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Higher serum alanine aminotransferase levels and the incidence of hypertension: The Kailuan cohort study

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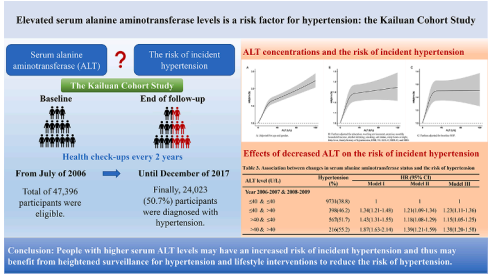
GRAPHICAL ABSTRACT



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ABSTRACT

Objective: The association between serum alanine aminotransferase (ALT) concentrations and the incidence of hypertension remains unclear. To explore the association between serum ALT levels and the risk of incident hypertension based on the Kailuan cohort study.

Methods: People who had participated in health check-ups in 2006–2007 without hypertension, cardiovascular, or liver diseases were enrolled and received follow-ups every two years until December 2017. Hypertension was defined as systolic blood pressure/diastolic blood pressure ≥140/90 mmHg or using anti-hypertensive medication. A multivariable-adjusted Cox regression model was used to estimate the hazard ratio (HR) and its corresponding 95 % confidence intervals (95 % CIs).

Results: During 10.5 years of follow-up, 24,023 (50.7 %) participants were diagnosed with hypertension. The HR of incident hypertension was 1.02 (95 % CI=1.01–1.03) for each 10 U/L increment of ALT concentrations. Participants with elevated ALT levels (>40 U/L) had an increased incidence of hypertension by 7 % (HR =1.07; 95 % CI=1.01–1.13). Besides, the HR was 1.10 (95 % CI=1.06–1.15), 1.13 (95 % CI=1.08–1.18), and 1.22 (95 % CI=1.16–1.30) ($P_{for\ trend}$ <0.001) in (10–20], (20–30], and (30–40] groups, compared with ≤10 U/L group. In

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addition, participants whose ALT levels decreased to the normal range at the first follow-up had a 23 % lower incidence of hypertension than those with elevated ALT levels at baseline and the first follow-up.
Conclusion: People with higher serum ALT levels may have an increased risk of incident hypertension and thus may benefit from heightened surveillance for hypertension and lifestyle interventions to reduce the risk of hypertension.

1. Introduction

Hypertension is the leading risk factor for cardiovascular disease. The prevalence of hypertension has been declining in high-income countries but still accelerating in low- or middle-income countries [1]. As of 2018, the hypertension prevalence was 23.2 % [2] and 37.2 % [3] among adults over 18 and 35–75 years old in China. The "Healthy China 2030″ blueprint, a signature national domestic population health policy proposed in 2016, pointed out that it is necessary to strengthen the screening and early detection of non-communicable chronic diseases and achieve full coverage of the management and intervention of hypertension and diabetes by 2030 [4]. The prevention and control of hypertension is an essential issue facing public health officials.

Previous studies confirmed hypertension is closely related to abnormal lipoprotein metabolism and liver fat accumulation. Abnormal metabolism disorders in the liver, including nonalcoholic fatty liver disease (NAFLD) and liver steatosis, are associated with hypertension [5]. Serum alanine aminotransferase (ALT), the most sensitive indicator of liver fat accumulation and NAFLD, was independently related to multiple components of metabolic syndrome (MetS) [6,7] and can be used as an independent predictor for MetS [8]. Moreover, it was demonstrated that ALT levels are correlated with multiple cardiometabolic risk factors beyond abnormal lipid metabolism, including hypertension [9]. Previous studies have explored the association between serum ALT levels and the risk or incidence of hypertension, but inconsistent findings were found [10–16]. Whether serum ALT levels affect the long-term risk of developing hypertension remains unclear. Besides, no study has systematically assessed the association of elevated serum ALT levels which have been returned to the normal range, on the risk of hypertension based on a large prospective cohort study.

Therefore, this study aimed to examine the association between serum ALT levels and the incidence of hypertension after long-term follow-up based on the Kailuan cohort study. We tested the hypothesis that serum ALT levels are associated with the risk of incident hypertension and that decreasing serum ALT levels into the normal range may correlate with a lower risk of incident hypertension.

2. Methods

2.1. Study design and population

The Kailuan study is a population-based prospective cohort study in the Kailuan community of Tangshan, Hebei province, China. The main aim of the Kailuan study is to prevent and control the occurrence and the development of chronic non-communicable diseases, including cardiovascular disease, cancer, and death, by providing health checkups for all employees of the Kailuan Group every two years since 2006. The detailed study design and procedures have been described previously [17]. This study was approved by the Ethics Committee of the Kailuan General Hospital. Written informed consent was obtained from all participants. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

In this study, a total of 101,510 individuals participated in the first health checkups from July 2006 to October 2007. Eligible participants at the baseline of this study were people with available data on BP and serum ALT. Individuals were excluded if they had a history of hypertension ($n = 47{,}102$), malignancy or cardiovascular diseases ($n = 1871$), severe liver diseases ($n = 1974$), or using lipid-lowering or hypoglycemic medicines ($n = 2379$). Participants with ALT of more than 300 U/L were also excluded ($n = 459$) in case participants had an acute liver injury, such as viral hepatitis, toxic hepatitis, or hepatic shock. The flowchart of the study population is shown in Fig. 1.

