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Independent effect of alanine transaminase on the incidence of type 2 diabetes mellitus, stratified by age and gender: A secondary analysis based on a large cohort study in China

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ABSTRACT

Background: Previous studies have revealed that alanine aminotransferase (ALT) may be one of the risk factors of developing diabetes. We aimed to demonstrate the independent effect of ALT on incident diabetes and to investigate whether the association between ALT and incident diabetes is modified by age and gender in the general Chinese population.

Methods: The present study was a retrospective cohort study, including 210,051 Chinese adult participants. The primary outcome was developing diabetes. The serum ALT activities were stratified by quintiles. We obtained data from 'DATADRYAD' website and used the data for secondary analysis.

Results: At a median follow-up of 3.0 y, 4144 of 210,051 (1.97%) participants developed diabetes. After adjustment for potential confounders, a significantly higher risk of the incident diabetes (HR: 1.43, 95% CI: 1.25–1.63) was found in participants in the fifth quintile (Q5, ≥31 U/L) compared to those in the first to fourth quintiles (Q1–4) for ALT activities. Among males aged 30 to 40 and 40 to 50 y with the fifth quintile of ALT activity had 2.4- and 1.5-fold increased odds of developing diabetes, respectively, in comparison with those in the lower ALT activities. Among females with age 30 to 40 and ≥ 70 y, the fifth quintile of ALT activity had 4.9- and 2.2-fold increased odds for incident diabetes.

Conclusion: Our result indicated that the ALT activity was positively associated with the incident diabetes among Chinese persons. Moreover, 30–40 y individuals, whether male or female, with elevated ALT activities had the greatest increased risk for diabetes compared with persons with lower ALT activities in the same age group.

1. Introduction

Type 2 diabetes mellitus (T2D) is one of the severe chronic diseases throughout the world. Diabetes increases the incidence of cardiovascular disease and premature death in the general population and brings a substantial economic burden to society. With the expansion of the economy, the transformation of lifestyles and the ageing of society, diabetes has become a significant public health concern in China [1].

A national survey conducted in China, including 98,658 adult participants, from 31 provinces, found that the prevalence of diabetes was 11.6% in 2010 [2]. The economic burden of diabetes also has increased over time in China, and in 2015, the annual expenditure was between $51.1 and $88.4 billion [3]. Age, gender, obesity, hypertension, and hyperlipemia were considered as risk factors for diabetes in Chinese adults [4].

Recently, the role of liver enzymes, mainly alanine transaminase (ALT), as a potential novel marker of diabetes risk is attracting increasing interest. The liver is a primary site of insulin clearance and plays an essential role in maintaining normal fasting and postprandial plasma glucose levels [5]. Serum alanine aminotransferase (ALT) found mainly in the liver, is considered the most sensitive marker of hepatocyte injury [6]. Nonalcoholic fatty liver disease (NAFLD), recognised as one of the leading causes of chronic liver disease, is the cause of most abnormal aminotransferase measurements, providing the possibility

Abbreviations: DBP, diastolic blood pressure; FPG, fasting plasma glucose; NAFLD, nonalcoholic fatty liver disease; SBP, systolic blood pressure; SD, standard deviation; T2D, Type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride

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Table 1
Baseline characteristics of study participants by alanine transaminase quintiles (N = 210,051).

