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Spatial Analysis and Biogeochemical Cycles: A Comparative Study of Kashin-Beck Disease Villages and Non-disease Villages in Linzhou County, Tibet

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Abstract: This study investigated Linzhou County in Tibet, which currently hosts the most serious outbreak of Kashin-Beck disease (KBD) in China. This study uses the geographical detector (GeoDetector) algorithm to measure the influences that several risk factors have on KBD prevalence and validates the spatial analysis results with environmental chemistry. Based on a comprehensive examination of 10 potentially related spatial factors and an environmental chemistry analysis of the soil-water-grain-human biogeochemical cycle in the local KBD and non-KBD villages, four main conclusions are drawn. (1) KBD in Linzhou County is a consequence of multiple interrelated environmental factors, of which the most important controlling factor is the stratum factor. (2) The concentrations of selenium (Se) in all environmental media (soil, water, and food) and human tissue in the KBD villages in Linzhou County are lower than those of the non-KBD villages. (3) The intake of Se and chromium (Cr) by local residents is seriously insufficient, especially the average daily dose by ingestion (ADD) for Se in the KBD village, which is only about 4% of the World Health Organization (WHO) recommended lower limit for adult elemental intake. (4) We speculate that the main cause for the local KBD outbreak is a lack of Se in the stratum. This absence leads to a serious Se deficiency in the local population through ecosystem migration and transformation, which will eventually lead to an endemic biogeochemical Se deficiency.

Key words: Kashin-Beck disease; Tibet; spatial analysis; biogeochemical cycle; selenium

1 Introduction

Kashin-Beck disease (KBD) is an endemic disabling osteoarticular disease that affects cartilage growth. China is one of the countries that is most seriously affected by KBD and this disease is prevalent mainly in north and central China and certain areas in Tibet (Tan, 1989; Mahmoodi et al., 1998; Guo, 2001; Yamamuro, 2001). With improvements in the nutritional status in China's rural areas, KBD prevalence decreased from 44% to 1% between 1970 and 1986 (FAO and WHO, 2002). However, due to geographical constraints, the most active and serious endemic area for the KBD in China is currently Tibet (Tibet Kaschin-Beck Disease Study Group, 2000; National Kashin-Beck Disease Surveillance Group, 2002; Hinsenkamp et al., 2009), where Linzhou County is one of the most severe endemic areas (Yang et al., 2006).

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The specific etiology of KBD is still unclear. However, previous studies have proposed three environmental etiological hypotheses for the cause of KBD, i.e., 1) Biogeochemical imbalances (endemic selenium deficiency) (Yang et al., 1993; Tan et al., 2002; Li et al., 2009; Stone, 2009; Li et al., 2012; Guo et al., 2015); 2) Grain mycotoxin poisoning (serious cereal contamination due to mycotoxin-producing fungi) (Pasteels et al., 2001; Chasseur et al., 2002; Malaisse and Mathieu, 2008; Sun et al., 2012); 3) Organic compound poisoning of the water (high humic acid levels in drinking water) (Peng et al., 1999; Grange et al., 2001; Hinsenkamp et al., 2009). Based on these three hypotheses, previous studies have largely endorsed endemic selenium (Se) deficiency as the principal etiology of KBD (Mahmoodi et al., 1998; Tan et al., 2002; Zhao et al., 2013) because neither the grain mycotoxin nor drinking water organic compound hypotheses can explain the focal distribution adjacent to KBD endemic areas for the epidemiology (Guo, 2008). After quantitative analysis using spatial analysis methods of the KBD exposure factors in Qamdo, Tibet, Zha and Gao (2019) showed that KBD was mainly influenced by geological structures (specifically, low Se stratum) and high moisture environments that are governed by precipitation and evaporation.

