of 20,702 eligible participants were enrolled. Our current study is a post-hoc analysis of the CSPPT, including a total of 14,393 participants with complete major data and who were free of diabetes [physician-diagnosed diabetes or using glucose-lowering drugs or fasting glucose (FG) was < 7.0 mmol/L (126 mg/dL)], as well as without liver disease (self-reported chronic hepatitis, hepatic adipose infiltration, or cirrhosis) at baseline (**Additional file 1: Figure S1**).

### Intervention And Follow-up

Eligible participants were randomized to receive a daily oral dose of one tablet containing 10-mg enalapril and 0.8-mg folic acid (single pill combination, the enalapril-folic acid group) or one tablet containing 10-mg enalapril only (the enalapril-only group).

Participants were scheduled for follow-up every three months. At each follow-up visit, BP was measured; study drug compliance, concomitant medication use, adverse events and possible endpoint events were documented by trained research staff and physicians.

### Laboratory Assessment

Serum fasting ALP, gamma glutamyl transpeptidase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total homocysteine (tHcy), creatinine, lipids and fasting glucose (FG) were

measured with the use of automatic clinical analyzers (Beckman Coulter) at the core laboratory of the National Clinical Research Center for Kidney Disease, Nanfang Hospital, Guangzhou, China. Serum folate at baseline were measured by a commercial lab using a chemiluminescent immunoassay (New Industrial, Shenzhen, China). Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [17].

### Study Outcomes

The primary study outcome was new-onset diabetes, defined as physician-diagnosed diabetes, or use of glucose-lowering drugs during follow-up, or new onset FG ≥ 7.0 mmol/L (126 mg/dL) at the exit visit.

The secondary study outcome was new-onset impaired fasting glucose (IFG), defined as FG < 6.1 mmol/L (110 mg/dL) at baseline and ≥ 6.1 mmol/L but < 7.0 mmol/L at the exit visit. The analysis of new-onset IFG included subjects whose FG < 6.1 mmol/L and without new-onset diabetes during the follow-up.

### Statistical analysis

Baseline characteristics are presented as means ± standard deviations (SDs) or medians [interquartile range (IQR)] for continuous variables and proportions for categorical variables. Statistical significance of differences in baseline characteristics was assessed in accordance with baseline serum ALP quartiles (< 79, 79 to < 96, 96 to < 116, and ≥ 116 IU/L) using ANOVA tests, signed rank tests or chi-square tests, accordingly.

We first explored the association between serum ALP and new-onset diabetes using thin plate regression splines in generalized additive models implemented by the R package *mgcv*. Then multivariable logistic regression models [odds ratio (OR) and 95% confidence interval (CI)] were used to evaluate relation of serum ALP with new-onset diabetes and new-onset IFG, without and with adjustment for age, sex, study center, treatment group, body mass index (BMI), smoking, alcohol drinking, family history of diabetes, SBP, FG, total cholesterol (TC), triglycerides (TG), eGFR, folate, tHcy and the use of antihypertensive drugs at baseline, as well as time-averaged SBP during the treatment period. As additional exploratory analyses, possible modifications on the association between serum ALP and new-onset diabetes were also evaluated by stratified analyses and interaction testing.

A two-tailed $P < 0.05$ was considered statistically significant in all analyses. R software, version 3.6.3 (http://www.R-project.org/) was used to perform all statistical analyses.

## Results

### Study participants and baseline characteristics

In this study, a total of 14,393 participants with complete major data and without diabetes and liver disease at baseline, were included in the final analyses (**Additional file 1: Figure S1**).

Baseline characteristics of participants by baseline ALP quartiles are presented in Table 1. The mean and median serum ALP levels were 100 IU/L (SD, 30.5) and 96 IU/L, respectively. Participants with higher ALP levels were older and more likely to be female; had higher SBP, TG, high-density lipoprotein (HDL) cholesterol, FG, folate levels at baseline and time-averaged on-treatment SBP during the treatment period; lower BMI, DBP, TC, tHcy levels at baseline and time-averaged on-treatment DBP during the treatment period; and lower frequency in use of antihypertensive drugs and antiplatelet drugs at baseline, as wells as lower frequency of current smoking, alcohol drinking and family history of diabetes (Table 1).

