Epidemiology

A spatial ecological study of selenoprotein P and Keshan disease

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ABSTRACT

Few spatial ecological studies on selenoprotein P (SePP) and Keshan disease (KD) have been reported. The main objective of this study is to investigate the relationships of SePP with KD, economic indicators and soil selenium and to visualize the evidence for KD precise prevention and control.

An ecological study design was employed. The serum SePP of 2351 subjects living in rural areas, general cities and developed cities in 15 KD endemic provinces and 13 KD non-endemic provinces in China were measured. Spatial description and spatial analysis of SePP were conducted. The subjects were adults aged.

The mean serum SePP level of KD endemic area residents was 14.20 mg/L, significantly lower than that in non-endemic areas, 15.30 mg/L (t = − 3.19, P = 0.0010). Serum SePP levels were low among the people in the KD endemic provinces of Shandong, Inner Mongolia, Heilongjiang, etc. The mean serum SePP level of the 2351 people was 15.04 (95% *CI*: 14.76 and 15.31) mg/L. The mean serum SePP levels of residents in developed cities, general cities and rural areas were 16.54 mg/L, 14.98 mg/L and 14.44 mg/L, respectively, and were significantly different (F = 17.00, P < 0.0010). Spatial regression analysis showed that the spatial distribution of SePP was positively correlated with per capita consumption expenditure and soil selenium.

Selenium deficiency may still exist among residents living in the KD endemic provinces. Shandong, Inner Mongolia, and Heilongjiang should be the target provinces, visualized by spatial analysis, for KD precise prevention and control.

1. Introduction

Keshan disease (KD) is a primary endemic cardiomyopathy occurring only in mainland China. Nationwide, KD has occurred in 2648 townships in 328 counties in 16 provinces (municipalities and autonomous regions) from the northeast to the southwest [1,2]. Since

Table 1

Serum SePP levels by demographic characteristics and endemic area.

Characteristic	Total		Endemic provinces		Non-endemic provinces		Statistics	*p*-Value
	n	SePP ($\overline{X} \pm s$)	n	SePP ($\overline{X} \pm s$)	n	SePP ($\overline{X} \pm s$)		
All	2351	15.04 ± 6.87	1984	14.65 ± 6.92	367	17.14 ± 6.21	t = -6.92	< 0.0010
Gender								
Male	805	15.32 ± 6.75	639	14.76 ± 6.76	166	17.48 ± 6.25	t = -4.92	< 0.0010
Female	1546	14.89 ± 6.94	1345	14.60 ± 7.00	201	16.85 ± 6.18	t = -4.74	< 0.0010
Statistics		t = 1.44		t = 0.48		t = 0.97		
p-Value		0.15		0.16		0.33		
Age(y)								
< 20	1233	17.40 ± 6.74	932	17.24 ± 6.94	301	17.88 ± 6.06	t = -1.54	0.12
20–24	894	12.52 ± 6.11	827	12.39 ± 6.12	57	14.48 ± 5.63	t = -2.50	0.012
25–29	210	11.91 ± 5.71	201	12.04 ± 5.73	9	9.02 ± 4.58	t = 1.55	0.12
≥30	14	14.63 ± 4.91	14	14.63 ± 4.91	0	—		
Statistics		F = 118.28		F = 94.57		F = 16.34		
p-Value		< 0.0010		< 0.0010		< 0.0010		
Areas								
Developed city	507	16.54 ± 6.50	348	15.96 ± 6.48	159	17.81 ± 6.36	t = -3.00	0.0030
General city	622	14.98 ± 6.74	540	14.62 ± 6.88	82	17.33 ± 5.21	t = -4.20	< 0.0010
Rural areas	1222	14.44 ± 7.00	1096	14.24 ± 7.03	126	16.17 ± 6.54	t = -2.93	0.0030
Statistics		F = 17.00		F = 8.23		F = 2.53		
p-Value		< 0.0010		< 0.0010		0.081		
Endemic areas								
Yes	553	14.20 ± 7.16	553	14.20 ± 7.16	—	—		
No	1798	15.30 ± 6.77	1431	14.82 ± 6.82	367	17.14 ± 6.21	t = -6.24	< 0.0010
Statistics		t = -3.19		t = 1.78				
p-Value		0.0010		0.070				

the late 1970s, the incidence of KD has been declining year by year, and KD has been well controlled in the past ten years [3–5]. It was proposed that the goal of prevention and control of KD was "To maintain the status eliminating KD, 95% of the counties with KD endemic areas to reach the elimination target" in the 2016–2020 National Plan for Prevention and Control of Endemic Diseases [6]. In disease elimination assessment, incidence is the most important index; however, it is equally important to consider the indicators of etiology, interventions and their effectiveness, especially for chronic and non-communicable diseases [7–9]. The findings of many community trials have shown that selenium supplementation effectively prevented the occurrence of acute and subacute KD and that KD is strongly associated with selenium deficiency [10–14]. Selenium is an essential trace element playing its biological functions through selenoproteins [15–20]. Selenoprotein P (SePP) is thus far regarded as the best marker of selenoproteins representing the status of human selenium nutrition [21–25]. Although, we have conducted a SePP study with a small sample size, little has been done regarding SePP at the population level [26]. Based on the endemic characteristics of KD, spatial epidemiology is very suitable for the prevention and control of KD [27]. Therefore, it is very important to conduct a spatial analysis of serum SePP in residents of both KD endemic and non-endemic areas in China. This not only helps to assess KD elimination in terms of etiological aspects but also provide evidence for KD precise prevention.