Characteristics	Q1	Q2	Q3	Q4	Q5	P for trend
	< 12.0 U/L	12.0 to < 15.8 U/L	15.8 to < 21.0 U/L	21.0 to < 31.0 U/L	≥ 31.0 U/L	
No. of participants	40,493	43,118	41,265	42,858	42,317	
Age (years)	38.3 ± 11.3	42.1 ± 13.1	44.4 ± 13.6	44.2 ± 12.9	41.3 ± 11.2	< 0.001
Male, N (%)	7983 (19.7%)	16,705 (38.7%)	23,877 (57.9%)	31,104 (72.6%)	35,437 (83.7%)	< 0.001
BMI (kg/m)	21.2 ± 2.5	22.1 ± 2.8	23.1 ± 3.0	24.1 ± 3.1	25.6 ± 3.3	< 0.001
SBP (mmHg)	112 ± 15	117 ± 16	120 ± 17	122 ± 16	124 ± 16	< 0.001
DBP (mmHg)	70 ± 10	72 ± 10	74 ± 11	76 ± 11	78 ± 11	< 0.001
Alanine transaminase (U/L)	9.7 ± 1.5	13.7 ± 1.1	18.0 ± 1.5	25.1 ± 2.8	52.7 ± 35.4	< 0.001
AST	17.8 ± 3.6	20.0 ± 3.8	22.0 ± 4.3	24.7 ± 5.2	35.4 ± 22.2	< 0.001
Fasting plasma glucose at first visit (mmol/L)	4.78 ± 0.56	4.86 ± 0.58	4.92 ± 0.61	4.98 ± 0.62	5.03 ± 0.65	< 0.001
Fasting plasma glucose at final visit (mmol/L)	4.96 ± 0.50	5.05 ± 0.56	5.14 ± 0.65	5.21 ± 0.70	5.31 ± 0.89	< 0.001
Total cholesterol (mmol/L)	4.45 ± 0.82	4.59 ± 0.87	4.72 ± 0.89	4.80 ± 0.89	4.97 ± 0.94	< 0.001
Triglyceride (mmol/L)	0.90 ± 0.54	1.06 ± 0.67	1.27 ± 0.86	1.53 ± 1.10	1.92 ± 1.39	< 0.001
HDL-C (mmol/L)	1.46 ± 0.30	1.42 ± 0.30	1.38 ± 0.31	1.33 ± 0.29	1.28 ± 0.29	< 0.001
LDL-C (mmol/L)	2.59 ± 0.62	2.71 ± 0.67	2.78 ± 0.68	2.83 ± 0.67	2.92 ± 0.71	< 0.001
Smoking Status (%)						
Current	892 (8.88%)	1700 (14.89%)	2357 (19.96%)	3204 (24.53%)	3635 (27.29%)	< 0.001
Former	172 (1.71%)	360 (3.15%)	528 (4.47%)	639 (4.89%)	837 (6.28%)	
Never	8980 (89.41%)	9356 (81.96%)	8925 (75.57%)	9220 (70.58%)	8846 (66.42%)	
Alcohol consumption (%)						
Current	96 (0.96%)	191 (1.67%)	258 (2.18%)	371 (2.84%)	403 (3.03%)	< 0.001
Former	749 (7.46%)	1267 (11.10%)	1765 (14.94%)	2318 (17.74%)	2757 (20.70%)	
Never	9199 (91.59%)	9958 (87.23%)	9787 (82.87%)	10,374 (79.42%)	10,158 (76.27%)	
Family history of diabetes (%)	919 (2.27%)	922 (2.14%)	785 (1.90%)	813 (1.90%)	884 (2.09%)	0.007
Year of follow up (years)	3.06 ± 0.93	3.12 ± 0.94	3.13 ± 0.94	3.15 ± 0.95	3.15 ± 0.94	< 0.001
Diabetes was diagnosed during follow-up (%)	214 (0.53%)	472 (1.09%)	754 (1.83%)	1040 (2.43%)	1664 (3.93%)	< 0.001

Data are mean ± SD; ANOVA test and Chi-square test were used for continuous variables and categorical variables, respectively.

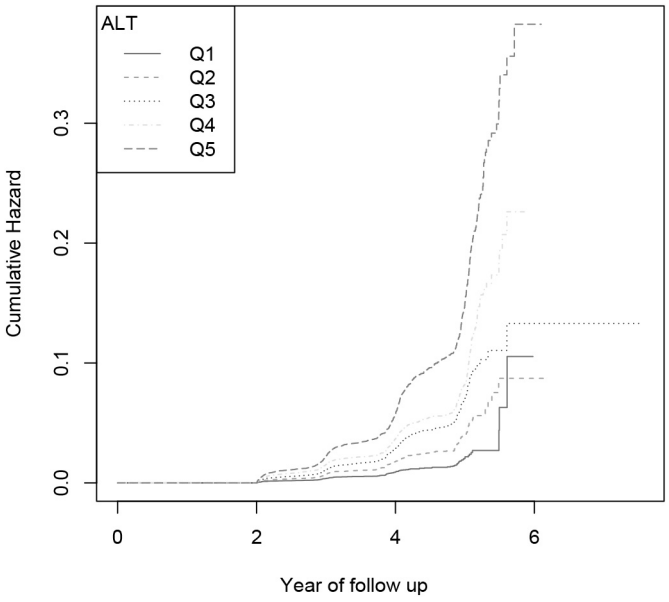

Fig. 1. Kaplan-Meier curves stratified by ALT quintiles. The curves showed different incidence of diabetes of participant with different ALT activities.

that the prospective relationship between ALT and diabetes [7].