Selenium is generally acknowledged as an essential trace element in the human body, which has many biological functions, including antioxidation, strengthening the immune system, and accelerating human development and growth (Rayman, 2000; Fordyce, 2013; Roman et al., 2013; Schroeder et al., 1970; Seale and Berry, 2013). The selenium intake level recommended by the World Health Organization (WHO) is 40 μg d^{-1}. Despite this, the adult Se intake in certain KBD areas in China is only 2.6–5.0 μg d^{-1} (Qi and Ming, 1995; FAO and WHO, 2002). After analyzing the environmental Se concentrations in Rangtang and Aba counties in the Sichuan Province (both belong to the Qinghai-Tibet Plateau), Zhang et al. (2011) suggested that soil Se deficiency plays a critical role in KBD prevalence and found that KBD prevalence is higher in areas with lower environmental Se levels. The amount of Se in the human body depends on the concentration of Se in the geographical area, soil, and plants, as well as an individual's diet (Konikowska and Mandecka, 2018). Li et al. (2009) analyzed soil Se concentrations in southeastern Tibet and reported that Se concentrations in cultivated and natural soil within KBD endemic areas were both lower than those in either non-KBD areas or average Chinese soil concentrations. They suggested that future research should focus on the influence of soil Se deficiency and relationships with Se concentrations in grains and humans in Tibet. Wang et al. (2013) discussed Se concentrations in soil and highland barley from Songpan County along the eastern margin of the Qinghai-Tibet Plateau, concluding that Se concentrations in agricultural products decrease with a decrease in the effective Se soil concentration. Furthermore, this pattern is closely related to geographically varying environmental characteristics. Wang et al. (2017) investigated the distribution and translocation of Se from soil to highland barley in both non-KBD and KBD areas, and showed that the Se concentration in highland barley was too low to meet the minimum requirements of daily human intake.

In this study, we attempt to understand the regional Se differentiation mechanism in Tibet's unique environment, by studying the biogeochemical cycles of Se between the KBD and non-KBD villages, and the Se concentrations in afflicted and non-afflicted people. Moreover, we measure the spatial consistency and statistical significance of KBD prevalence and the potential impact factors of KBD in Linzhou County using the GeoDetector based on spatial stratified heterogeneity. Finally, we discuss the possible causes of KBD in Linzhou County from a biogeochemistry and geographic information system perspective, which will help provide a scientific basis for current and future research on KBD pathogenesis.

2 Materials and methods

2.1 Regional setting

In this study, both environmental and human samples were collected from Linzhou County, Lhasa, Tibet Autonomous Region (Fig. 1). Linzhou County is located in the middle of Tibet and the Pengbo River basin (in the upper reaches of the Lhasa River), with a total area of 4512 km^2 and an average elevation of 4200 m. The average annual precipitation is 437 mm, the total number of villages is 45 and the population is 59320.

KBD prevalence in Linzhou County is very serious. Currently, there are 104 patients with KBD distributed in four villages (which are defined as KBD villages; while villages without any KBD patients are defined as non-KBD villages), including 46, 35 and 23 patients with the I, II and III degree stages of the disease, respectively (Table 1). The average age is 53.60 years old, while the minimum and maximum ages are 6 and 80 years old, respectively. The prevalence rates based on Bayesian smoothing in the four afflicted villages are Kari Village (1.42%) in Jiangrexia township, Bugang (0.09%) and Galie Villages (3.54%) in Alang township, and Kebu Village (3.48%) in Kazi township (Fig. 2).

2.2 Samples and analytical methods

2.2.1 Sampling and preparation

The Global Position System (GPS) location at each collection point was recorded using a handheld device (Rino 530HCx, GARMIN, Taipei, Taiwan). All samples were collected according to the following collection and pretreatment methods:

(1) Ten drinking water samples were stored in colorless polyethylene bottles (ca. 500 mL) that had been previously

