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Regional variation of alanine aminotransferase serum levels in the People's Republic of China

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Abstract

The regional variation of the blood concentration of alanine aminotransferase (ALT), a sensitive predictor of liver damage, was studied in the People's Republic of China with reference to its potential association with environmental variables and geographic location. The research results presented are based on 121,977 blood samples from healthy adults in 93 cities in the country using correlation analysis, ridge regression estimation and trend surface analysis that were applied to explore if there was any tendency of spatial variation. A regression formula using a simulation equation under the condition of known local geographic factors was used. Statistical significance was set at $P<0.05$. A positive correlation between ALT concentration altitude and sunshine hours and a negative correlation between ALT concentration and temperature, humidity and precipitation were found. With respect to geographical location, there was a negative correlation between ALT concentration and longitude. Higher ALT values were found in western China compared to eastern regions, dividing the country into three different regions with respect to serum ALT levels.

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Introduction

The internal organs of the human body and the geographical environment in which people reside can be seen as an integrated whole, *i.e.* life is maintained at an equilibrium by the body obtaining what it needs from the natural environment. For example, Hippocrates, the father of western medicine, stresses that the effect of seasons should be considered in clinical medical research (Hippokrates, about 400 BC) and the Chinese classical work *Spring and Autumn Annals* (Lv, about 200 BC) reports that baldness and goitre are produced by soft water, while freshwater furthers beauty. These ancient observations acknowledge and support the idea that the functions of the body's organs are to some degree directly influenced by outside factors. Still today, some Chinese scholars are committed to the study of the effect of the environment on the body. For example, Ge *et al*. (2014) studied its impact on the peak expiratory flow in male children and Liu *et al*. (2015) discussed its effect on the P wave in the electrocardiogram value, while Ma *et al*. (2008) discovered that the height of people is affected by the geographical surroundings where they grow up.

Alanine aminotransferase (ALT) is an important enzyme found in muscles and various internal organs, such as the kidneys, heart and, most abundantly, the liver. Elevated serum ALT levels accompanies injury of these organs, and since this enzyme plays an important role in hepatic enzyme metabolism, an increased value is a strong indicator of liver damage (Xiao, 2014; Liu, 2015; Wang *et al*., 2015; Ekiz *et al*., 2016; Knudsen *et al*., 2016). Reviewing reported studies and published literature, we found a strong biological variability of ALT levels also without pathological organ changes, which must then be due to other factors (Drabkin, 1975; Mörl, 1983). For example, when the aerial concentration of oxygen decreases, the arterial blood oxygen also decreases and this may have an effect on the liver, which is sensitive for hypoxia (Ušaj and Burnik, 2016). Moreover, under the condition of cold temperatures and hypoxia, or other situations including low partial oxygen pressure in cold climates, regenerative cell changes (cytothesis) can decline, while increased levels of sodium and potassium ions contribute to increased cell vulnerability (Song and Wang, 2006; Wang and An, 2010) that may lead to increased release of ALT into the blood. Thus, although variations of the ALT serum level is a sensitive indicator of the liver function in clinical practice, there is also a variation of this enzyme with respect to variables such as sex, age, *etc*. that does not indicate disease. However, recognition of an association between ALT reference values and the natural environment in healthy subjects is limited. To provide a new perspective on this issue and ALT reference values, this paper explored the regional, spatial variation of ALT values in China that was studied employing ridge regression and trend surface analysis.

Materials and Methods

Study area and subjects

Measurements of serum ALT levels in a cohort of 121,977 healthy adults from 93 cities in mainland China (excluding Hong Kong, Macao and Taiwan) were collected. These sera came from 18-90 years old volunteers who were predominantly from eastern areas (47.3%) with fewer people from middle China (30.5%) and western parts of the country (22.2%) due to disparities of population density. The ratio of males (67,941) to females (54,036) was 1:1.3. The subjects were all apparently healthy with the inclusion criteria being normal weight and height, *i.e*. body mass index (BMI) between 18.5 and 25.0 kg/m^2), normal blood pressure and normal blood glucose after 8 hours' fasting. The exclusion criteria were diagnosed, ongoing disease, such as hepatobiliary and kidney diseases (fatty liver, liver cirrhosis, hepatitis, nephritis, kidney stone, *etc*.), blood diseases (haemangioma, disturbance of blood circulation, other blood abnormities) or abnormal blood chemistry covering an array of different tests as used by Xue (2014). They were also subjected to abdominal ultrasonography to make sure that no hidden abnormality existed at the time of testing.