Some studies have described a positive relationship between ALT activities and incident diabetes [8–16]. However, some studies are cross-sectional studies, which cannot address the question of whether the abnormalities in ALT activities precede the incident of diabetes or whether the incident diabetes leads to increased ALT activities [15,16]. Moreover, studies in Japan and Mexican showed no association between increased ALT activities and incident diabetes [17,18]. The relationship between ALT activities and incident diabetes among individuals may be controversial.

Age and gender are well known as risk factors for developing diabetes. Moreover, persons of different age and sex might have different normal range of serum ALT. Dufour et al. demonstrated that ALT activities are substantially higher in males than in females and vary with age in adults [19]. Therefore, the effect of ALT activities on the incident diabetes might be affected by age and gender. However, there are no studies to explore the independent effect of ALT activities on incident diabetes, stratified by age and gender.

2. Materials and methods

2.1. Study participants and design

We obtained data from the 'Dryad Digital Repository' website (www.Datadryad.org). This website makes the raw data of published papers freely reusable for secondary analysis. According to Dryad Terms of Service, we cited the Dryad data package in the present study [20]. Chen et al. conducted a retrospective cohort study of adult individuals across 11 cities in China [21]. 211,833 persons free of diabetes at baseline and with at least 2 visits between 2010 and 2016 were recruited. We downloaded the raw data and did a secondary analysis. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University. No informed consent was required because the data are anonymised.

2.2. Data collection

We extracted variables from the database as follows: age, gender, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), smoking and drinking status, family history of diabetes, alanine aminotransferase (ALT), fasting plasma glucose (FPG), total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein cholesterol (HDL-C), triglyceride (TG), year of follow up, and finally diagnosed of diabetes. Participants were interviewed to complete questionnaires about demographics, lifestyle, medical history and family history of chronic disease. Physical measurements were measured by trained staff including height, weight and blood pressure. Fasting venous blood samples were collected after at least a 10-hour fast at each visit. Laboratory parameters including plasma glucose, lipids and ALT

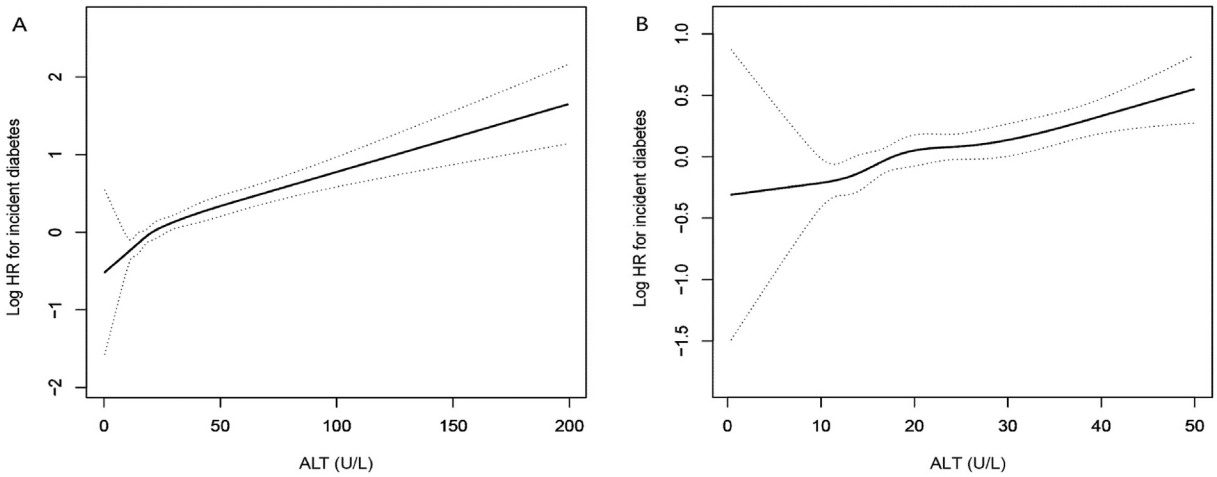

Fig. 2. The relationship between ALT and incident diabetes. Adjusted for age, sex, BMI, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, fasting plasma glucose at first visit, smoking status, drinking status, family history of diabetes. (B) ALT within normal range.