2.2. Exposure assessment

All the routine clinical laboratory examinations were performed in Kailuan General Hospital by experienced doctors trained according to standard clinical operational guidelines. Participants were required to keep a light diet for three days and arrived at the blood sampling room at 7:00–9:00 am on the day of health checkups. After 8 h of fasting, venous blood samples were taken and centrifuged for serum separation immediately.

A unified standard automatic biochemical analyzer (Hitachi 747, Hitachi High-Technologies, Tokyo, Japan) was used for biochemical index testing within 24 h. ALT concentration (UV-LDH method) was measured using reagents from the Shanghai Mingdian Bioengineering company (Shanghai, China). All operations were strictly implemented by the instructions and laboratory protocols to ensure the minimum measurement error. Besides, Hitachi 747 automatic analyzer was calibrated every 12 months by the manufacturers to ensure its precision and accuracy in the detection process.

In addition to numeric values, ALT concentrations were classified into two levels (Group I), including normal ALT ($\leq$40 U/L) and elevated ALT (>40 U/L), according to the standard reference range of the clinical biochemical test in China [18]. Besides, to explore the possible association between elevated serum ALT levels within the normal range and the incidence of hypertension, serum ALT levels were divided into five groups (Group II), including (0–10] U/L, (10–20) U/L, (20–30] U/L, (30–40] U/L and (40–300) U/L.

2.3. Follow-up and outcomes

Until 31 December 2017, participants received five follow-up visits in 2008–2009, 2010–2011, 2012–2013, 2014–2015, and 2016–2017, respectively. It averaged about 1.5 years for all participants to complete the health checkup at each follow-up. For each participant, the follow-up period started from 2008 to 2009 to the occurrence of hypertension, censoring, or 31 December 2017, whichever came first.

Blood pressure was measured at 7:00–9:00 am during health checkups. Participants were required not to smoke, drink tea or caffeinated beverages, and keep quiet for at least 10 min. Seated blood pressures were measured by trained physicians or nurses using a calibrated mercury sphygmomanometer from the right brachial artery with the elbow at heart level, and arm extended. A total of 3 measurements for each participant were conducted at 1–2 min intervals and averaged blood pressures were calculated. If the difference in interval blood pressures exceeded five mmHg, it was required to be remeasured.

Hypertension was defined as the average systolic blood pressure (SBP)/diastolic blood pressure (DBP) $\geq$140/90 mmHg or self-reported using anti-hypertensive medications, according to the Guidelines for Prevention and Treatment of Hypertension in China (2018 Revised Edition) [19]. Censoring was defined as participants' death from diseases or emergencies unrelated to hypertension during the follow-up period.

For participants diagnosed with hypertension during the follow-ups, the time of health checkup at the first diagnosis was recorded as the time

of hypertension observed. Among people without hypertension, setting 31 December 2017 was the time of non-hypertensive observed. For people who were confirmed with censoring, using the death time was the time without hypertension being observed.

2.4. Assessment of covariates

Sociodemographic characteristics (age, sex, education, working environment, and monthly household income), personal or family history of diseases (diabetes, hypertension), and lifestyles (exercise, alcohol drinking, smoking, salt intake, and sleep hours at night) at baseline were collected by trained staff using standard questionnaires. In this study, education level was sorted as "below high school" and "high school or above"; and working environment was classified as "on the ground" and "underground"; monthly household income per capita was divided into <600 and ≥ 600 yuan; salt intake was grouped into <6, 6–12 and ≥12 g/day; and sleep duration at night was classified as <8 and ≥8 h. As self-reported, participants who had regular exercise/history of smoking/history of drinking were defined as physical exercisers/smokers/drinkers, respectively.

Laboratory indexes detected at baseline include triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and fasting blood glucose (FBG). Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters. Besides, the diagnosis of fatty liver disease was based on the results of ultrasound examinations, which found diffusely echogenic parenchyma [20].

2.5. Statistical analysis

Baseline characteristics regarding numeric variables, categorical variables, or percentages were described using mean values and standard deviation, median and interquartile range (IQR), or numbers and percentages, respectively. The *t*-test and χ^2 test were performed to evaluate the differences in baseline characteristics between normal and elevated ALT groups. The cumulative incidence and the person-year incidence rate of hypertension were calculated to describe the incidence of hypertension, and χ^2 tests were used to compare the differences in hypertension incidences among people with different characteristics.

The strength of associations (hazard ratio [HR] and their corresponding 95 % confidence interval [95 % CI]) between baseline serum ALT and the incidence of hypertension were assessed using age-sex-adjusted (Model I) and multivariable-adjusted (Model II and Model III) Cox regression models. Covariates in Model II included general characteristics (age, sex, education, working environment, and monthly household income per capita), life behaviors (physical exercise, alcohol drinking, smoking, average salt intake, and sleep hours at night), history of diseases (fatty liver and family history of hypertension), and physiological or biochemical indexes (BMI, TG, LDL-C, HDL-C, and FBG). Model III was further adjusted for baseline SBP based on Model II, which was used as the final model in our analysis. The dose-response relationship between serum ALT levels and the incidence of hypertension was presented by multivariable-adjusted restricted cubic spline (RCS) models. Subgroup and stratified analyses were performed to evaluate the association between serum ALT levels and the incidence of hypertension among subgroups with common risk factors and find the potential modifiers. In addition, the association between baseline serum