Table 1

Characteristics of the study participants by baseline serum alkaline phosphatase (ALP) quartiles*

| Variables | Serum ALP, IU/L | | | | *P* value |
|---|---|---|---|---|---|
| | Q1 (< 79) | Q2 (79–<96) | Q3 (96–<116) | Q4 (≥ 116) | |
| N | 3486 | 3623 | 3577 | 3707 | |
| Age, yr | 58.3 ± 8.1 | 59.7 ± 7.5 | 60.7 ± 7.1 | 61.3 ± 6.6 | < 0.001 |
| Male, No. (%) | 1773 (50.9) | 1609 (44.4) | 1377 (38.5) | 1059 (28.6) | < 0.001 |
| Body mass index, kg/m$^2$ | 25.4 ± 3.6 | 25.1 ± 3.6 | 24.8 ± 3.6 | 24.4 ± 3.7 | < 0.001 |
| Current smoking, No. (%) | 963 (27.6) | 938 (25.9) | 810 (22.6) | 664 (17.9) | < 0.001 |
| Current drinking, No. (%) | 1143 (32.8) | 949 (26.2) | 778 (21.8) | 567 (15.3) | < 0.001 |
| Family history of diabetes, No. (%) | 151 (4.3) | 145 (4.0) | 125 (3.5) | 116 (3.1) | 0.036 |
| Enalapril group, No. (%) | 1727 (49.5) | 1838 (50.7) | 1800 (50.3) | 1850 (49.9) | 0.769 |
| **BP, mmHg** | | | | | |
| SBP at baseline | 165.6 ± 20.5 | 167.2 ± 20.4 | 167.5 ± 20.5 | 168.2 ± 20.3 | < 0.001 |
| DBP at baseline | 95.4 ± 11.9 | 94.5 ± 11.9 | 94.3 ± 11.8 | 93.3 ± 11.7 | < 0.001 |
| Time-averaged SBP | 138.4 ± 10.6 | 139.1 ± 10.3 | 138.8 ± 10.6 | 139 ± 10.6 | 0.022 |
| Time-averaged DBP | 84.1 ± 7.2 | 83.3 ± 7.2 | 82.6 ± 7.0 | 81.7 ± 7.3 | < 0.001 |
| **Laboratory results, mmol/L** | | | | | |
| Total cholesterol | 5.6 ± 1.1 | 5.6 ± 1.1 | 5.5 ± 1.1 | 5.3 ± 1.1 | < 0.001 |
| Triglycerides | 1.6 ± 1.9 | 1.6 ± 0.9 | 1.6 ± 0.9 | 1.7 ± 0.9 | < 0.001 |

*Continuous variables are presented as Mean ± SD or IQR (25th, 75th ), categorical variables are presented as n (%)