Table 2
Effect modification of ALT on incident of diabetes.

	Crude		Adjusted Model I		Adjusted Model II	
	HR (95% CI)	*P* value	HR (95% CI)	P value	HR (95% CI)	P value
ALT (U/L) Per SD	1.10 (1.10, 1.11)	< 0.001	1.11 (1.10, 1.13)	< 0.001	1.11 (1.08, 1.15)	< 0.001
Categories						
ALT Q1	Ref	Ref	Ref	Ref	Ref	Ref
ALT Q2	1.94 (1.65, 2.28)	< 0.001	1.14 (0.97, 1.34)	NS	1.05 (0.75, 1.47)	NS
ALT Q3	3.22 (2.77, 3.75)	< 0.001	1.23 (1.05, 1.44)	0.009	1.10 (0.80, 1.50)	NS
ALT Q4	4.19 (3.62, 4.86)	< 0.001	1.28 (1.10, 1.49)	0.002	1.28 (0.94, 1.75)	NS
ALT Q5	6.79 (5.89, 7.83)	< 0.001	1.74 (1.50, 2.03)	< 0.001	1.68 (1.23, 2.30)	0.001
Categories						
ALT Q1-Q4	Ref	Ref	Ref	Ref	Ref	Ref
ALT Q5	2.57 (2.42, 2.73)	< 0.001	1.43 (1.33, 1.53)	< 0.001	1.43 (1.25, 1.63)	< 0.001

Model I adjusted for age, sex, BMI, systolic blood pressure, diastolic blood pressure, fasting plasma glucose at first visit, family history of diabetes.
Model II adjusted for age, sex, BMI, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, fasting plasma glucose at first visit, smoking status, drinking status, family history of diabetes.

were measured on an autoanalyser (Beckman 5800). More specific details are presented in the original report [21].

2.3. Outcomes

The primary outcome was developing diabetes during the follow-up period (2010–2016). Diagnosis of diabetes was based on (1) fasting plasma glucose ≥7.00 mmol/L, and/or (2) self-reported diabetes, and/or (3) receiving oral hypoglycemic or insulin treatment.

2.4. Statistical analyses

We excluded participants (n = 1782) who had no available alanine transaminase (ALT) measurements. Continuous variables were expressed as mean ± SD, and categorical variables were expressed as number (%). Cumulative hazard curves were plotted using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards models were used to identify the association of parameters with the incident diabetes. The hazard ratio (HR) was reported with a 95% confidence interval (CI). In sensitivity analyses, we estimated adjusted HRs of diabetes incidence associated with ALT activities at baseline, stratified by age (10-y groups), sex, BMI, FPG at first visit, smoking, drinking, family history of diabetes. We also tested the interaction effects in different subgroups. For propensity-score matching, we matched patients by age, gender, BMI, SBP, DBP, smoking and drinking status, FPG at first visit, total cholesterol, triglyceride, family history of diabetes, and year of follow up. Matching was performed with the use of a 1:2 matching protocol, with the propensity score in a range of ± 0.05. All the tests were 2-sided, and a $P < .05$ was considered statistically significant. Statistical packages R (version 3.4.3, The R Foundation; http://www.r-project.org) was used for statistical analyses.