Environmental variables

Information on three classes of environmental factors were collected: spatial location and terrain indices from relevant maps and dictionaries, a meteorological index provided by the meteorological data sharing service system in China (http://www.cma.gov.cn) and a soil index obtained from the Harmonious World Soil Database (HWSD) of Vienna International Institute of Applied Systems (IIASA) supplied by the Food and Agriculture Organization (FAO) (http://www.fao.org/nr/land/soils/harmonized-world-soil-database/zh/). In all, 22 different geographic locations and environmental variables (referred to by abbreviations X_1-X_{22}) were utilised as shown in Table 1.

Statistical approaches

The regional variation of ALT and the potential relationship with 22 environmental variables were explored using correlation analysis (Bonett and Wright, 2000), ridge regression (Hoerl and Kennard, 1970) and trend surface analysis (Watson, 1971) while paying attention to the possibility of multiple collinearity. Student's t-test was used to the disparities of ALT values among different regions and the two sexes.

Correlation analysis

This analysis, comparing the correlation between the different datasets collected, was carried out with the Spearman method (SPSS, v. 21.0 - https://www-01.ibm.com/support/docview.wss?uid=swg21608060). P values were set at <0.05 for statistical significance, while P values <0.01 indicated highly significant correlations (Zar, 1972). Geographical factors constitute an organic whole as they are all connected and the statistical effectiveness can be reduced due to collinearity between the variables involved. Therefore, it was necessary to control for multicollinearity, a significant correlation between explanatory variables caused by the specific characteristics of the variables investigated that reduces the accuracy of the results (Liu and Li, 2009). This was done using SPSS v. 21.0

Ridge regression analysis

This is a regression method proposed by Hoerl and Kennard (1970) based on a biased least square method. According to the Markoff Gauss theorem (Baksalary and Kala, 1981), the regression coefficients estimation is unbiased and has a minimum variance based on the least square method under the condition of linear regression. In other words, the estimation of unbiased and minimum variance is not affected by multiple collinearity (Yang, 2004). Thus, the accuracy of this method is superior to the least square method. In this study, ridge regression was employed to explore environmental determinants on ALT values building an equation regarding ALT values and environment. The key of the ridge regression model is to confirm ridge parameter K (Liu and Li, 2009), the optimal solution of which depends on the unknown

Table 1. Environmental variables investigated.

Variables 1-11	Code	Variables 12-22	Code
Longitude	X_1	Soil clay percentage	X_{12}
Latitude	X_2	Soil reference bulk density	X_{13}
Altitude	X_3	Soil bulk density	X_{14}
Sunshine hours*	X_4	Soil organic matter content	X_{15}
Average temperature*	X_5	Soil pH value	X_{16}
Average relative humidity*	X_6	Soil (clay) cation exchange capacity	X_{17}
Precipitation*	X_7	Soil (silt) cation exchange capacity	X_{18}
Temperature	X_8	Soil base saturation	X_{19}
Average wind speed*	X_9	Total exchangeable volume of soil**	X_{20}
Percentage of sandy soil	X_{10}	Soil alkalinity	X_{21}
Soil particle percentage	X_{11}	Soil salinity	X_{22}

*Annual; **an indicator evaluating the capacity of the soil to interact with air, water as well as with organic and inorganic substances.

parameters β_i and X_i in the model. The linear, analogue equation is as follows:

$$Y = \sum_{i=1}^{n} \beta i \bullet Xi + \varepsilon \quad \text{Eq. 1}$$

where X_i and K are calculated as follows:

$$\beta\,(Ki) = (X^T X + Ki)^{-1} \bullet X^T Y \quad \text{Eq. 2}$$

where Eq. 1, $Xi=\{X_1...X_n\}$ presents the input variables (the 22 environmental variables in this study). Y is the dependent variable (*i.e.* the calculated ALT values), while $\beta i=\{\beta_0...\beta n\}$ are the parameter vectors of the function and ε a residual error. In Eq. 2, $\hat{\beta}(K_i)$ is a function regarding parameter Ki, i=1…n.