2. Material and methods

2.1. Study design

This was a spatial ecological study designed to investigate the levels of mean serum SePP in residents living in KD endemic and non-endemic areas and different cities and to visualize the evidence for KD precise prevention.

2.2. Study populations

In 2015, 2351 residents who had lived in their residence for more

than 6 months each year were selected as study subjects in cities and rural areas in 28 provinces in mainland China, including 15 KD endemic provinces of Gansu, Guizhou, Hebei, Hainan, Heilongjiang, Jilin, Liaoning, Inner Mongolia, Shandong, Shanxi, Shaanxi, Sichuan, Yunnan, Chongqing, and Hubei and 13 KD non-endemic provinces of Anhui, Beijing, Fujian, Guangdong, Guangxi, Hainan, Hunan, Jiangsu, Jiangxi, Shanghai, Tianjing, Xinjiang, and Zhejiang. The inclusion criteria of participants were permanent residents who were ≥18 years old, healthy, no major illnesses, were able to communicate normally, and volunteered to participate in the study. All participants gave informed consent.

2.3. Definition of a KD endemic area

Previously or currently, if there has been or is acute or subacute KD occurring or there has been or are chronic KD cases, we can judge the township as a KD endemic township [2]. The endemic areas are all rural. In a KD endemic province, only some counties are KD endemic counties, and in a KD endemic county, only some townships are KD endemic townships. Township is the smallest administrative division. According to the Keshan Disease Endemic Area Definition and Classification [2], the study subjects were divided into endemic and non-endemic areas.

2.4. Classification of cities in China

The study subjects living in cities, not rural areas, were further classified into general cities and developed cities according to the "New Classification List of Chinese Cities" [28].

2.5. Questionnaire survey

Gender, age, ethnicity/race, consumer expenditures, current residence and address, etc. were investigated using pre-designed questionnaires.
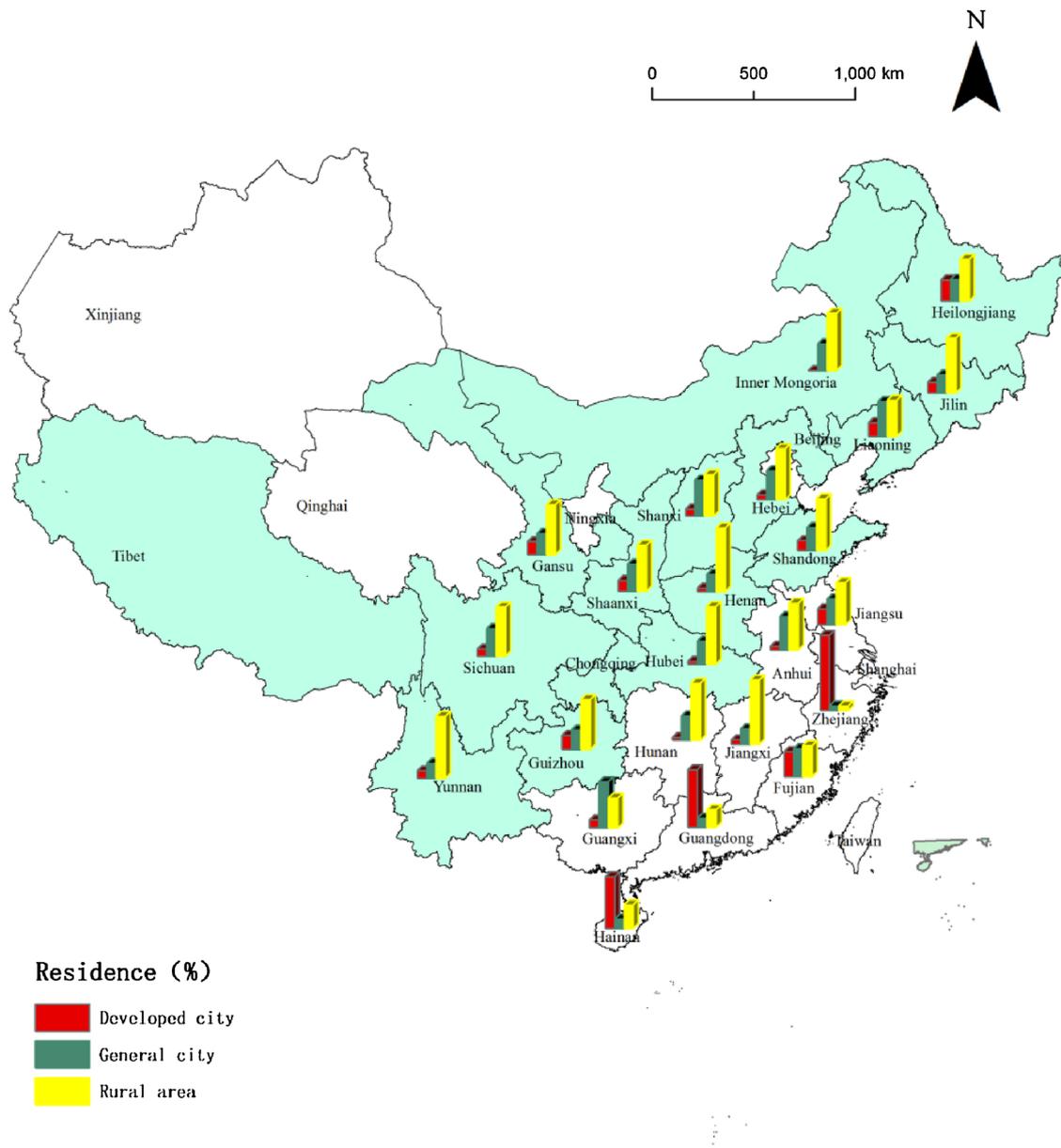
Fig. 1. Spatial distribution of the subjects investigated.