| Variables | Serum ALP, IU/L | | | | *P* value |
|---|---|---|---|---|---|
| | Q1 (< 79) | Q2 (79–<96) | Q3 (96–<116) | Q4 (≥ 116) | |
| HDL cholesterol | 1.3 ± 0.4 | 1.3 ± 0.4 | 1.4 ± 0.4 | 1.4 ± 0.4 | < 0.001 |
| Fasting glucose | 5.5 ± 0.7 | 5.4 ± 0.7 | 5.4 ± 0.7 | 5.3 ± 0.7 | < 0.001 |
| eGFR, mL/min1.73/$m^2$ | 93.7 ± 13.1 | 93.8 ± 12.8 | 93.3 ± 12.1 | 93.6 ± 12.2 | 0.455 |
| Folate, ng/mL | 7.8 ± 3.3 | 8.2 ± 3.8 | 8.5 ± 3.8 | 9.3 ± 4.4 | < 0.001 |
| Total homocysteine, μmol/L | 14.9 ± 9.9 | 14.5 ± 8.8 | 14.5 ± 8.0 | 14.1 ± 6.9 | < 0.001 |
| Alkaline phosphatase, IU/L | 66.1 ± 10.4 | 87.1 ± 4.8 | 104.9 ± 5.8 | 140.0 ± 24.1 | < 0.001 |
| Aspartate transaminase, IU/L | 21.4(18.0,26.0) | 22.7(19.2,27.8) | 24.0(20.1,29.5) | 26.7(21.9,33.1) | < 0.001 |
| Alanine transaminase, IU/L | 11.0(8.0,14.1) | 12.0(9.0,16.0) | 12.8(10.0,17.0) | 14.0(11.0,19.0) | < 0.001 |
| Gamma glutamyl transpeptidase, IU/L | 19.1(14.3,27.6) | 19.3(14.6,27.5) | 19.3(14.6,28.1) | 19.9(14.9,28.7) | 0.005 |
| **Medication use, No. (%)** | | | | | |
| Antihypertensive drugs | 1794 (51.5) | 1708 (47.1) | 1621 (45.3) | 1531 (41.3) | < 0.001 |
| Lipid lowering drugs | 37 (1.1) | 26 (0.7) | 19 (0.5) | 25 (0.7) | 0.065 |
| Antiplatelet drugs | 161 (4.6) | 109 (3.0) | 102 (2.9) | 71 (1.9) | < 0.001 |

*Continuous variables are presented as Mean ± SD or IQR (25th, 75th ), categorical variables are presented as n (%)

In addition, during the treatment period, participants with higher ALP levels had higher frequency in use of calcium channel blockers; lower frequency in use of diuretics and antiplatelet drugs. (**Additional file 1: Table S1**)

### Association Between Baseline Serum Alp And Study Outcomes

During median follow-up of 4.5 years (IQR, 4.2–4.7 years), 1,549 (10.8%) participants developed new-onset diabetes.

Overall, there was a positive relation of serum ALP and the risk of new-onset diabetes (per SD increment, adjusted OR, 1.07; 95%CI: 1.01, 1.14) (Fig. 1A) and new-onset IFG (per SD increment, adjusted OR, 1.07; 95%CI: 1.02, 1.14) (Fig. 1B). Consistently, compared with participants with serum ALP < 96 IU/L (median), significantly higher risks of new-onset diabetes (adjusted OR, 1.13; 95%CI: 1.00, 1.27) and new-onset IFG (adjusted OR, 1.13; 95%CI: 1.02, 1.27) were found in those with serum ALP ≥ 96 IU/L (Table 2).

Table 2
The association between baseline serum alkaline phosphatase (ALP) and new-onset diabetes

| ALP, IU/L | N | No. of Events (%) | Crude Model | | Adjusted Model* | |
|---|---|---|---|---|---|---|
| | | | OR (95%CI) | *P* value | OR (95%CI) | *P* value |
| **New-onset diabetes** | | | | | | |
| Continuous, per SD (30.5 IU/L) increment | 14393 | 1549 (10.8) | 1.07 (1.02,1.13) | 0.007 | 1.07 (1.01,1.14) | 0.027 |
| Quartiles | | | | | | |
| Q1 (< 79) | 3486 | 343 (9.8) | *1.00 (ref.)* | | *1.00 (ref.)* | |
| Q2 (79-<96) | 3623 | 381 (10.5) | 1.08 (0.92,1.26) | 0.346 | 1.09 (0.93,1.28) | 0.291 |
| Q3 (96-<116) | 3577 | 390 (10.9) | 1.12 (0.96,1.31) | 0.143 | 1.14 (0.96,1.34) | 0.130 |
| Q4 (≥ 116) | 3707 | 435 (11.7) | 1.22 (1.05,1.42) | 0.010 | 1.24 (1.05,1.48) | 0.013 |
| *P* for trend | | | 0.009 | | 0.013 | |
| Categories | | | | | | |
| Q1-2 (< 96) | 7109 | 724 (10.2) | *1.00 (ref.)* | | *1.00 (ref.)* | |
| Q3-4 (≥ 96) | 7284 | 825 (11.3) | 1.13 (1.01,1.25) | 0.027 | 1.13 (1.00,1.27) | 0.046 |
| **New-onset IFG †** | | | | | | |
| Continuous, per SD (30.8 IU/L) increment | 11062 | 1876 (17.0) | 1.04 (0.99,1.09) | 0.105 | 1.07 (1.02,1.14) | 0.012 |
| Quartiles | | | | | | |
| Q1 (< 79) | 2629 | 446 (17.0) | *1.00 (ref.)* | | *1.00 (ref.)* | |
| Q2 (79-<96) | 2788 | 446 (16.0) | 0.93 (0.81,1.08) | 0.337 | 0.94 (0.81,1.09) | 0.415 |