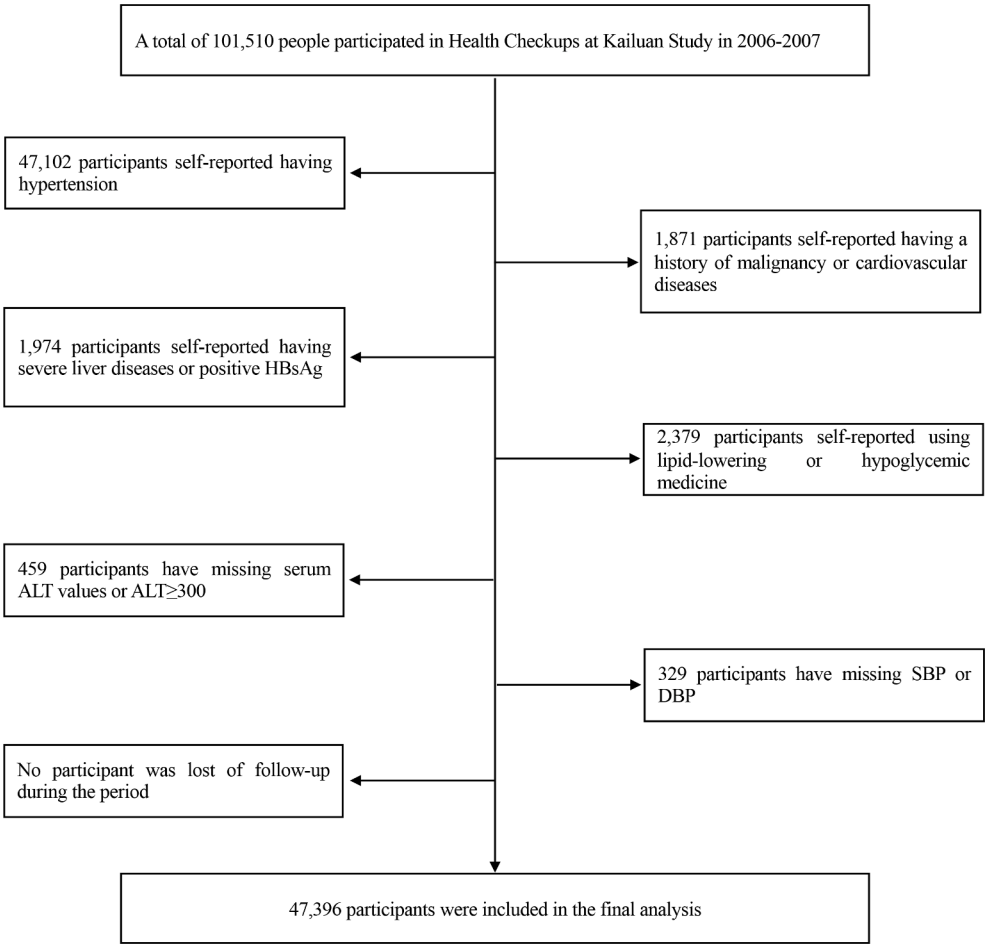

Fig. 1. Flowchart of the study population in the association between serum alanine aminotransferase and the risk of hypertension.

ALT levels and the SBP or DBP at the last follow-up was assessed by multivariable-adjusted linear regression models after excluding participants who had taken antihypertensive medicines simultaneously, in which the covariates were the same as the Model III.

The effects of serum ALT level changes on the incidence of hypertension were evaluated among participants who had available ALT concentrations both at baseline (2006–2007) and the first follow-up health checkup (2008–2009). Finally, several sensitivity analyses were also conducted to assess the robustness of the association between serum ALT levels and the incidence of hypertension by excluding 1) participants who were diagnosed with hypertension at the first follow-up in 2008–2009 years; 2) participants who were diagnosed with hypertension in only one health checkup of five follow-ups; or 3) participants who were diagnosed with fatty liver diseases at baseline. Time-varying Cox proportional hazard models were also used to re-assess the association between serum ALT levels and the incidence of hypertension.

All analyses were performed using R, version 4.0.4. All statistical tests were 2-sided, and P values < 0.05 were considered statistically significant.

2.6. Patient and public involvement

Patients and members of the public were not involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. The results of the physical examination and biochemical test were disseminated to each study participant.

3. Results

3.1. Differences between the normal group and the elevated ALT group

A total of 47,396 participants, including 35,525 men (75.0 %) and 11,871 (25.1 %) women, were included in the current study. The average serum ALT concentration among enrolled participants was 20.1 ± 14.8 U/L, with a mean age of 47.7 ± 12.3 at baseline. Only 2646(5.6 %) participants had elevated serum ALT levels (>40 U/L) with an average value of 63.1 ± 30.5 U/L, which was significantly higher than those with normal ALT concentrations (≤40 U/L) (17.6 ± 7.9 U/L) ($P <$ 0.001). Compared with people who had normal serum ALT levels, participants with elevated serum ALT levels at baseline were more likely to be younger, working underground, alcohol drinkers, smokers and diagnosed with fatty liver, and were more likely to have a higher salt intake, shorter sleep duration at night, higher BMI, TC, TG, FBG levels, and lower HDL-C levels (Table 1).