3. Results

3.1. Baseline characteristics of study participants

We included 210,051 Chinese adult persons (115,106 male and 94,945 female) in our study. The mean age was 42 y old, and the median serum ALT was 18 U/L. Participants' baseline characteristics were presented by ALT quintiles in Table 1. Baseline ALT activities were positively associated with age, the proportion of male, BMI, SBP, DBP, FPG, total cholesterol, triglyceride, LDL-C, history of drinking, history of smoking, and were inversely associated with HDL-C and family history of diabetes. Fig. 1 shows Kaplan-Meier curves illustrating the cumulative incidence of diabetes stratified by ALT quintiles. Participants with the fifth ALT quintile (Q5) showed the highest risk of diabetes compared to those in the lower ALT quintiles (3.93% vs 1.48%, $P < .001$).

3.2. Independent effect of ALT on the incident diabetes

During a median of 3.0-y follow-up, 4144 of 210,051 (1.97%)

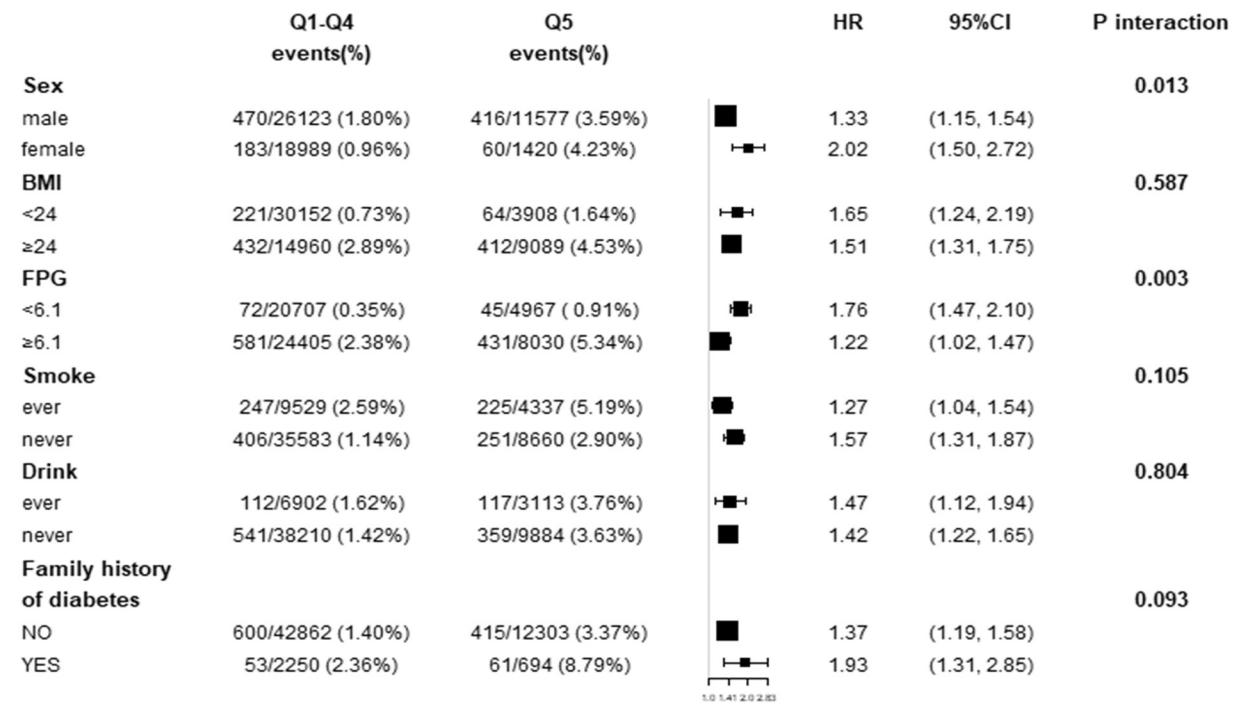

Fig. 3. Effect size of ALT on incident diabetes in different subgroups. Note: Adjusted for age, sex, BMI, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, fasting plasma glucose at first visit, smoking status, drinking status, family history of diabetes. Not adjusted for the stratification variable.

Table 3
Effect modification of ALT (Q5 vs. Q1–4) on incident of diabetes, stratified by age and gender.