*Adjusted for age, sex, study center, treatment group, body mass index (BMI), smoking, alcohol drinking, family history of diabetes, SBP, fasting glucose (FG), total cholesterol (TC), triglycerides (TG), eGFR, folate, total homocysteine and the use of antihypertensive drugs at baseline, as well as time-averaged SBP during the treatment period.

†Subjects with baseline FG < 6.1 mmol/L and without new-onset diabetes during follow-up were included in the analysis.

| ALP, IU/L | N | No. of Events (%) | Crude Model | | Adjusted Model* | |
|---|---|---|---|---|---|---|
| | | | OR (95%CI) | *P* value | OR (95%CI) | *P* value |
| Q3 (96-<117) | 2825 | 487 (17.2) | 1.02 (0.89,1.17) | 0.788 | 1.06 (0.91,1.23) | 0.431 |
| Q4 (≥ 117) | 2820 | 497 (17.6) | 1.05 (0.91,1.21) | 0.520 | 1.14 (0.97,1.34) | 0.101 |
| *P* for trend | | | 0.302 | | 0.042 | |
| Categories | | | | | | |
| Q1-2 (< 96) | 5417 | 892(16.5) | *1.00 (ref.)* | | *1.00 (ref.)* | |
| Q3-4 (≥ 96) | 5645 | 984 (17.4) | 1.07 (0.97,1.18) | 0.177 | 1.13 (1.02,1.27) | 0.024 |

*Adjusted for age, sex, study center, treatment group, body mass index (BMI), smoking, alcohol drinking, family history of diabetes, SBP, fasting glucose (FG), total cholesterol (TC), triglycerides (TG), eGFR, folate, total homocysteine and the use of antihypertensive drugs at baseline, as well as time-averaged SBP during the treatment period.

†Subjects with baseline FG < 6.1 mmol/L and without new-onset diabetes during follow-up were included in the analysis.

Similar results were also found in participants with a normal range of baseline serum ALP (20–140 IU/L) [18] levels (per SD increment; adjusted OR, 1.07; 95%CI: 1.01, 1.14) (**Additional file 1: Figure S2**). More importantly, further adjustment for use of calcium channel blockers, diuretics and antiplatelet drugs during the treatment period (per SD increment; adjusted OR, 1.07; 95%CI: 1.01, 1.14) (**Additional file 1: Table S2**), or other liver enzymes, including GGT, ALT, AST (per SD increment; adjusted OR, 1.06; 95% CI: 1.00, 1.13) (**Additional file 1: Table S3**) did not substantially change the results.

### Stratified Analyses

In the stratified analyses, a stronger positive association between baseline ALP with new-onset diabetes was found in participants with tHcy < 10 μmol/L (per SD increment; adjusted OR, 1.24; 95%CI: 1.10, 1.40 *vs.* ≥10 μmol/L: adjusted OR, 1.03; 95%CI: 0.96, 1.10; *P*-interaction = 0.007) and FG ≥ 5.9 mmol/L (quartile 3) (per SD increment; adjusted OR, 1.16; 95%CI: 1.07, 1.27 *vs.* <5.9 mmol/L: adjusted OR, 1.00; 95%CI: 0.93, 1.08; *P*-interaction = 0.009) (Fig. 2).