2.6. Blood samples

We collected 3 mL venous blood samples in vacuum blood collection tubes without anticoagulant. After the blood samples were naturally agglutinated for 10–20 minutes at room temperature, they were separated by centrifugation at $2500 \times g$ for 20 min. Serum was carefully collected and stored at $-80 °C$ until analysis.

2.7. Serum SePP

Serum SePP was measured using enzyme-linked immunoassay kits (Shanghai Enzyme-linked Biotechnology Co., Ltd.) according to the manufacturer's instructions. The serum SePP kit includes a set of SePP standards for calibration. The SePP standards were assayed at the same time as the serum samples of the study subjects, so a standard curve of optical density (OD) versus SePP concentration was produced. The concentration of SePP in serum was then determined by comparing the OD of the samples with the standard curve. The optical density (OD) was measured by using the BioTek Cytation 3 MFD at a wavelength of

450 nm.

2.8. Economic data

Data on per capita Gross Domestic Product (GDP) and per capita consumption expenditure were collected through the China Statistical Yearbook 2015–2016 [29].

2.9. Soil selenium

Soil selenium content data in 28 provinces were collected from the Background Value of Soil Elements in China (1990) [30].

2.10. Statistical analysis

Statistical analyses were performed using SPSS (version 17.0). Summary statistics were calculated for each variable (the mean ± SD for SePP concentration). Comparison between two groups was conducted using the *t*-test Multiple groups were compared using analysis of
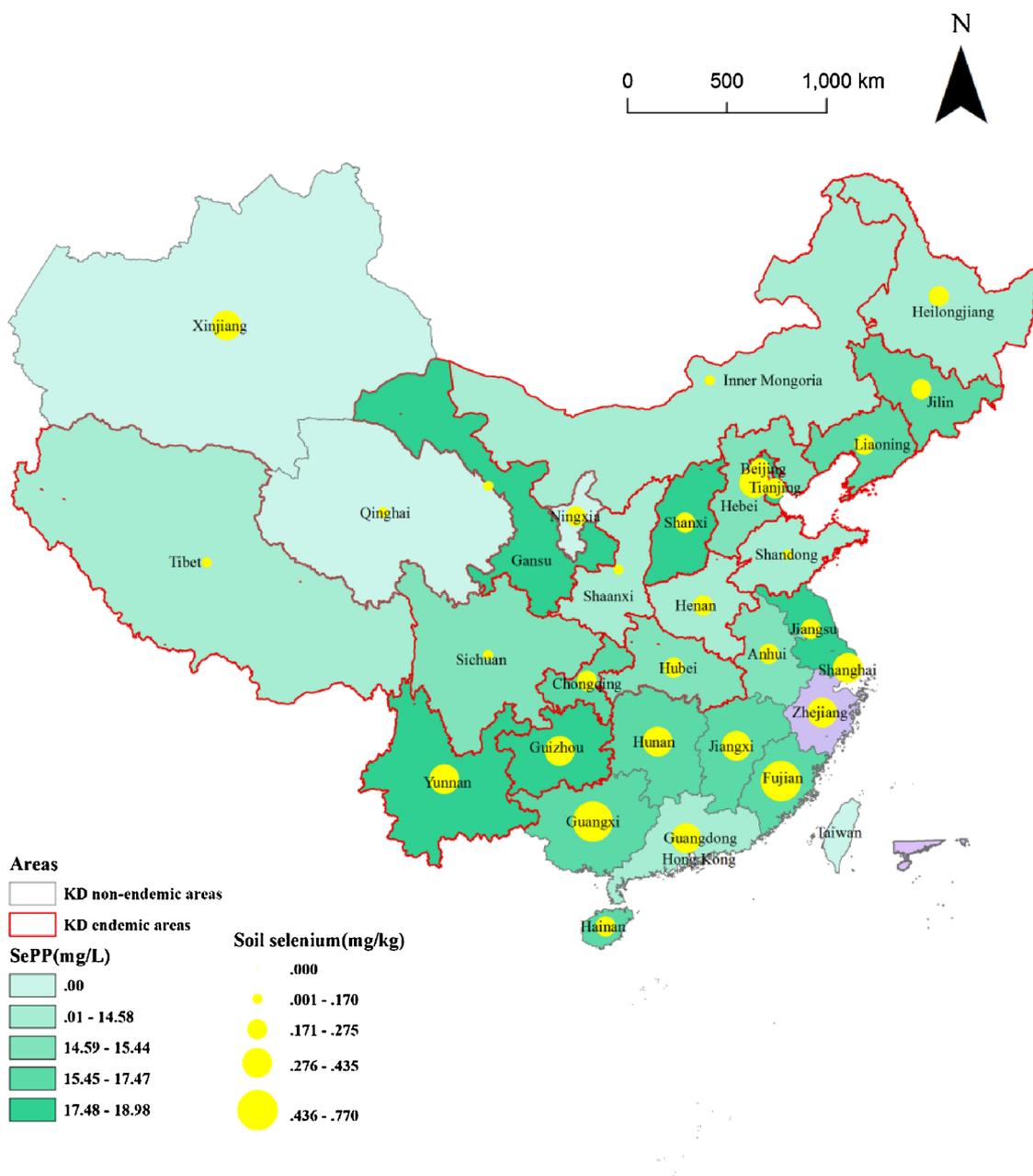
Fig. 2. Spatial distribution of the serum SePP and soil selenium levels.