However, this is not the best formula to express the relation between ALT values and environmental variables, because it is difficult to assess K. If it tends to zero, the equation will become the same as the least squares estimate deviating from the biased estimation; however, if it tends to infinity, the ridge trace tends to zero and the equation will not have any practical significance (He and Wang, 2008). In the actual calculation, the K value of the ridge trace curve tends to the ridge parameter (Yu, 2007), which means that the square error cannot be increased too much. The ridge regression estimation was simulated by the use of SAS software (http://www.statisticssolutions.com/statistical-analysis-software-sas/).

Trend analysis

The spatial variation tendency of ALT values was calculated with the statistical analysis module of the ArcGIS, v. 10.2 software (ESRI, Redlands, CA, USA) based on the simulated data from 2,322 cities and counties in China on the basis of the ridge regression equations. In this study, the spatial variation curves were plotted with longitude, latitude and ALT values a as x-axis, y-axis and z-axis, respectively.

A normal distribution test should be applied on the simulated dataset to select the proper method before interpolation. It is reliable that to test the normality with the K-S test method (Fasano and Franceschini, 1987). Thus, the simulated dataset was a test for normality with the SPSS software, v. 21.0, the results of which showed a Z value of 10.130 at the $P<0.05$ level. These calculations inferred that the simulated dataset was not a normal distribution. Therefore, Kriging interpolation (Rathbun, 2012) should be selected. The geographical ALT distribution in healthy adults was mapped by disjunctive Kriging (Thakur *et al*., 2016) using the statistical analysis module ArcGIS, v 10.2.

Firstly, the simulated values were added into a layer as analysed points. Secondly, an approach of disjunctive Kriging in the statistical analysis module was employed to interpolate the unknown points. Lastly, the map of ALT distribution was extracted by the mask method. It is noteworthy that the basic layer needed to be transferred into a grid layer (http://resources.arcgis.com/zh-cn/help/main/10.1/).

Results

The t-test applied to the disparities of ALT values among different regions and the two sexes showed $P=0.001<0.05$ and $P=0.108>0.05$, respectively, which indicates there was a significant difference of ALT values between regions but not between the sexes.

Correlation analysis

As can be seen from Table 2, the condition indices were >10 and the Eigen-values close to zero (apart from latitude and longitude) indicating that there might exist multicollinearity between these factors (Velleman and Welsch, 1981). However, as shown in Table 3, we found a negative correlation between ALT values and environmental factors including longitude, annual average temperature, annual average relative humidity and annual precipitation, and there was a positive correlation between ALT values and both altitude and the annual sunshine hours.

Table 2. Results of the collinearity control.

Variable	Eigen-value	Condition index
Longitude	0.854	2.641
Altitude	0.145	6.400
Sunshine hours	0.024	15.643
Average temperature	0.017	18.959
Average relative humidity	0.001	65.018
Precipitation	0.000	111.011

Table 3. Correlation and significance of alanine aminotransferase in healthy Chinese adults with respect to the set of environmental variables investigated.

Variable	Code	*r*	P
Longitude	X_1	-0.277**	0.000
Latitude	X_2	0.025	0.694
Altitude	X_3	0.405**	0.000
Sunshine hours	X_4	0.171**	0.008
Average temperature	X_5	-0.192**	0.003
Average relative humidity	X_6	-0.277**	0.000
Precipitation	X_7	-0.175**	0.006
Temperature	X_8	-0.085	0.185
Average wind speed	X_9	-0.071	0.271
Percentage of sandy soil	X_{10}	0.032	0.822
Soil particle percentage	X_{11}	-0.049	0.444
Soil clay percentage	X_{12}	0.018	0.782
Soil reference bulk density	X_{13}	-0.012	0.851
Soil bulk density	X_{14}	-0.028	0.667
Soil organic matter content	X_{15}	0.103	0.109
Soil pH value	X_{16}	-0.029	0.651
Soil (clay) cation exchange capacity	X_{17}	0.090	0.160
Soil (silt) cation exchange capacity	X_{18}	0.121	0.059
Soil base saturation	X_{19}	-0.082	0.334
Total exchangeable volume of soil	X_{20}	-0.125	0.052
Soil alkalinity	X_{21}	0.068	0.289
Soil salinity	X_{22}	-0.024	0.760

