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

**Additional file 1:**

**Figure S1.** Flow chart of the participants

**Figure S2.** The association between baseline alkaline phosphatase (ALP) and new-onset diabetes in normal ALP levels (20-140 IU/L)

**Table S1.** Concomitant medication usage during the treatment period by baseline serum alkaline phosphatase quartiles

**Table S2.** The association between baseline serum alkaline phosphatase (ALP) and new-onset diabetes, with further adjustment for the use of calcium channel blockers, diuretics and antiplatelet drugs during the treatment period

**Table S3.** The association between baseline serum alkaline phosphatase (ALP) and new-onset diabetes, with further adjustment for AST, ALT and GGT

20,702 participants in CSPPT

Excluded n=3,749

Missing fasting glucose at baseline, n=375;

Missing fasting glucose at exit visit (unless physician-diagnosed diabetes or use of glucose-lowering drugs during the follow-up), n=3,374

16,953 participants in this analysis

Excluded n=1,975

With diabetes (physician-diagnosed diabetes or using glucose-lowering drugs or fasting glucose (FG) was ≥7.0 mmol/L) at baseline, n=1,975

14,978 participants in this analysis

Excluded n=585

Missing alkaline phosphatase measurements or having self-reported history of hepatobiliary disease at baseline, n=585

14,393 participants in final analysis

No new-onset diabetes n=12,844 (89.2%)

New-onset diabetes n=1,549 (10.8%)

**Figure S1. Flow chart of the participants**

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**Figure S2. The association between baseline alkaline phosphatase (ALP) and new-onset diabetes in normal ALP levels (20-140 IU/L)\***

\*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.

**Table S1. Concomitant medication usage during the treatment period by baseline serum alkaline phosphatase quartiles\***

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variables | Baseline serum alkaline phosphatase quartiles, IU/L | | | | *P* value |
| Q1 (<79) | Q2 (79-<96) | Q3 (96-<116) | Q3 (≥116) |
| N | 4695 | 4919 | 5182 | 4951 |  |
| Antihypertensive drugs |  |  |  |  |  |
| Calcium channel blockers | 2804 (80.4) | 2954 (81.5) | 2958 (82.7) | 3110 (83.9) | <0.001 |
| Diuretics | 2011 (57.7) | 2028 (56.0) | 1901 (53.1) | 1750 (47.2) | <0.001 |
| Lipid-lowering drugs | 5 (0.1) | 3 (0.1) | 6 (0.2) | 5 (0.1) | 0.790 |
| Antiplatelet drugs | 33 (0.9) | 35 (1.0) | 26 (0.7) | 17 (0.5) | 0.045 |

\*Regular concomitant medication usage was defined as 180 or more cumulative days of taking the drug of interest.

**Table S2. The association between baseline serum alkaline phosphatase (ALP) and new-onset diabetes, with further adjustment for** **the use of** **calcium channel blockers, diuretics and antiplatelet drugs during the treatment period**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| ALP, IU/L | N | No. of  Events (%) | Crude Model | | Adjusted Model\* | |
| OR (95%CI) | *P* value | OR (95%CI) | *P* value |
| Continuous, per SD increment | 14393 | 1549 (10.8) | 1.07 (1.02,1.13) | 0.007 | 1.07 (1.01,1.14) | 0.026 |
| 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) | 0.290 |
| Q3 (96-<116) | 3577 | 390 (10.9) | 1.12 (0.96,1.31) | 0.143 | 1.14 (0.96,1.34) | 0.127 |
| 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 |  |

\*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, the use of calcium channel blockers, diuretics and antiplatelet drugs during the treatment period.

**Abbreviations:** ALP, serum alkaline phosphatase; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; SD, standard deviations; SBP, systolic blood pressure

**Table S3. The association between baseline serum alkaline phosphatase (ALP) and new-onset diabetes, with further adjustment for AST, ALT and GGT**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| ALP, IU/L | N | No. of  Events (%) | Crude Model | | Adjusted Model\* | |
| OR (95%CI) | *P* value | OR (95%CI) | *P* value |
| Continuous, per SD increment | 14393 | 1549 (10.8) | 1.07 (1.02,1.13) | 0.007 | 1.06 (1.00,1.13) | 0.045 |
| 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 | 1.08 (0.92,1.28) | 0.327 |
| Q3 (96-<116) | 3577 | 390 (10.9) | 1.12 (0.96,1.31) | 0.143 | 1.13 (0.96,1.33) | 0.148 |
| Q4 (≥116) | 3707 | 435 (11.7) | 1.22 (1.05,1.42) | 0.010 | 1.23 (1.03,1.46) | 0.020 |
| *P* for trend |  |  | 0.009 |  | 0.019 |  |

\*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, AST, ALT, GGT at baseline, as well as time-averaged SBP during the treatment period.

**Abbreviations:** ALP, serum alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; eGFR, estimated glomerular filtration rate; GGT, gamma glutamyl transpeptidase; OR, odds ratio; SD, standard deviations; SBP, systolic blood pressure