Age, y	Gender	Unadjusted				Adjusted[a]		
		ALT Q1-Q4 Events (%)	ALT Q5 Events (%)	HR (95%CI)	P value	HR (95%CI)	P value	P value for interaction
20 to < 30								
	Male	16/11529 (0.14%)	36/4168 (0.86%)	6.48 (3.59, 11.67)	< 0.001	1.19 (0.25, 5.60)	NS	NS
	Female	17/12179 (0.14%)	6/512 (1.17%)	8.16 (3.22, 20.71)	< 0.001	0.00 (0.00, Inf)	NS	
30 to < 40								
	Male	96/28748 (0.33%)	334/16005 (2.09%)	6.30 (5.02, 7.90)	< 0.001	**2.41 (1.54, 3.76)**	**< 0.001**	NS
	Female	75/35546 (0.21%)	38/2123 (1.80%)	9.00 (6.09, 13.29)	< 0.001	**4.89 (2.00, 11.98)**	**< 0.001**	
40 to < 50								
	Male	227/15161 (1.50%)	382/8350 (4.57%)	2.94 (2.50, 3.47)	< 0.001	**1.53 (1.09, 2.16)**	**0.014**	NS
	Female	139/19945 (0.70%)	35/1498 (2.34%)	3.32 (2.29, 4.81)	< 0.001	1.37 (0.54, 3.48)	NS	
50 to < 60								
	Male	536/12532 (4.28%)	391/4650 (8.41%)	1.81 (1.59, 2.06)	< 0.001	1.09 (0.84, 1.40)	NS	NS
	Female	190/10938 (1.74%)	92/1503 (6.12%)	3.57 (2.79, 4.58)	< 0.001	1.36 (0.69, 2.66)	NS	
60 to < 70								
	Male	445/7833 (5.68%)	186/1762 (10.56%)	1.67 (1.40, 1.98)	< 0.001	0.99 (0.69, 1.43)	NS	NS
	Female	260/6832 (3.81%)	82/993 (8.26%)	1.87 (1.46, 2.40)	< 0.001	1.71 (0.98, 2.98)	NS	
≥70								
	Male	257/3495(7.35%)	44/444(9.91%)	1.39 (1.03, 1.87)	0.030	0.94 (0.54, 1.64)	NS	NS
	Female	182/2326(7.82%)	25/200(12.5%)	1.35 (0.92, 1.96)	NS	**2.23 (1.15, 4.33)**	**0.018**	

[a] Adjusted for age, sex, BMI, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, fasting plasma glucose at first visit, smoking status, drinking status, family history of diabetes. Bold: statistical significance ($p < 0.05$)

participants developed diabetes. In the overall sample, the unadjusted HR for every one SD increase in ALT was 1.10 (95% CI, 1.10–1.11, P < .001). After full adjusted for age, sex, family history of diabetes, BMI, SBP, DBP, total cholesterol, triglyceride, FPG at first visit, smoking and drinking status, there was a positive association between ALT activities and incident diabetes (Fig. 2). An SD increase in ALT concentrations was associated with an 11% increase in the adjusted risk of developing diabetes (HR: 1.11, 95% CI: 1.08–1.15; *P* < .001). Consistently, when ALT was assessed as quintiles, compared with the first ALT quintile, the fully adjusted HR for incident diabetes of the fifth ALT quintile was 1.68 (1.23–2.30). A significantly higher risk of incident diabetes (HR: 1.43 95% CI: 1.25–1.63) was also found in those in the fifth quintile (Q5) compared with participants in the first to fourth quintiles (Q1–4) (Table 2). When the analysis was restricted to participants with ALT activities within the normal range (≤40 IU/L, *N* = 186,269), higher ALT activities were still associated with the development of diabetes, even after full adjustment (per SD increase, HR: 1.30, 95%CI (1.05–1.61), *P* = .015) (Supplementary Table 1).

3.3. Subgroup analysis by important covariables

We performed analyses after stratification according to major covariables known to affect the incident diabetes, including sex, age, family history of diabetes, BMI, FPG at first visit, smoking and drinking status (Fig. 3). Regardless of the subgroup, the fifth ALT quintile (ALT Q5) resulted in a significant increase in the incidence of diabetes. For

Table 4
Characteristics of participants after Propensity-Score Matching.