3.2. Risk of incident hypertension according to serum ALT levels

The median follow-up time in this prospective cohort study was 10.5 years (IQR: 3.9–11.0). A total of 24,023 (50.7 %) participants were diagnosed with hypertension during the follow-up period. The cumulative incidence of hypertension among people with elevated serum ALT levels was significantly higher than those with normal ALT levels (61.6% vs. 50 %, $P <$ 0.001) (Table S1). The associations between serum ALT levels at baseline and the incidence of hypertension are shown in Table 2. With each 10 U/L rise in ALT concentration, the incidence of hypertension was increased by 2 % (HR=1.02; 95 % CI=1.01–1.03) in the final multivariable-adjusted model. The dose-response relationship shown in the RCS curve is presented in Fig. 2. For participants with elevated ALT levels, the incidence of hypertension increased by 7 % (HR =1.07; 95 % CI=1.01–1.13). In addition, participants who had higher ALT levels within the normal range at baseline, including (10–20], (20–30], and (30–40] groups, also had higher risks of hypertension by 10 %(HR=1.10; 95 % CI=1.06–1.15), 13 %(HR=1.13; 95 % CI=1.08–1.18) and 22 % (HR=1.22; 95 % CI=1.16–1.30) (P for trend <0.001), compared with ≤10 U/L group. Similar associations that SBP

Table 1
Baseline characteristics of the study population according to serum alanine aminotransferase levels.

Variable	Total (N = 47,396)	Normal ALT (n = 44,750)	Elevated ALT (n = 2646)	P
Male, No.(%)	35,525 (75.0)	33,239 (74.3)	2286(86.4)	<0.001
Age, mean(SD), years	47.7(12.3)	47.9(12.3)	44.4(11.4)	<0.001[a]
<35, No.(%)	7716 (16.3)	7093(15.9)	623(23.5)	<0.001
35–44, No.(%)	11,605 (24.5)	10,883 (24.3)	722(27.3)	
45–54, No.(%)	15,838 (33.4)	14,951 (33.4)	887(33.5)	
≥55, No.(%)	12,237 (25.8)	11,823 (26.4)	414(15.7)	
Below high school, No.(%)	35,552 (75.1)	33,717 (75.4)	1835(69.4)	<0.001
Working Underground, No.(%)	14,759 (31.2)	13,786 (30.9)	973(36.8)	<0.001
Household income, ≥600 per capita, No.(%)	33,965 (71.7)	32,076 (71.8)	1889(71.4)	0.725
Exercise, No.(%)	42,980 (90.9)	40,558 (90.8)	2422(91.7)	0.117
Drinking, No.(%)	19,474 (41.2)	18,007 (40.3)	1467(55.5)	<0.001
Smoking, No.(%)	18,661 (39.4)	17,344 (38.8)	1317(49.9)	<0.001
Salt-intake, No.(%), g/d				
<6	4271(9.0)	4021(9.0)	250(9.5)	<0.001
6–12	38,320 (81.0)	36,254 (81.2)	2066(78.2)	
≥12	4722 (10.0)	4396(9.8)	326(12.3)	
Sleep < 8 h at night, No.(%)	19,789 (41.9)	18,525 (41.5)	1264(47.9)	<0.001
BMI, mean(SD), kg/m^2	24.2(3.3)	24.1(3.3)	26.1(3.5)	<0.001[a]
<18.5, No.(%)	1205(2.6)	1187(2.7)	18(0.7)	<0.001
18.5–23.9, No.(%)	21,828 (46.3)	21,124 (47.5)	704(26.7)	
24–27.9, No.(%)	18,225 (38.7)	17,031 (38.3)	1194(45.3)	
≥28, No.(%)	5865 (12.5)	5144(11.6)	721(27.3)	
SBP, mean(SD), mmHg	117.2 (11.1)	117.1(11.1)	118.9(10.6)	<0.001[a]
≥120, No.(%)	25,367 (53.5)	23,832 (53.3)	1535(58.0)	<0.001
DBP, mean(SD), mmHg	76.4(6.9)	76.3(6.9)	77.8(6.4)	<0.001[a]
≥80, No.(%)	24,583 (51.9)	23,132 (51.7)	1451(54.8)	0.002
TG, mean(SD), mmol/L	1.5(1.3)	1.5(1.2)	2.1(1.6)	<0.001[a]
≥2.26, No.(%)	6821 (14.4)	6031(13.5)	790(29.9)	<0.001
TC, mean(SD), mmol/L	4.9(1.1)	4.9(1.1)	5.1(1.2)	<0.001[a]
≥6.20, No.(%)	4215(8.9)	3872(8.7)	343(13.0)	<0.001
LDL-C, mean(SD), mmol/L	2.3(0.8)	2.3(0.8)	2.3(0.8)	0.472[a]
≥4.10, No.(%)	1005(2.1)	962(2.2)	43(1.6)	0.070
HDL-C, mean(SD), mmol/L	1.5(0.4)	1.5(0.4)	1.5(0.4)	0.003[a]
<1.0, No.(%)	2564(5.4)	2387(5.3)	177(6.7)	0.003
FBG, mean(SD), mmol/L	5.2(1.3)	5.2(1.3)	5.5(1.6)	<0.001[a]
≥7.0, No.(%)	2031(4.3)	1834(4.1)	197(7.5)	<0.001
Fatty liver, No.(%)	10,880 (23.0)	9409(21.0)	1471(55.6)	<0.001

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose.

[a] The analysis of mean value was used to examine the differences in baseline characteristics between two groups; others used χ^2 test.

Table 2
Association between serum alanine aminotransferase levels and the risk of hypertension.