The correlation coefficient is indicated by r (r>0 indicates a positive correlation; and r<0 indicates a negative correlation). **Strong statistical significance.

Ridge regression

Table 4 shows that the variance inflation factor (VIF) of each coefficient was <10 in our study. When the ridge parameter *K* increased by 0.1, following the tendency of the ridge trace to gradually stabilise, the mean square error (MSE) also increased leading to a simultaneous decrease in accuracy. Compared with the least square method, the MSE only increased by 0.08201. Considering this, the ridge parameter *K*=0.3 was selected since the ridge trace tended to be stable at this value.

The ridge traces of ALT for the healthy adults are presented in Figure 1, where the variation of the *K* parameter is shown and the estimated coefficients read. When the ridge parameter *K* equalled 0.3, the MSE amounted to 6.90123 (Table 4) and at that *K*-level, the constant becomes 30.4476 (Table 5) and the coefficients -0.05713, 0.00230, 0.00702, 0.00618, -0.04830, 0.00026 of X_1, X_2, X_3, X_4, X_5 and X_6, respectively. The ALT equation is the following:

$$Y=30.45 - 0.05713X_1 + 0.002300X_2 + 0.007020X3 + 0.006180X_4 - 0.04830X_5 + 0.0002600X_6 \pm 6.901 \quad \text{Eq. 3}$$

From Eq. 3, the actual ALT of local, healthy adults can be calculated in relation to the geographical variables under study. The simulated values and true values were tested by the paired t-test using SPSS, v. 21.0 (Zhu and He, 2009) (Table 6). The results designated by P=0.127>0.05 are considered not to be significant with 95% confidence intervals between the true and simulated values. Put another way, the simulated values can be used as reference.

Trend analysis

As presented in Figure 2, the ALT values for healthy adults along the longitude showed a decreasing trend from west to east (the red curve), while it first increased from south to north along the latitude and then decreased slightly in the extreme North (the

Table 4. The ridge parameters.

K-value	MSE	VIF					
		X_1	X_2	X_3	X_4	X_5	X_6
0.0	6.81922	5.16801	5.63270	3.68974	5.07754	6.29636	3.97702
0.1	6.85304	1.30908	1.63045	1.33548	1.66241	1.83292	1.62458
0.2	6.88086	0.72647	0.86383	0.83947	0.91555	0.92751	0.94244
0.3	6.90123	0.51061	0.56371	0.61156	0.60512	0.57764	0.63726
0.4	6.91763	0.39823	0.41016	0.47708	0.44055	0.40301	0.46955
0.5	6.93169	0.32821	0.31894	0.38765	0.34068	0.30240	0.38555
0.6	6.94421	0.27962	0.25923	0.32387	0.27457	0.23847	0.29568
0.7	6.95524	0.24346	0.21739	0.27618	0.22804	0.19502	0.24601
0.8	6.96625	0.21527	0.18655	0.23929	0.19378	0.16393	0.20915
0.9	6.97621	0.19254	0.16292	0.21000	0.16764	0.14077	0.18089
1.0	6.98564	0.17376	0.14426	0.18624	0.14713	0.12296	0.15863

MSE, mean square error; VIF, variance inflation factor.