variance, and then, multiple comparisons were conducted using the Bonferroni test. A *p*-value < 0.05 was considered significant.

Spatial description of the subjects, serum SePP, etc. was conducted using ArcGIS (version 9.0) by producing thematic maps.

Spatial analysis of serum SePP levels was conducted using ArcGIS (version 9.0). Moran's *I* was used for global spatial autocorrelation, and the spatial distribution characteristics of human serum SePP levels were investigated from the overall level to determine whether there was spatial clustering. Getis-Ord Gi* was used for local spatial autocorrelation, and the correlations of the SePP levels in provinces (municipalities and autonomous regions) and their neighboring provinces (municipalities and autonomous regions) were described to explore types of spatial clustering. Based on the results provided by the clustering analysis, spatial regression analysis using ordinary least squares (OLS) was used to explore the influencing factors of human serum SePP clustering.

The study protocol was approved by the Ethical Committee Review Board of Harbin Medical University.

3. Results

3.1. Demographic characteristics and spatial distribution of the subjects

General demographic characteristics of the study subjects are shown in Table 1. In total, 2351 participants, including 805 (34.24%) males and 1546 (65.76%) females, were surveyed. Among them, 1222 (51.98%) were living in rural areas, 622 (26.46%) in general cities, and 507 (21.56%) in developed cities. There were 1984 (84.39%) people living in the KD endemic provinces. Among them, 1096 (55.24%) were living in rural areas. Among the 1096 rural residents, 553 (50.46%) were living in KD endemic areas. In total, 1798 (76.48%) participants were not residents of the KD endemic areas. The spatial distribution of subjects is shown in Fig. 1.

3.2. SePP

The mean serum SePP levels of subjects living in KD endemic rural

Table 2
Serum SePP, soil selenium, per capita GDP and per capita consumption expenditure by region.

Regions	Provinces	n	SePP(mg/L, $\overline{X} \pm s$)	Soil selenium(mg/kg, $\overline{X} \pm s$)	Per capita GDP(yuan)	Per capita consumption expenditure(yuan)
National		2351	15.04 ± 6.87	0.290 ± 0.255	49,351	13,220.4
Endemic areas		1984	14.65 ± 6.92	0.213 ± 0.099	45,177	13,417.6
	Gansu	32	17.63 ± 7.23	0.160 ± 0.077	26,165	10,950.8
	Guizhou	47	17.65 ± 7.24	0.373 ± 0.233	29,847	10,413.8
	Hebei	92	14.75 ± 6.72	0.341 ± 0.211	40,255	13,030.7
	Henan	127	13.36 ± 7.04	0.200 ± 0.124	39123	11,835.1
	Heilongjiang	934	14.40 ± 6.81	0.195 ± 0.094	39462	13,402.5
	Jilin	70	15.84 ± 7.23	0.200 ± 0.078	51,086	13,763.9
	Liaoning	71	16.65 ± 6.97	0.199 ± 0.114	65,354	17,199.8
	Inner Mongolia	103	13.82 ± 7.26	0.103 ± 0.074	71,101	17,178.5
	Shandong	193	12.53 ± 6.45	0.130 ± 0.060	64,168	14,578.4
	Shanxi	61	18.04 ± 5.79	0.180 ± 0.120	34,919	11,729.1
	Shaanxi	71	14.52 ± 7.08	0.115 ± 0.089	47,626	13,087.2
	Sichuan	59	14.93 ± 6.81	0.095 ± 0.054	36,775	13,632.1
	Yunnan	34	17.59 ± 5.02	0.423 ± 0.375	28,806	11,005.4
	Chongqing	34	16.53 ± 7.64	0.205 ± 0.154	52,321	15,139.5
	Hubei	56	15.36 ± 6.74	0.275 ± 0.350	50,654	14,316.5
Non-endemic areas		367	17.14 ± 6.21	0.337 ± 0.164	65,452	19584.7
	Anhui	45	15.03 ± 6.68	0.234 ± 0.158	35,997	12,840.1
	Beijing	41	18.12 ± 5.83	0.247 ± 0.091	10,6497	33,802.8
	Fujian	30	16.89 ± 6.86	0.548 ± 0.211	67,966	18,850.2
	Guangdong	20	13.97 ± 6.04	0.288 ± 0.189	67,503	20,975.7
	Guangxi	33	17.14 ± 4.92	0.770 ± 0.440	35,190	11,401.0
	Hainan	21	17.29 ± 4.76	0.211 ± 0.130	40,818	13,575.0
	Hunan	33	16.57 ± 5.56	0.329 ± 0.220	42,754	14,267.3
	Jiangsu	26	18.10 ± 5.31	0.222 ± 0.143	87,995	20,555.6
	Jiangxi	38	16.31 ± 6.72	0.290 ± 0.121	36,724	12,403.4
	Shanghai	3	18.98 ± 7.23	0.298 ± 0.264	10,3796	34,783.6
	Tianjing	38	18.61 ± 7.15	0.176 ± 0.103	10,7960	24,162.5
	Xinjiang	1	14.16	0.330 ± 0.212	40,036	12,867.4
	Zhejiang	38	19.65 ± 5.23	0.435 ± 0.219	77,644	24,116.9