ALT (U/L)	Hypertension (%)	HR (95 % CI) Model I	Model II	Model III
ALT, per 10 U/L increment	24,023(50.7)	1.06 (1.05–1.07)	1.02 (1.01–1.03)	1.02 (1.01–1.02)
Group I				
≤40	22,394(50.0)	1	1	1
>40	1629(61.6)	1.39 (1.32–1.46)	1.10 (1.05–1.16)	1.07 (1.01–1.12)
Group II				
≤10	3532(43.1)	1	1	1
(10–20]	10,801(49.6)	1.15 (1.11–1.20)	1.10 (1.06–1.15)	1.10 (1.06–1.14)
(20–30]	6140(52.9)	1.29 (1.24–1.34)	1.13 (1.08–1.18)	1.12 (1.08–1.17)
(30–40]	1921(60.9)	1.52 (1.44–1.61)	1.23 (1.16–1.30)	1.22 (1.15–1.29)
>40	1629(61.6)	1.65 (1.55–1.75)	1.23 (1.16–1.31)	1.19 (1.11–1.26)
$P_{for\ trend}$ [a]		<0.001	<0.001	<0.001

Abbreviations: ALT, alanine aminotransferase; HR: hazard ratio; CI: confidence intervals; HR: hazard ratio.
Model I: adjusted for age and sex (male/female).
Model II: adjusted for age, sex (male/female), education levels (below high school/high school and above), working environment (on the ground/underground), household monthly income per capita (<600/≥ 600 Yuan), drinking (yes/no), smoking (yes/no), exercise (yes/no), salt intake (<6 g /6–12 g/≥12 g per day), sleep hours at night (<8 h/≥8 h), fatty liver (yes/no), family history of hypertension (yes/no), body mass index, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and fasting blood glucose at baseline.
Model III: further adjusted for baseline systolic blood pressure based on model II.
[a] *P* for trend was calculated by substituting ALT levels as a continuous variable into models.

and DBP were increased with elevating serum ALT concentrations are shown in Tables S2-S3.

Subgroup and stratified analyses in Fig. 3-4 summarized the association between ALT levels and the incidence of hypertension among participants with different characteristics, including different groups of age, sex, fatty liver, alcohol drinking, BMI, TG, and FBG. Except for the elder age (≥45 years) group, participants who had elevated serum ALT levels combined with characteristics of male, fatty liver, drinking, BMI ≥24 kg/m^2, TG ≥2.26 mmol/L, and FBG ≥7.0 mmol/L had a higher incidence of hypertension (Fig. 4). Moreover, multiple sensitivity analyses found that the association between serum ALT levels and the incidence of hypertension was robust and consistent, as shown in Table S4-S7.

3.3. The effect of changes in serum ALT levels on the risk of incident hypertension

Finally, Table 3 shows the effects of serum ALT changes on the incidence of hypertension from the baseline in 2006–2007 to the first follow-up in 2008–2009. Compared with participants who had normal serum ALT levels both at baseline and at the first follow-up, people who only had elevated serum ALT levels at the first follow-up in 2008–2009 had an increased incidence of hypertension by 23 % (HR=1.23; 95 % CI=1.11–1.36); participants who had elevated serum ALT levels at both the baseline and the first follow-up had the highest incidence of hypertension, which was increased by 38 % (HR=1.38; 95 % CI=1.20–1.58); whereas, people who had elevated serum ALT level at baseline and normal serum ALT level at the first follow-up had a slightly increased incidence of hypertension, which only increased by 15 % (HR=1.15; 95 % CI=1.05–1.25).

4. Discussion

This study provided substantial evidence that elevated serum ALT levels or higher ALT levels within the normal range remarkably increased the incidence of hypertension. It is noted that we reported the changes from elevated ALT levels to the normal range might reduce the higher incidence of hypertension for the first time. Our findings suggest that ALT elevation or modest elevations within the normal range may be a significant precursor to incident hypertension, which alerts people with elevated ALT levels should pay more attention to cardiovascular disease health.

Several cohort studies have been conducted to explore the association between serum ALT levels and the risk of hypertension, but inconsistent findings were found. One study showed that the baseline serum ALT levels were associated with the risk of hypertension after univariable adjustment, which lost statistical significance after multivariable adjustment [21]. Lau et al. found that serum ALT levels were related to hypertension and blood pressure at baseline rather than the risk of hypertension or blood pressure after five years of follow-up [22].

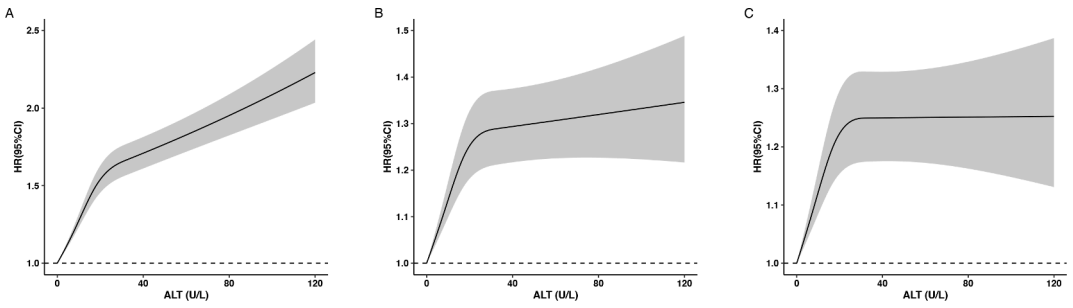

Fig. 2. Dose-response relationship between serum alanine aminotransferase concentrations (per 1 U/L) and the risk of hypertension (HR, 95 % CI)
Abbreviations: HR: hazard ratios; CI: confidence interval.
The dose-response relationship between serum alanine aminotransferase concentrations and the risk of hypertension was modeled with a restricted cubic spline model. Solid lines represent point estimates of HRs and shaded areas represent its 95 % confidence intervals.
A. Adjusted for sex and age.
B. Further adjusted for education, working environment, exercise, household monthly income, alcohol drinking, smoking, salt intake, sleep hours at night, fatty liver, family history of hypertension, body mass index, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and fasting blood glucose at baseline based on Fig. 2A.
C. Further adjusted SBP at baseline based on Fig. 2B.
Imaging packages: "rms", "ggplot2".