Variables	No Diabetes (n = 2102)	Diabetes (n = 1051)	P value
Age (y)	54.5 ± 14.0	54.2 ± 13.1	NS
Male, N (%)	1611 (76.6%)	824 (78.4%)	NS
BMI (kg/m)	26.0 ± 3.4	26.1 ± 3.4	NS
SBP (mmHg)	130 ± 17	130 ± 19	NS
DBP (mmHg)	80 ± 11	80 ± 11	NS
Fasting plasma glucose at first visit (mmol/L)	5.83 ± 0.60	5.83 ± 0.72	NS
Total cholesterol (mmol/L)	5.08 ± 0.94	5.09 ± 0.91	NS
Triglyceride (mmol/L)	2.13 ± 1.71	2.17 ± 1.50	NS
Smoking Status (%)			
Current	730 (34.7)	358 (34.1)	0.016
Former	90 (4.3)	70 (6.7)	
Never	1282 (61)	623 (59.3)	
Alcohol consumption (%)			
Current	81 (3.9)	46 (4.4)	NS
Former	335 (15.9)	174 (16.6)	
Never	1686 (80.2)	831 (79.1)	
Family history of diabetes (%)	219 (10.4)	102 (9.7)	NS
Year of follow up (y)	3.33 ± 0.97	3.32 ± 1.01	NS
Alanine transaminase (U/L)	30 ± 22	37 ± 30	< 0.001

Data are mean ± SD and N (%); Sudent t-test and Chi-square test were used for continuous variables and categorical variables, respectively.

Table 5
Effect ALT on incident of diabetes after Propensity-Score Matching.

	Unadjusted		Adjusted[a]	
	HR (95%CI)	P value	HR (95%CI)	P value
ALT (U/l)	1.01 (1.01, 1.01)	< 0.001	1.01 (1.01, 1.01)	< 0.001
ALT per SD	1.29 (1.20, 1.39)	< 0.001	1.30 (1.21, 1.40)	< 0.001
ALT category				
Q1-Q4 (< 31 U/L)	Ref	Ref	Ref	Ref
Q5 (≥31 U/L)	1.65 (1.41, 1.92)	< 0.001	1.67 (1.43, 1.96)	< 0.001

[a] Adjusted for the propensity score and smoking status.

ALT activities, the HRs for diabetes appeared stronger in women than in men, and the heterogeneity test was significant (P = .013). To examine the robustness of the joint effect of age, gender, and ALT activities on diabetes, the HRs of incident diabetes according to the baseline ALT activities after stratification into six groups of age (10-y groups) and 2 groups of gender (male and female) were shown in Table 3. After full adjustment, age 30 to 40 and 40 to 50 y males within the highest quintile (Q5) of ALT activities had 2.4- and 1.5-fold increased odds for incident diabetes, respectively, compared with men in the lower ALT activities. Among women with age 30 to 40 and ≥ 70 y, ALT activities in the highest quintile had 4.9- and 2.2-fold increased odds of incident diabetes after median 3.0-year follow-up compared with those in the lower ALT activities. In contrast, the risk increase was modest or non-significant among other age subgroups.

3.4. The outcome of propensity score matching

To further confirm that the findings observed in the multivariate analysis. We matched 2102 participants without diabetes to 1051 participants with diagnosed diabetes, after correcting for age, sex, family history of diabetes, BMI, SBP, DBP, total cholesterol, triglyceride, FPG at first visit, smoking and drinking status, year of follow up in a range of ± 0.05. Participants finally diagnosed diabetes had higher baseline ALT activity (37 ± 30 U/L vs 30 ± 22 U/L, P < .001) (Table 4). After further adjusted for the propensity score and smoking status, increased ALT concentrations remained positively associated with the incidence of diabetes (per SD HR 1.30 (1.21–1.40), Table 5).

4. Discussion

We demonstrated that ALT was one of the independent risk factors for incident diabetes among participants form different regions of China. Moreover, we found that high ALT at baseline predicted the development of type 2 diabetes, especially in males with age 30–50 and females with age 30–40 or ≥70 y.