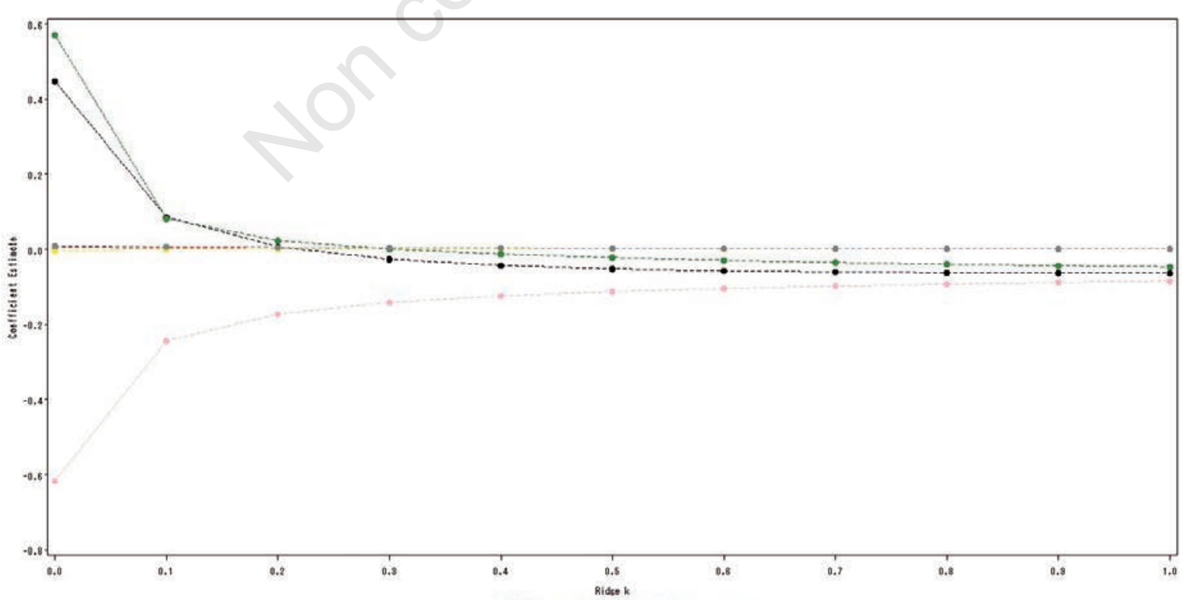

Figure 1. The ridge traces of alanine aminotransferase for healthy Chinese adults. The X_1-X_6 lines signify the variation trends of the K parameter at different levels of the estimated equation coefficients.

blue curve). Although the two curves reflect the change of ALT values along purely geographic directions, the topographic map of China reveals that they also changed with respect to altitude. With the ordinate (x axis) depicting longitude, the abscissa (y direction) latitude and Z the ALT concentration, it can be seen that the ALT values decrease in the eastern direction (the red slope), while they first increase in the northern direction along the latitude and then decreased slightly at the end (the blue curve).

The ALT values in healthy adults were found to be affected by the environment as governed by geographic location. The ALT values in healthy adults varied from 20.24 to 41.24 units per litre (U/L) serum. The average rate of ALT values in south-western regions (red areas on the map) varied between 34.24 and 41.24 U/L serum, while the rate of average ALT values (orange areas on the map) varied from 27.24 to 37.24 U/L serum. The values in the remaining areas (green on the map) varied from 20.24 to 27.24 U/L. Thus, the highest values were mainly found on the Tibetan Plateau, while the eastern plains and western regions had lower values (Figure 3).

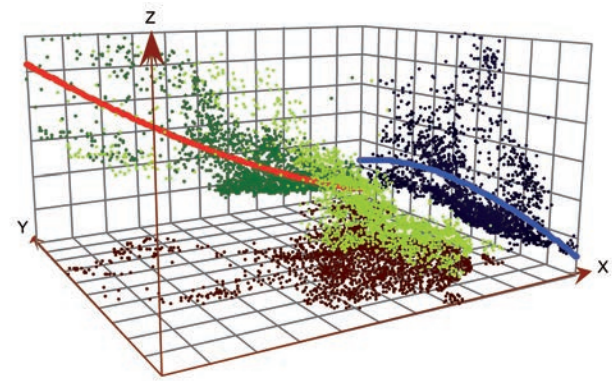

Figure 2. Variation of alanine aminotransferase values for healthy Chinese adults along geographic directions.