Variables	Subgroups	ALT Levels (U/L)	Hypertension (%)	HR [95%CI]	*P* for interaction
Age	<45	≤40	7052(39.25)	1	<0.001
		>40	793(59.00)	1.09[1.01-1.18]	
	≥45	≤40	15342(57.28)	1	
		>40	836(64.21)	1.03[0.96-1.10]	
Gender	Female	≤40	4386(38.10)	1	0.184
		>40	168(46.67)	0.91[0.78-1.06]	
	male	≤40	18008(54.18)	1	
		>40	1461(63.91)	1.11[1.05-1.17]	
Fatty Liver	No	≤40	16312(46.19)	1	0.044
		>40	649(55.28)	1.16[1.08-1.26]	
	Yes	≤40	6076(64.58)	1	
		>40	979(66.55)	1.03[0.96-1.11]	
Drinking	No	≤40	12347(46.29)	1	0.731
		>40	676(57.53)	1.13[1.04-1.22]	
	Yes	≤40	10004(55.56)	1	
		>40	951(64.83)	1.07[0.99-1.14]	
BMI	<24	≤40	9286(41.62)	1	0.099
		>40	365(50.55)	1.20[1.08-1.33]	
	≥24	≤40	12991(58.58)	1	
		>40	1258(65.69)	1.10[1.04-1.17]	
TG	<2.26	≤40	18719(48.37)	1	0.208
		>40	1109(59.82)	1.12[1.05-1.19]	
	≥2.26	≤40	3665(60.77)	1	
		>40	520(65.82)	1.05[0.96-1.16]	
FBG	<7.0	≤40	21247(49.54)	1	0.515
		>40	1491(60.91)	1.11[1.05-1.17]	
	≥7.0	≤40	1134(61.83)	1	
		>40	137(69.54)	1.02[0.84-1.23]	

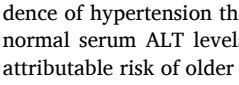

Fig. 3. Subgroup analysis of the association between serum alanine aminotransferase levels and the risk of hypertension (HR, 95 % CI)
Abbreviations: ALT: alanine aminotransferase; HR: hazard ratio; CI: confidence interval; BMI: body mass index; TG: triglycerides; FBG: fasting blood glucose.
Covariates in subgroup analyses were the same as variables contained in Model III, except for the grouping variable.
The reference group was ALT ≤40 U/L level in each subgroup.
Imaging packages: "forestplot", "ggplot2".

Yu et al. demonstrated that the association between high ALT levels and the progression of hypertension was only found in men [11]. Besides, serum ALT levels were negatively correlated with systolic blood pressure in two cohort studies, one from 1112 young military males [15] and another from 12,000 treated hypertensive individuals [16]. Liu et al. indicated no statistical correlation between baseline serum ALT levels and blood pressure after two years of follow-up [12]. Our previous work found serum ALT levels correlated with hypertension prevalence in a nationalized cross-sectional study in China [23]. Recently, a small cohort study from the Chinese population also found a bi-directional association between elevated ALT and hypertension, and probably elevated ALT levels antedate the development of hypertension [10]. These findings provide more clues for the causal relationship between serum ALT elevations and the risk of hypertension. The main reason for these inconsistent results might be the insufficient sample size, short-term follow-ups, or selection bias of enrolled participants in previous cohort studies. Whereas in this large sample-sized prospective cohort study with an average of 10.5 years follow-up, the risk of incident hypertension was remarkably increased by 7 % among participants who had elevated serum ALT levels after multivariable adjustments including age, sex, drinking, smoking, BMI, TG, and other common risk factors. The incidence of hypertension and SBP or DBP values increased monotonically with the rising serum ALT concentrations. In addition, our study extended findings that even among participants with higher serum ALT concentrations within the normal range, the incidence of hypertension was still increased, which was similar to previous results that serum ALT in the normal range (<40 U/L) was associated with the prevalence of hypertension in the Framingham Heart Study [9]. These findings in this study suggest that serum ALT levels represent a continuum risk and are closely related to the incidence of hypertension and blood pressure after ten years.

Moreover, our study was the first to find that decreasing elevated serum ALT levels into the normal range might reduce the higher incidence of hypertension during ten years of follow-up in a large population-based prospective cohort study. Compared with participants who had normal serum ALT levels at baseline and the first follow-up, the incidence of hypertension among participants with elevated ALT levels at baseline and the first follow-up increased by 38 %. Besides, compared with participants who had elevated ALT levels at baseline and the first follow-up, those with elevated ALT levels at baseline but decreased to normal range at the first follow-up time reduced their incidence of hypertension by 23 %. These findings suggest that the higher incidence of hypertension might be reduced as the elevated ALT levels decrease to the normal range. However, it is still higher than those with normal serum ALT levels at baseline and the first follow-up. Until now, no related studies have been reported, especially on the possible association of decreasing serum ALT levels on their long-term incidence of hypertension.