However, other variables, including sex, age, BMI, treatment group, current smoking, current alcohol drinking, SBP, TC levels at baseline, as well as time-averaged SBP, calcium channel blockers usage and diuretics usage over the trial period, did not significantly modified the association between baseline serum ALP and new-onset diabetes (all *P*-interactions > 0.05) (Fig. 2).

# Discussion

Our study demonstrated that there was a positive association between baseline serum ALP levels and new-onset diabetes, independent of other liver aminotransferases, treated BP and other important confounders, among hypertensive patients. Moreover, our study expanded the results of previous studies by demonstrating that the positive association between baseline serum ALP levels and new-onset diabetes was more pronounced in participants with lower tHcy or higher FG levels.

Previous studies have linked serum ALP levels and the risk of diabetes, but reported controversial results. Nannipieri M et al (n = 1,441) [8], Nakanishi N et al (n = 3,260) [9], and Hanley AJ et al (n = 906) [10] found that there was no significant association between ALP and incident diabetes. However, a study conducted in Taiwan [11], including 132,377 non-diabetic individuals, showed that higher ALP level was significantly related to increased risk of diabetes. Of note, this study did not consider the effect of some major risk factors for diabetes, such as initial FG levels and the concomitant medications, and therefore, could not provide an accurate measurement of the association between ALP and incident diabetes. In addition, a recent mendelian randomization study demonstrated that there was a modest negative effect of genetically predicted ALP on type 2 diabetes (OR, 0.91; 95%CI: 0.86, 0.97) [19]. At the same time, another mendelian randomization study suggested that ALP was not associated with the risk of diabetes [20]. It must be pointed out that both studies [19, 20] only included European origin participants whose genetic background may be different with other population. Overall, to data, the association between ALP and incident diabetes remains uncertain. The explanations for these discrepant results might be due to differences in study population characteristics and/or sample sizes. More importantly, no previous study has comprehensively investigated the modifiers on the relation of ALP with new-onset diabetes.

Our study provided a rare opportunity to evaluate the temporal and dose-response relation of serum ALP with new-onset diabetes in hypertension adults, with a comprehensive adjustment and stratified analysis for almost all the pertinent clinical information and laboratory measurements. This is the first study of this kind in a hypertensive population. Our study has made some new contributions to the field. First, we demonstrated that higher serum ALP associated with increased new-onset diabetes in hypertensive patients, independent of other liver enzymes, treated BP and traditional or suspected risk factors. Our study findings are biological plausible based on available literature, although the potential mechanisms by which serum ALP increases diabetes risk remains to be delineated. (1) ALP was reported to contribute to vascular calcification [21], which linked to insulin resistance, subsequently leading to the development of diabetes [22]. Animal experiments showed that ALP upregulation was demonstrated in the vascular wall of diabetic rat and mouse models of vascular calcification [23]. (2) Higher serum ALP was associated with increased risk of endothelial dysfunction, a process related to insulin resistance, an initial process to diabetes [24]. This was explained that ALP could reduce nitric oxide (NO) bioavailability by inhibiting tyrosine kinase activity into endothelial cells [25], leading to the consequent impairment of endothelial NO synthase function [26]. (3) Higher serum ALP levels had been reported to be associated with increased inflammation status in CKD patients or general population [27, 28]. Notably, both endothelial dysfunction [29, 30] and chronic inflammation [31, 32] has been considered as the early

events in the development of the diabetes. Taken together, the aforementioned biological functions of ALP may be in part underlying our observed positive association between ALP and incident diabetes. However, more mechanistic studies are still needed.