areas and KD non-endemic areas were 14.20 (95% *CI*: 13.60, 14.80) and 15.30 (95% *CI*: 14.98, 15.61) mg/L, respectively. The mean serum SePP levels of subjects living in KD endemic areas were significantly lower than those in non-endemic areas (t = -3.19, *P* = 0.0010). Details are shown in Table 1.

The mean serum SePP level of the 1984 subjects living in the KD endemic provinces was 14.65 (95% *CI*: 14.34 and 14.95) mg/L and was significantly different among those living in developed cities, general cities and rural areas (F = 8.23, *P* < 0.0010). The mean serum SePP level of the 367 subjects living in KD non-endemic provinces was 17.14 (95% *CI*: 16.50 and 17.78) mg/L. The mean serum SePP level of males in KD endemic provinces was significantly lower than that of males in non-endemic provinces (t = −4.92, *P* < 0.0010). The mean serum SePP level of females in KD endemic provinces was lower than that of females in KD non-endemic provinces (t = −4.74, *P* < 0.0010). The mean serum SePP level of residents in developed cities in KD endemic provinces was lower than that in KD non-endemic provinces (t = −3.00, *P* = 0.0030). The mean serum SePP level of residents in general cities in KD endemic provinces was lower than that in KD non-endemic provinces (t = −4.20, *P* < 0.0010). The mean serum SePP level of rural residents in KD endemic provinces was lower than that in KD non-endemic provinces (t = −2.93, *P* = 0.0030).

The spatial distribution of mean serum SePP levels and soil selenium are shown in Fig. 2 and Table 2, indicating that mean serum SePP levels were low among people in the KD endemic provinces of Shandong, Hainan Inner Mongolia, Heilongjiang and Shaanxi.

The mean measured serum SePP level was 15.04 (95% *CI*: 14.76 and 15.31) mg/L, as shown in Table 1, and ranged from 0.07 mg/L to 30.97 mg/L. The mean serum SePP levels of males and females were 15.32 (95% *CI*: 14.85 and 15.78) and 14.89 (95% *CI*: 14.54 and 15.23) mg/L, respectively. There was no significant difference between males and females (t = 1.44, *P* = 0.15).The mean serum SePP levels of subjects living in developed cities, general cities and rural areas were 16.54 (95% *CI*: 15.98 and 17.11) mg/L, 14.98 (95% *CI*: 14.45 and 15.51) mg/

L and 14.44 (95% *CI*: 14.05 and 14.84) mg/L, respectively, (F = 17.00, *P* < 0.0010). The Bonferroni test showed that SePP levels in developed cities were significantly higher than those in general cities (*P* < 0.0010) and rural areas (*P* < 0.0010), and there was no significant difference between general cities and rural areas (*P* = 0.33).

3.3. SePP, per capita GDP, per capita consumption expenditure and soil selenium

The levels of SePP, per capita GDP, and per capita consumption expenditure by province are shown in Table 2. In 2015, the per capita GDP of China was 49,351 yuans, and the per capita consumption expenditure was 13,220.4 yuans. In KD endemic provinces, the mean serum SePP of residents was 14.65 mg/L, the per capita GDP was 45,177 yuans, and the per capita consumption expenditure was 13,417.6 yuans. In KD non-endemic provinces, the mean serum SePP of residents was 17.14 mg/L, the per capita GDP was 65,452 yuans, and the per capita consumption expenditure was 19,584.7 yuans. In Inner Mongolia and Heilongjiang, the mean serum SePP of residents and the per capita consumption expenditure were both at relatively low levels.

The levels of mean serum SePP and soil selenium by province are displayed in Table 2. The mean soil selenium levels were 0.290 mg/kg in China, 0.213 mg/kg in KD endemic provinces and 0.337 mg/kg in KD non-endemic provinces. In Shandong and Inner Mongolia, the mean serum SePP of residents and the mean soil selenium were both at relatively low levels.