We also found that the incidence of hypertension was higher among participants with elevated serum ALT levels combined with male, fatty liver, drinking, BMI ≥24 kg/m^2, TG ≥2.26 mmol/L, and FBG ≥7.0 mmol/L, which suggests that elevated serum ALT levels may further increase the incidence of hypertension among participants with these common risk factors. However, participants with elevated serum ALT levels combined with older age (≥ 45 years) had a slightly lower incidence of hypertension than participants with older age combined with normal serum ALT levels. It might be related to the fact that 1) the attributable risk of older age is higher than that of elevated serum ALT levels and 2) serum ALT concentration being decreased with age increase [24,25]. Besides, people with elevated serum ALT levels combined with FBG ≥7.0 mmol/L had the highest point estimation of HR for hypertension but with non-statistical significance confidence intervals

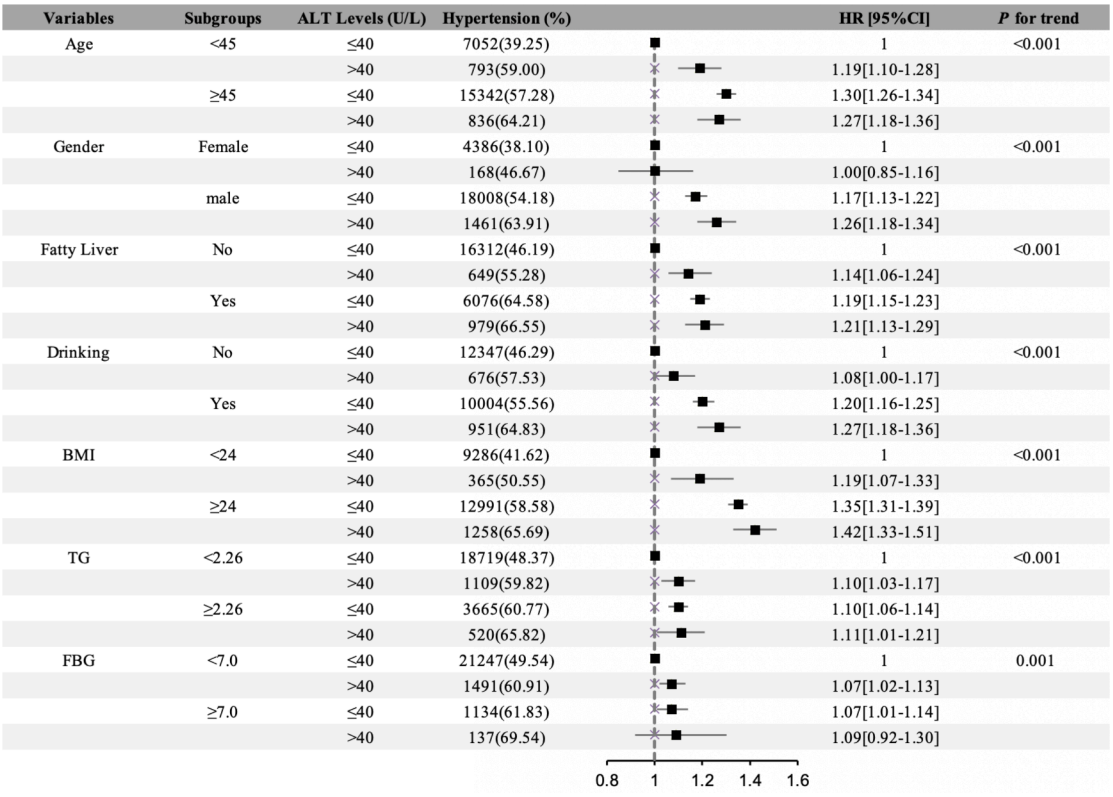

Fig. 4. Stratified analysis of potential modifiers on the association between serum alanine aminotransferase levels and the risk of hypertension (HR, 95 % CI)
Abbreviations: ALT: alanine aminotransferase; HR: hazard ratio; CI: confidence interval; BMI: body mass index; TG: triglycerides; FBG: fasting blood glucose.
Covariates in stratified analyses were the same as variables contained in Model III, except for the stratified variable.
The reference group was the combined ALT ≤40 U/L level and lower-risk subgroup.
Imaging packages: "forestplot", "ggplot2".

Table 3
Association between changes in serum alanine aminotransferase status and the risk of hypertension.