Previous studies have reported that impaired hepatic function is related to insulin resistance and type 2 diabetes. The exact pathophysiological mechanisms underlying the relationship are not fully understood. ALT appears to be associated with hepatic insulin resistance, decline in hepatic insulin sensitivity, and abnormal elevation of hepatic gluconeogenesis. There are several hypotheses. First, the aberrant accumulation of lipids in the liver, usually termed NAFLD, is tightly associated with insulin resistance and type 2 diabetes [22,23]. ALT is sensitive in the detection of NAFLD and NALFD accounts for the most of increased ALT activities. Second, increased ALT activities may reflect chronic subclinical inflammation, which may induce oxidative stress and impair insulin signalling [24]. Vozarova et al. observed that ALT activities were positively associated with white blood cell levels even after adjusting for obesity and insulin resistance [9]. Third, ALT plays an important role in gluconeogenesis by converting alanine into pyruvate for glucose production [25]. Increased hepatic gluconeogenesis is associated with the development of diabetes [26].

Our results are in agreement with the findings of previous studies, which reported that high ALT activity was a risk factor for developing diabetes independent of other confounding factors (obesity, plasma glucose, and lipid, family history of diabetes). Besides, because most individuals had ALT activities below normal upper limits, the observation may highlight the importance of variation within what are considered to be “normal ranges” for ALT concentrations. Therefore, we further conducted an analysis restricted to ALT activities within the normal range. Wannamethee and Goessling et al. both found that increased ALT within the normal range was significantly associated with incident diabetes, which is consistent with our findings [11,12]. Some physicians have advocated lowering the normal range, because patients with non-alcoholic fatty liver disease may have ALT activities in the normal range [27].

Considering alcohol consumption and smoking status might increase transaminase levels, we performed subgroup analysis by dividing participants into ever drinking (smoking) group and never drinking (smoking) group. The result was unchanged after stratification analysis.

Recently, Wu et al. indicated that the relationship of ALT with metabolic syndrome was stronger in women than in men [28]. In the subgroup analysis, we also found that females had a higher risk of diabetes than men in the same ALT activity. ALT activities are normally higher in men than women. Therefore, the same ALT activity may be normal for men but be abnormal for women. Kim et al. reported that ALT activities were positive correlated with glucose levels in women, and were negative correlated with age in men [27]. Moreover, we found the relationship between ALT and incident diabetes varied in different age groups. The mechanism responsible for the heterogeneity of ALT effect regarding age and sex is unclear. Men and women in different age ranges might need to establish separate reference limits of ALT.

The major strength of our study is that, to best of our knowledge, this is the first and largest study to report different associations between ALT and incident diabetes according to the different sex and age groups in Chinese persons. Besides, some sensitivity analyses including multivariate Cox proportional hazards model, subgroup analyses, and propensity score matching were used to confirm the robustness of the results.

There are several limitations to our study. Limited by retrospective and observational nature of this study, 1782 participants who had no available alanine transaminase (ALT) measurements were excluded. There were differences in the several baseline characteristics between

included and excluded participants, and this might cause the bias. However, the significant variables, including the fasting glucose concentration (included vs excluded: 4.91 ± 0.61 vs 4.98 ± 0.59 mmol/L) and the percentage of the final diagnosis of diabetes (1.97% vs 1.68%, $P = .38$), were similar between included and excluded participants. Therefore, it is unlikely to severely underestimate or overestimate the association between ALT activities and incident diabetes. Secondly, the 2-h post-load glucose and glycated haemoglobin levels were not measured, we cannot exclude the possibility that participant with diabetes at baseline may include in the study. Thirdly, our results were based on secondary analyses. Despite extensive adjustments for potential confounders, some unrecorded risk factors might affect our results. Lastly, the median 3.0 y follow-up might be too short to evaluate the long-term effect of ALT on incident diabetes.

5. Conclusion

It is a large study in Chinese cohort to investigate whether the association between ALT and incident diabetes is modified by age and gender. Our result indicated that 30–40 y individuals, whether male or female, with increased transaminase levels had the greatest increased risk for diabetes in comparison with persons with lower ALT activities. The measurement of ALT is convenient, low-cost, and standardised in routine clinical practice. This biomarker may be clinically useful in identifying people at higher risk of developing diabetes. Therefore, if more future prospective studies verify the result, our findings may provide evidence for controlling a relatively low ALT activity in persons especially aged 30–40 y aimed at the prevention of diabetes.

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