3.4. Spatial autocorrelation analysis

For 2015, global spatial autocorrelation analysis showed that the global Moran's *I* was 0.22, *P* = 0.0014, suggesting that the spatial autocorrelation was significant, and there was spatially positive correlation between serum SePP levels. The results of the analysis are shown in Fig. 3.
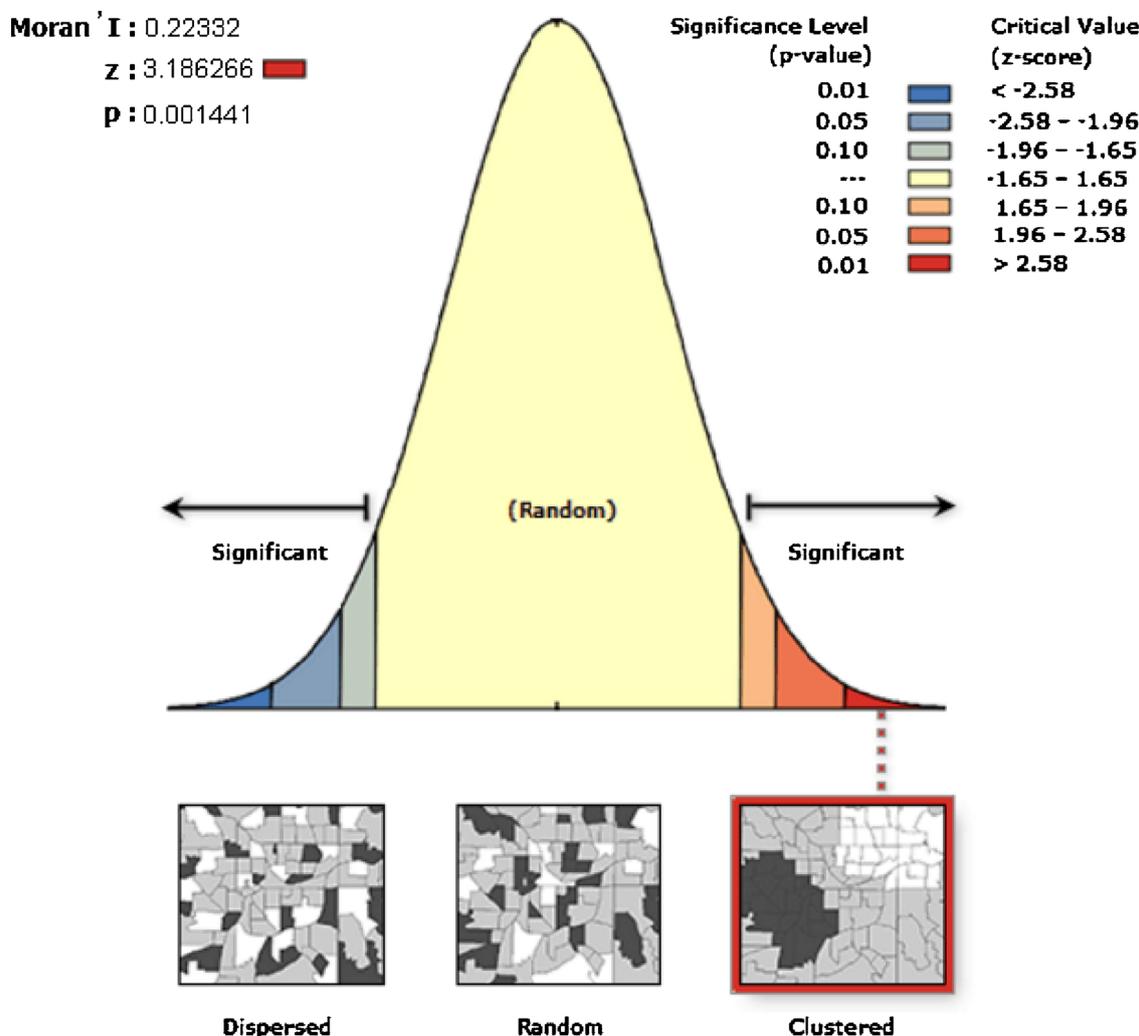
Fig. 3. Global spatial autocorrelation analysis of the serum SePP levels.

Getis-Ord Gi* was used to carry out local spatial autocorrelation analysis, and the corresponding Z-values of the 90%*CI*, 95%*CI* and 99%*CI* of Getis-Ord Gi* were ± 1.65, ± 1.96 and ± 2.58, respectively. According to the different confidence intervals of Getis-Ord Gi*, the 2015 national mean serum SePP levels were divided into different grades to draw local heat maps. A blue area is a low value area, a "cold spot" area; a red area is a high value area, a "hot spot" area; and a white area indicates that there is no agglomeration area. The results of the analysis are shown in Fig. 4. There are six "hot spots" in mean serum SePP levels, namely, Shanghai, Jiangsu, Shandong, Henan, Shanxi, and Shaanxi.

3.5. Spatial regression analysis

Table 3 shows that the Variance Inflation Factor (VIF) values of per capita GDP and per capita consumption expenditure in this model are greater than 7.5, indicating that there is multicollinearity between variables. After removing per capita GDP as an independent variable, the results show that soil selenium (t = 2.55, $P = 0.016$) and per capita consumption expenditure (t = 3.54, $P = 0.0013$) entered the spatial regression model. Table 4 shows that the VIF values in this model are all less than 7.5, indicating that there is no multicollinearity between variables. The model residuals were analyzed by spatial autocorrelation analysis. The results show that Moran's *I* was 0.34, $P = 0.42$, indicating that the model residuals are independent and there is no spatial autocorrelation. The establishment of the least squares model was

significant, and the human serum SePP level was positively correlated with soil selenium and per capita consumption expenditure.