Table 5. The regression coefficients.

K-value	Constant	Regression coefficient					
		X_1	X_2	X_3	X_4	X_5	X_6
0.0	5.1834	0.18383	0.00537	-0.00062	0.19905	-0.09925	0.00046
0.1	22.2690	0.00830	0.00399	0.00054	0.05710	-0.05345	0.00051
0.2	27.8197	-0.03784	0.00269	0.00070	0.02287	-0.04909	0.00038
0.3	30.4476	-0.05713	0.00230	0.00072	0.00618	-0.04830	0.00026
0.4	31.8658	-0.06645	0.00205	0.00070	-0.00350	-0.04793	0.00017
0.5	32.6727	-0.07110	0.00186	0.00068	-0.01005	-0.04752	0.00010
0.6	33.1342	-0.07329	0.00172	0.00066	-0.01477	-0.04702	0.00004
0.7	33.3861	-0.07406	0.00161	0.00064	-0.01834	-0.04643	-0.00001
0.8	33.5047	-0.07399	0.00151	0.00062	-0.02109	-0.04580	-0.00005
0.9	33.5357	-0.07341	0.00143	0.00060	-0.02325	-0.04512	-0.00008
1.0	33.5079	-0.07250	0.00058	0.00058	-0.02497	-0.04443	-0.00011

Table 6. Comparison between actual and calculated values of serum alanine aminotransferase levels in healthy Chinese adults.

Sample point	X_1	X_3	X_4	X_5	X_6	X_7	True value	Simulated value
Shen Yang	123.29	44.7	2574	8.4	63	690.3	21.67	22.17
Yu Xi	102.53	1636.5	2300	15.8	75	906.8	29.34	26.23
Bao Ding	115.50	85.0	2750	12.3	62	570.0	21.36	22.96
A-K Tao	75.93	1471.0	2900	11.2	48	62.8	29.34	29.30
Guangzhou	113.22	6.3	1906	21.8	79	1694.1	20.67	21.23
Nan Jing	118.80	7.1	2155	15.3	77	1062.4	21.37	21.95
Nan Cong	106.11	309.7	1223	17.3	80	987.2	21.48	21.30
Zun Yi	106.93	860.0	1200	15.2	80	1098.0	21.35	23.10
An Yang	114.34	98.0	2400	13.6	66	606.1	21.39	22.59
Mei Shan	103.83	422.0	1060	17.2	85	1057.0	23.10	21.96

Discussion

On the condition of hypoxia, sugar in the human body produced pyroracemic acid by the means of glycolysis is turned into alanine under the catalysis of ALT (Wang and Wang, 2010). However, decrease of ALT activity in cold climates leads to a corrective increase of the concentration of this enzyme. Under the colder and drier climate in north-western China, residents have adapted to a propensity for eating food with high fat and protein but with only little fibre content (Jiang and Hu, 2005). The magnitude of fat and protein in this diet is greater than what can be metabolised. On the one hand, the long-term accumulation of lipids in the liver cells increase sensitivity to exogenous damage, while lipids increase the content of bile excretion on the other, a situation which makes cells release excess ALT into serum (Yu *et al*., 2014). This leads to a change in the internal environment with regional higher levels of ALT as a result.

The effects of soil on ALT values are indirect. Firstly, soil texture has an impact on soil properties in that gravel has better aeration and water permeability, causing a loss of nutrients (Shi *et al*., 2016) making the soil infertile, as is the case in north-western China. In contrast, the phaiozem soil in north-eastern China has abundant organic matter that produces agriculture products of rich in nutrition (Ling *et al*., 2016). All else being equal, people in different regions have different diets depending on the local food and this leads to a slight diversity of body fluids and function, *e.g*., with respect to the need for ALT, which leads to divergent values of the concentration of this enzyme. Secondly, soil pH in China has an evidently regional variation (Yang *et al*., 2015). The soil on southern China mostly is mostly acid, while alkaline soils are principally clustered in northern China. To balance the pH, people in northern China prefer acidic food, especially people in north-western regions, while people in southern regions dislike acidic food. On this condition, ALT values for healthy adults in north-western regions are higher than those in south-eastern people. Thirdly, the soil cation exchange capacity is an important determinant that to some extent reflects the chemical elements in the soil. Studies have demonstrated that there exists a close link between chemical elements in soil and body fluids that is reflected in a spatial distribution (Wang *et al*., 2014).