Second, our results showed that tHcy and FG levels significantly modified the association between serum ALP and the risk of new-onset diabetes. A stronger association was found in those with lower tHcy (< 10 μmol/L) or higher FG (≥ 5.9 mmol/L) levels at baseline. The higher FG levels may partially represent the abnormal glucose metabolic state, due to the impairment of pancreatic alpha and beta cell function and the induced impaired insulin secretion [33, 34]. This population usually had a significantly increased risk of diabetes [35]. Since higher ALP was mainly associated with insulin resistance, our results suggested that increased ALP and higher FG levels may synergistically increase the risk of incident diabetes. On the other hand, it had been reported that elevated tHcy could also promote the calcification of vessels [36], and was related to endothelial dysfunction, inflammation and oxidative stress [12, 37]. It seemed that elevated tHcy and ALP levels may share some common pathway in the development of diabetes. As such, the detrimental effects of higher tHcy levels may attenuate the positive relation of serum ALP levels with the risk of diabetes. Our studies suggested that the combination of optimal ALP, tHcy and FG levels may be a better strategy for the primary prevention of diabetes in hypertensive adults. However, further studies are warranted to verify this hypothesis and further examine the underlying mechanisms.

Our study has some limitations. First, this is a post-hoc analysis. Although our current study adjusted for a broad array of covariates in the regression models, the possibility of residual confounding cannot be excluded. Second, we did not measure glycosylated hemoglobin A1c and insulin or perform glucose tolerance tests. However, our definition of diabetes was similar to that of previous studies [38, 39]. Third, in the current study, we collected total serum ALP rather than ALP isozymes. Although bone-specific ALP (BALP) is a more sensitive and specific marker for bone histology, it is not measured routinely due to its lack of availability and the cost associated with the assay.

# Conclusions

In summary, higher serum ALP was significantly associated with increased risk of new-onset diabetes among hypertensive patients, especially in those with lower tHcy or higher FG levels. If further confirmed, our findings support the strategy to identify and modulate diabetes risk in hypertensive patients by measuring and optimizing individual serum ALP levels.

# Abbreviations

ALP, alkaline phosphatase; BMI, body mass index; BP, blood pressure; CCB, calcium channel blockers; CVD, cardiovascular disease; CSPPT, China Stroke Primary Prevention Trial; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FG, fasting glucose; HDL-C, high-density lipoprotein; IFG, impaired fasting glucose; SBP, systolic blood pressure.

# Declarations

## Ethics approval and consent to participate

The parent study (the CSPPT) and the current study were approved by the Ethics Committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China (Federalwide Assurance Number 00001263). All participants provided written informed consent.

## Consent for publication

Not applicable.

## Availability of data and material

The data and study materials that support the findings of this study will be available from the corresponding authors (pharmaqin@126.com) upon request, after the request is submitted and formally reviewed and approved by the Ethics Committee of the Institute of Biomedicine, Anhui Medical University.

## Competing interests

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## Authors' contributions

YYZ, XPX and XHQ conceived and designed the study. YYZ, XHQ and CZ contributed to statistical analysis. YYZ and XHQ drafted the manuscript. All authors contributed to collect data and

reviewed/edited the manuscript important intellectual content. All authors read and approver the final manuscript.