4. Discussion

As shown in Table 1, the proportion of subjects living in endemic areas in this study was only 23.52% (553/2351), although a large proportion of subjects were from KD endemic provinces. The reason is that not all counties in the KD endemic provinces are KD endemic counties, nor are all the townships in the KD endemic counties. Only the residents living in the KD endemic townships were classified in the category of residents of KD endemic areas.

As seen in Table 1, this ecological study shows that the mean serum SePP levels of people living in the KD endemic areas were significantly lower than those of people not living in the KD endemic areas, for both males and females and in rural and urban centers. These levels not only indicated that selenium deficiency may still exist among residents living in the KD endemic areas but also supplemented the etiological evidence in the area of human serum SePP. The spatial description of the geographical distribution of SePP reveals that the levels of mean serum SePP were low among people in the KD endemic provinces of Shandong, Hainan Inner Mongolia, Heilongjiang and Shaanxi (Fig. 2 and Table 2). This visualized evidence may be used to target key provinces for precise prevention and control of Keshan disease. As shown in Tables 3 and 4, the results of spatial regression indicated that per capita consumption expenditure and soil selenium interpreted 44% of serum
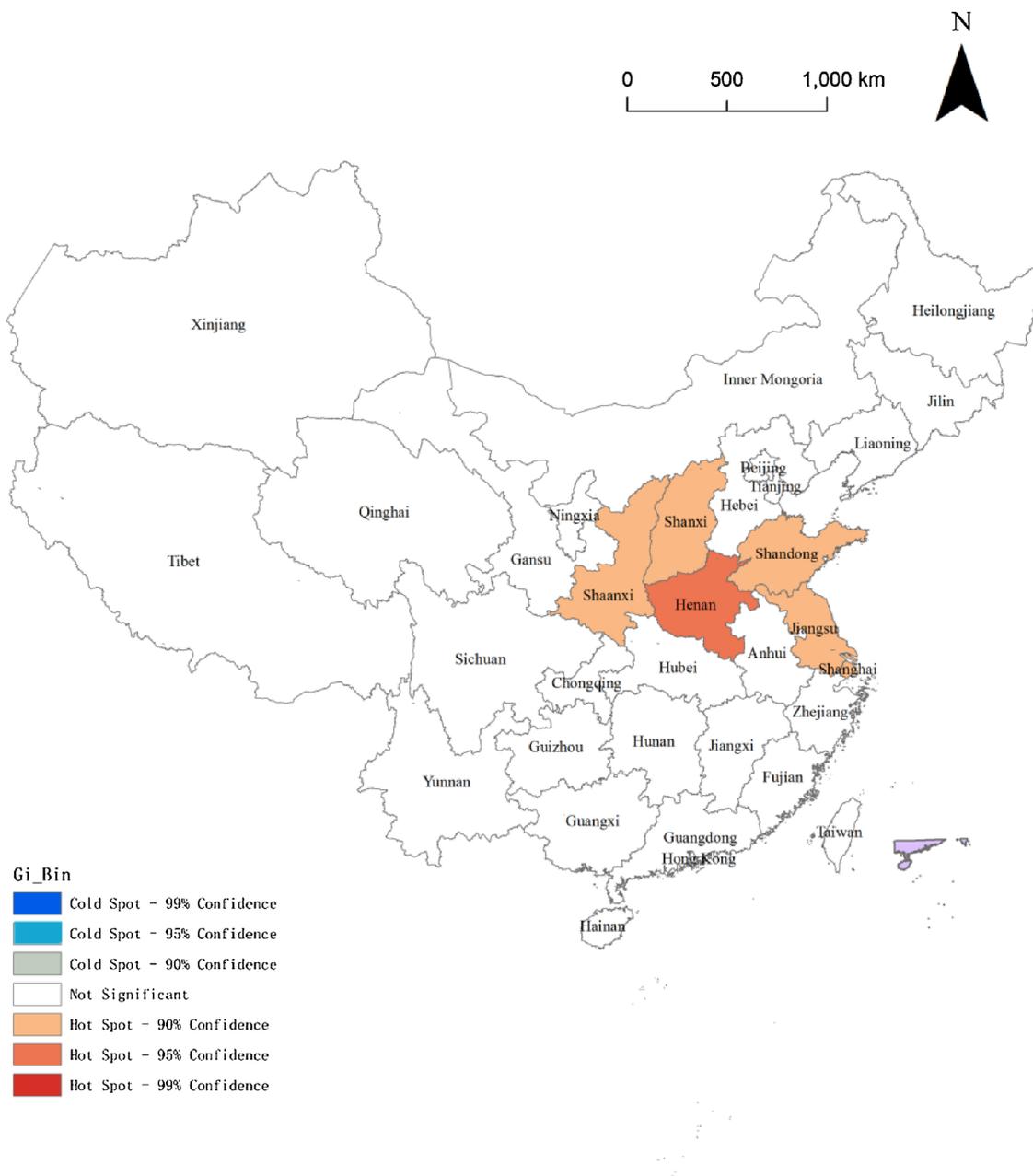
Fig. 4. Local hot spot analysis of the serum SePP levels.

Table 3
Spatial Regression Analysis of SePP.