Conclusions

In summary, the ALT values in healthy adults show significant regional differences in correlation with the ambient geographical environment. In general, the values of this enzyme in the western regions of China are higher than in the East. Knowledge of this is significant for the interpretation of clinical test values and is also important for treatment.

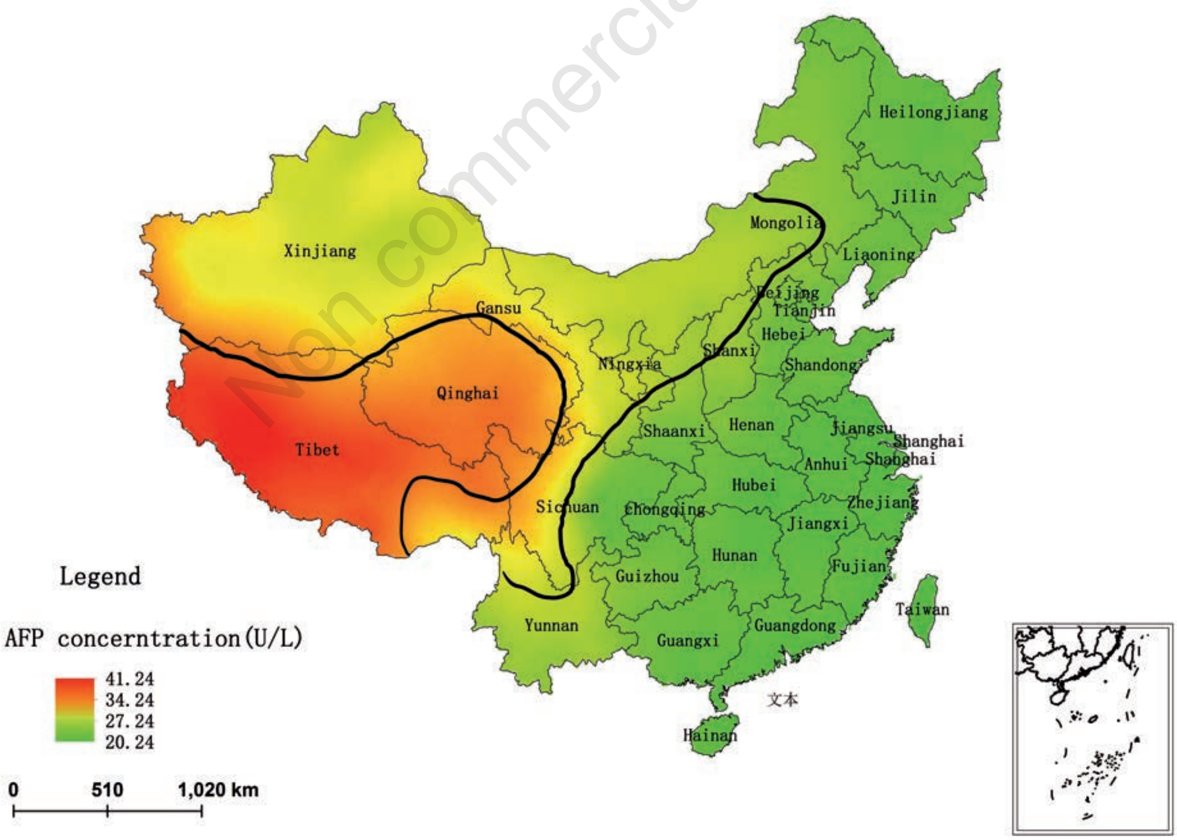

Figure 3. The spatial variation of alanine aminotransferase values in Chinese healthy adults in relation to geography.

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