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# Figures

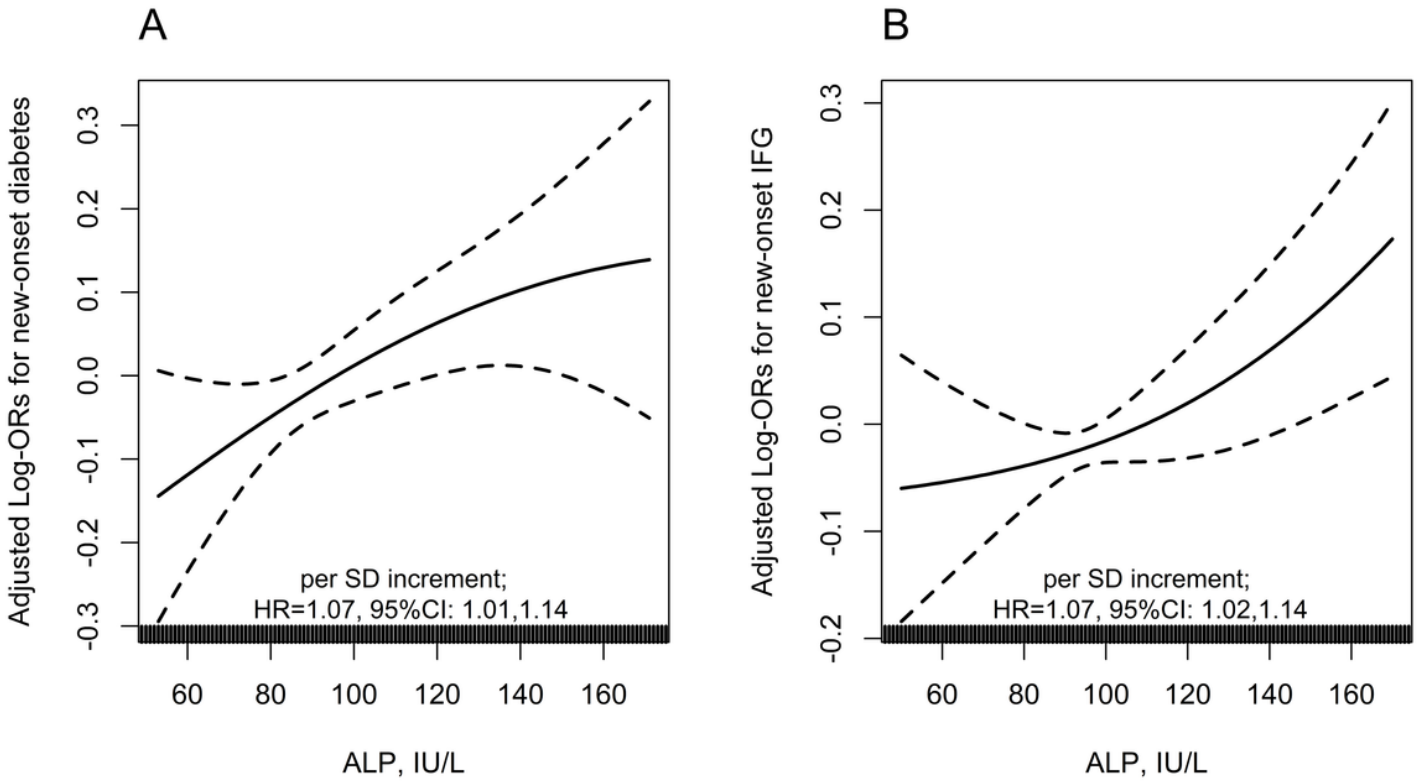


**Figure 1**

The association between baseline serum alkaline phosphatase (ALP) and new-onset diabetes (A) and new-onset impaired fasting glucose (IFG)† (B) in hypertensive adults* *Adjusted for age, sex, study center, treatment group, body mass index (BMI), smoking, alcohol drinking, family history of diabetes, SBP, fasting glucose (FG), total cholesterol (TC), triglycerides (TG), eGFR, folate, total homocysteine and the use of antihypertensive drugs at baseline, as well as time-averaged SBP during the treatment period. †Subjects with baseline FG <6.1 mmol/L and without new-onset diabetes during follow-up were included in the analysis.