Characteristic	Regression coefficients	Standard deviation	t	*p*-Value	VIF
β_0	3.63	2.05	1.77	0.087	—
Soil selenium	15.15	6.12	2.49	0.019	1.19
Per capita GDP	0.17	1.04	0.17	0.87	10.62
Per capita consumption expenditure	3.65	3.86	0.94	0.35	11.22

Note : $R^2 = 0.48$, $R_{adj}^2 = 0.42$, F = 9.04, P < 0.01.

Table 4
The Second Spatial Regression Analysis of SePP.

Characteristic	Regression coefficients	Standard deviation	t	*p*-Value	VIF
β_0	3.65	2.02	1.81	0.080	—
Soil selenium	14.91	5.84	2.55	0.016	1.12
Per capita consumption expenditure	4.26	1.20	3.54	0.0013	1.12

Note : $R^2 = 0.47$, $R_{adj}^2 = 0.44$, F = 13.81, P < 0.01.

SePP.

In 1965, the Keshan Disease Research Office of Xi'an Medical College selected the endemic areas for pilot test for the first time. The effectiveness of supplementing sodium selenite to the residents of KD endemic areas to prevent KD was significant [10]. Subsequently, the

Keshan Disease Research Team composed of Yang Guangqi and the Collaboratory Group of Preventing Keshan Disease by Sodium Selenite also carried out oral sodium selenite prevention in KD endemic areas. Most of the trial results showed that the effect of selenium supplementation on KD was statistically significant [11–14]. In recent years, a large number of studies on selenium deficiency and myocardial damage have been conducted at the molecular level [31–33].

Although incidence is the most important indicator for assessing whether a disease has been eliminated, indicators of etiology, intervention against the cause/risk of disease and its effectiveness are also key information for assessing disease elimination. All these indices are more informative for assessing the elimination of a disease than just incidence. The definition of disease elimination requires "deliberate efforts," which implies that there should be adequate evidence of the incidence or prevalence of the disease to be eliminated, clear goals, effective interventions implemented, strong supporting policies, long-term planning, sufficient funding, detailed implementation plans and the masses actively participating. The etiology of KD is not yet fully clear. KD is not a notifiable disease, so we are not able to obtain information on incidence at the population level (passive surveillance) of the KD endemic areas; we can only perform sample surveys (active surveillance) to estimate the incidence or prevalence of the overall population in the KD endemic areas. Not only KD elimination but also assessment of KD elimination is challenging because KD is neither a known-cause disease nor a notifiable disease. The fundamental reasons for the declining KD incidence are rapid economic development and improvement in the living standards of residents of the KD endemic areas in the past 40 years.

For all participants, the mean serum SePP was 15.04 (95% *CI*: 14.76 and 15.31) mg/L, 15.32 (95% *CI*: 14.85 and 15.78) for males and 14.89 (95% *CI*: 14.54 and 15.23) mg/L for females. Obviously, these are valuable references for the foundational data of selenium and/or selenoprotein nutrition in the Chinese population. The mean serum SePP level of the residents in developed cities was higher than that in general cities, and the latter was higher than that in rural areas. These values indicated that serum SePP levels were associated with socio-economic factors because city classification is mainly based on GDP and per capita consumption expenditure. Spatial autocorrelation analysis reveals that human serum SePP levels were not completely random and overall showed a spatially positive correlation between regions. Global spatial autocorrelation explores the spatial distribution characteristics of human serum SePP levels from the overall level and determines whether there is spatial clustering. Moran's *I* is a widely used global spatial autocorrelation statistic. Local spatial autocorrelation provides a description of the correlation between the levels of human serum SePP in provinces (municipalities and autonomous regions) and their neighboring provinces (municipalities and autonomous regions) and explores types of spatial clustering. Getis-Ord Gi* is a commonly used indicator for evaluating local autocorrelation. Spatial regression analysis showed that the spatial distribution of serum SePP was positively related to per capita consumption expenditure and soil selenium. However, soil selenium was probably a confounder. The reason for this may be that first, data were from the year 1990; although soil selenium may not have changed much in the past 25 years, people living in rural China only eat a small proportion of grains grown locally by themselves. Second, per capita consumption expenditure is an indicator of income and living standards, which in turn can be an indicator of consumption of protein, which ultimately is the major dietary source of selenium.

The major strength and/or innovation and the importance of this study are that we measured the serum SePP of people living in KD endemic areas, non-endemic areas, and urban centers across mainland China. The results are valuable for KD prevention and control and the assessment of KD elimination in terms of selenoprotein nutrition. This is a research translating advances of selenoproteins and spatial epidemiology into KD prevention and control. The limitations of this study are that the study design was not a simple random design and that the proportion of subjects living in the KD endemic areas was small; thus, the representativeness of the population sample in terms of gender, age, occupation, etc. in mainland China might not be high. Another limitation of this study is the lack of selenium measurements and therefore a missing correlation of serum SePP and selenium values. Without this analysis, our study relies on the assumption that the commercial SePP assay used is yielding meaningful values, even though they appear

slightly higher than in other clinical studies [22,34,35].

In summary, selenium deficiency may still exist among residents living in KD endemic provinces. A spatial description of the SePP distribution is visualized evidence for targeting key provinces for precise prevention and control of Keshan disease, including assessment of KD elimination.

Conflict of interest

The authors declare no conflict of interest.

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