ALT level (U/L)	Hypertension (%)	HR (95 % CI) Model I	Model II	Model III
Year				
2006–2007 & 2008–2009				
≤40 & ≤40	9737(38.8)	1	1	1
≤40 & >40	398(46.2)	1.34 (1.21–1.48)	1.21 (1.09–1.34)	1.23 (1.11–1.36)
>40 & ≤40	567(51.7)	1.43 (1.31–1.55)	1.18 (1.08–1.29)	1.15 (1.05–1.25)
>40 & >40	216(55.2)	1.87 (1.63–2.14)	1.39 (1.21–1.59)	1.38 (1.20–1.58)

Deleted participants who had been diagnosed with hypertension at the first follow-up from 2008 to 2009 years.
Abbreviations: ALT, alanine aminotransferase; HR: hazard ratio; CI: confidence intervals; HR: hazard ratio.
Model I: adjusted for age and sex(male/female).
Model II: adjusted for age, sex(male/female), education levels (below high school/high school and above), working environment (on the ground/underground), monthly household income per capita (<600/≥ 600 Yuan), drinking (yes/no), smoking (yes/no), exercise (yes/no), salt intake (<6 g /6–12 g/≥12 g per day), sleep hours at night (<8 h/≥8 h), fatty liver (yes/no), family history of hypertension (yes/no), body mass index, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and fasting blood glucose at baseline.
Model III: further adjusted for baseline systolic blood pressure based on model II.

due to the insufficient sample size in our analysis. The effects of higher FBG and elevated serum ALT levels on the incidence of hypertension are still of concern. Therefore, evidence from this study revealed that elevated serum ALT levels might further increase the incidence of hypertension among male participants or be accompanied by fatty liver, alcohol consumption, overweight or obesity, hyperlipidemia, and hyperglycemia. Based on these findings, we appeal that people with these common factors should pay more attention to serum ALT indicators in daily physical examinations.

Physiologically, aminotransferase is a ubiquitous enzyme that can catalyze the reversible transfer of amino groups from amino acids to α-keto acids and plays a vital role in the metabolism of amino acid [26]. Previous studies found that serum ALT level, as the most sensitive indicator of liver fat accumulation, is closely related to the function of the metabolic system [27]. Many studies showed elevated serum ALT levels are related to higher serum TG, LDL-C, non-HDL-C, and lower HDL-C [28,29]. Besides, elevated ALT levels were found to be associated with the risk of impaired glucose tolerance and insulin resistance [13]. Moreover, elevated serum ALT levels could also promote vascular endothelial dysfunction, activate inflammation and oxidative stress, and increase the risk of carotid atherosclerosis [30,31]. In addition, it was evidenced that serum ALT levels are positively correlated with heart rate [13] and could also be used as early biomarkers to predict left ventricular hypertrophy and carotid artery changes [32]. Elevated serum ALT levels might be indirectly associated with the risk of incident hypertension through any of the above-mentioned pathophysiological features responsible for hypertension development.

5. Strengths and limitations

This study systematically assessed the association between serum

ALT levels and the incidence of hypertension after ten years for the first time and has several advantages over previous research. First, we used data from a population-based prospective cohort with a large sample size, which can ensure sufficient statistical power in all statistical analyses. Second, strict inclusion and exclusion criteria were used in the study population selection, which can well demonstrate the chronological association between elevated serum ALT levels and the risk of incident hypertension. Third, this cohort study has a long-term follow-up, with a median of 10.5 years, which was long enough to observe the natural history and the development of hypertension. Fourth, the study population in this cohort had lower mobility and good compliance. All participants' health examinations, medical insurance, death registration, and other information were well-recorded and easy to search. In addition, potential confounders of hypertension, including sociodemographic characteristics, lifestyles, family history of hypertension, and laboratory tests, were well controlled in all statistical analyses. Finally, we reassessed the robustness of the observed association between serum ALT levels and the incidence of hypertension through multiple sensitivity analyses.

However, this study also has several limitations. First, most of the study population in this cohort were male, less educated, and older, which might lead to significant differences in the distribution of baseline characteristics and overestimated incidence of hypertension in 10 years compared with the general population. Second, the information collected by self-reported according to structured questionnaires might introduce recall biases. Third, other liver enzymes were not tested in the laboratory tests, so other liver enzymes could not be used to verify the association between serum ALT levels and the incidence of hypertension. Finally, the study population in this cohort were the in-service and retired employees mainly engaged in industries of coal working, building materials, chemicals, and construction, which cannot represent the local general population. Thus, this study's findings might not apply to people with other characteristics.

6. Conclusions

In summary, this study found that serum ALT levels were associated with the incidence of hypertension in 10 years. People with elevated serum ALT levels may have a higher incidence of hypertension, which promotes awareness of focusing on future cardiovascular health among those with elevated ALT levels.

7. Authors' contributions

Dr. Yang and Dr. Wu had full access to all of the data in the study and took responsibility for the data's integrity and the data analysis's accuracy.

Concept and design: Jia,Yang, Ma, and Wu.

Acquisition, analysis, or interpretation of data: Jia, Yang, Chen, Wang, and Wu.

Drafting of the manuscript: Jia.

Critical revision of the manuscript for important intellectual content: Yang and Liu.

Statistical analysis: Jia and Yang.

Obtained funding: Ma.

Administrative, technical, or material support: Yang, Deng, Guo, Peng, and Wang.

Supervision: Yang, Ma, and Wu.

8. Availability of data and materials

The data underlying this article will be shared on reasonable request to the corresponding author.

CRediT authorship contribution statement

Jiajing Jia: Writing – original draft, Writing – review & editing, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ying Yang:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization. **Fangchao Liu:** Writing – review & editing, Methodology. **Shuohua Chen:** Resources, Investigation, Data curation. **Yuzhi Deng:** Validation, Investigation, Data curation. **Tonglei Guo:** Validation, Investigation, Data curation. **Zuoqi Peng:** Project administration, Investigation, Data curation. **Xingyu Wang:** Supervision, Resources, Project administration, Data curation. **Xu Ma:** Supervision, Resources, Project administration, Funding acquisition. **Shouling Wu:** Supervision, Resources, Project administration, Investigation, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2024.100644.

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