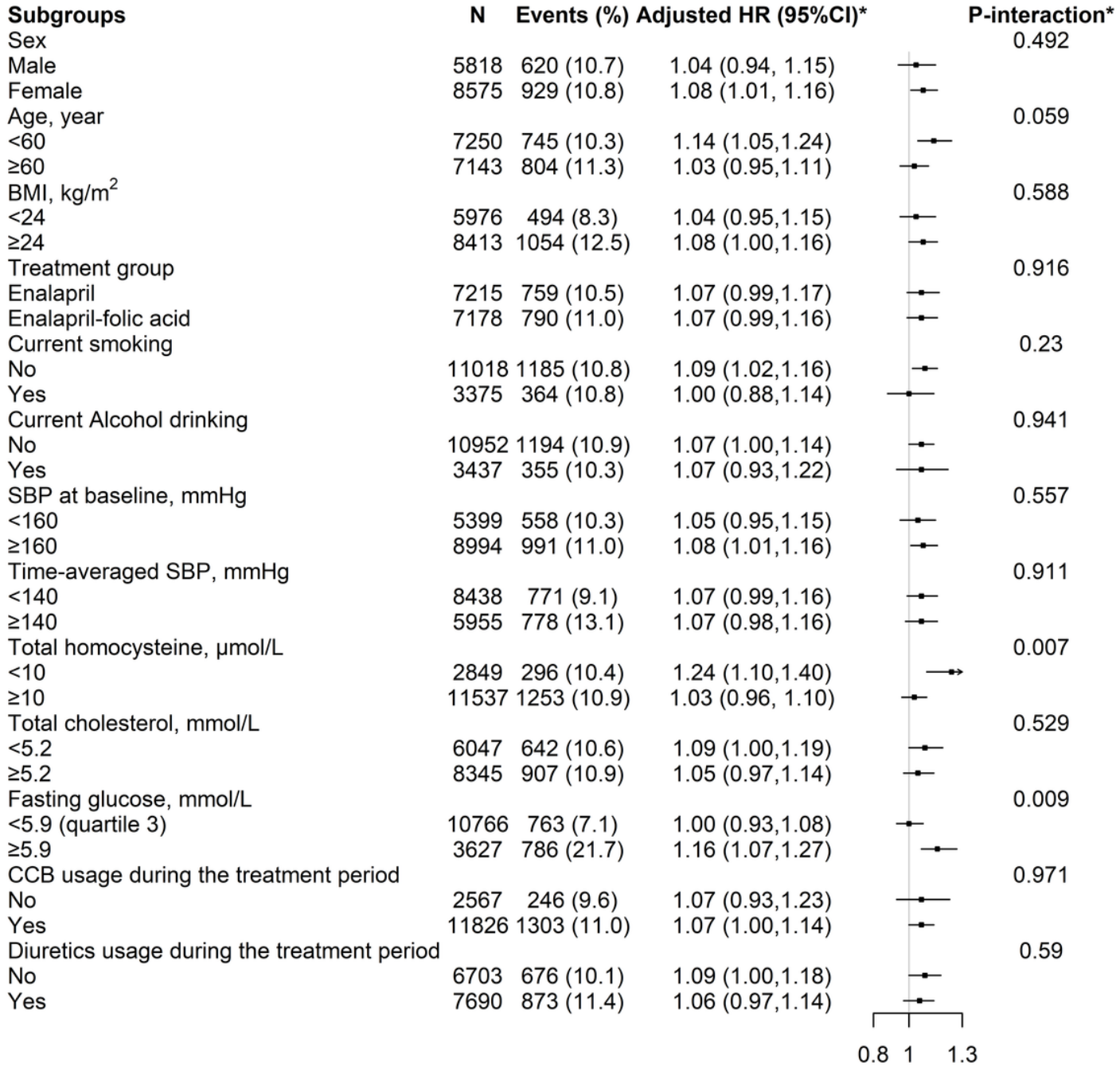


**Figure 2**

The association between baseline serum alkaline phosphatase (ALP, per SD increment) and new-onset diabetes in various groups* *Adjusted for age, sex, study center, treatment group, body mass index (BMI), smoking, alcohol drinking, family history of diabetes, SBP, fasting glucose (FG), total cholesterol (TC), triglycerides (TG), eGFR, folate, total homocysteine and the use of antihypertensive drugs at baseline, as well as time-averaged SBP during the treatment period, if not be stratified.

# Supplementary Files

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