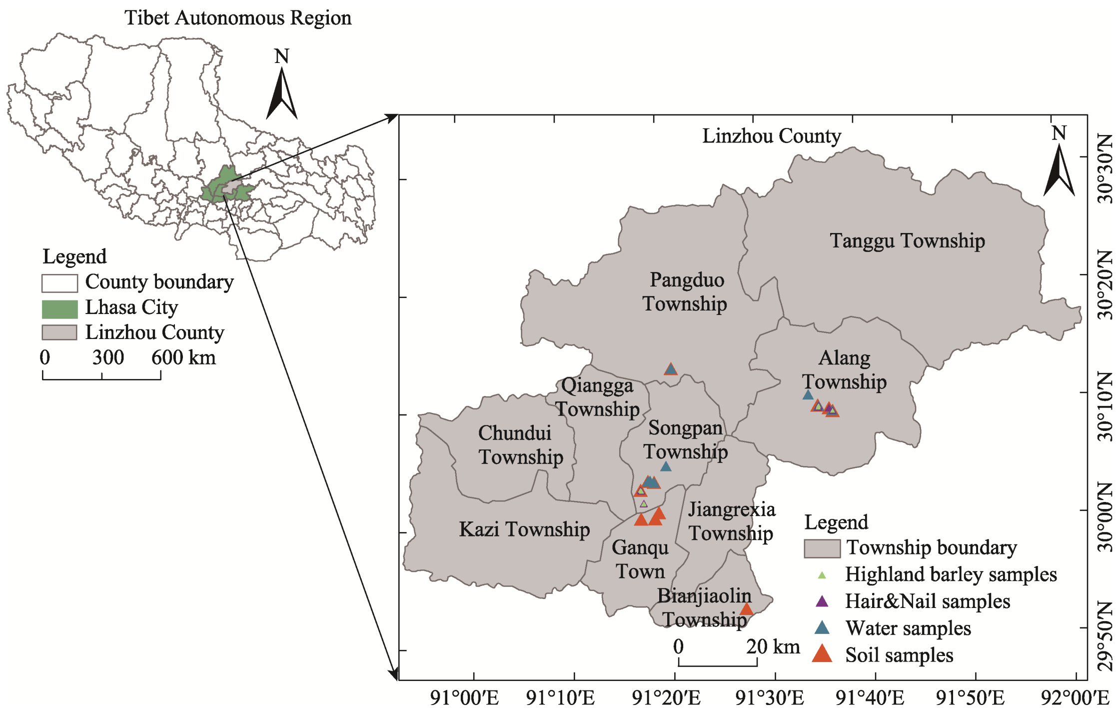

Fig. 1 Geographical location of study area and distribution of sampling points

Table 1 Coordinates of sampling villages in Linzhou County

Sampling point	Latitude (°N)	Longitude (°E)	Elevation (m)	Village type
Galie village, Alang township	30.094922	91.508903	3972	KBD villages
Bugang village, Alang township	30.092983	91.533863	3997	KBD villages
Baiding village, Songpan township	29.942123	91.231942	3801	non-KBD villages
Songpan village, Songpan township	29.981803	91.268711	3896	non-KBD villages
Dangjie village, Dangjie township	29.889292	91.288264	3727	non-KBD villages
Sana village, Gandanquguo township	29.901486	91.239625	3746	non-KBD villages

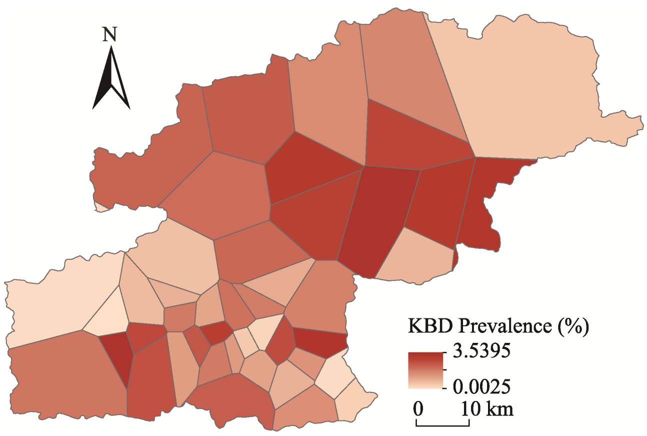

Fig. 2 Prevalence of KBD in villages in Linzhou County determined using the Thiessen polygon method after Bayesian smoothing

cleaned with deionized water and maintained at 4°C following collection. We collected and stored the water samples based on the Standard Examination Methods for Drinking Water (GB/T 5750-2006) (MH, 2007a).

(2) Eleven cultivated soil samples were collected from the surface (5–10 cm) using the quadruple method and stored in colorless polyethylene plastic bags (about 0.2 kg for each sample). In the laboratory, all samples were dried naturally after removing gravel and plant roots, then crushed, and pulverized with a 100-mesh size sieve for geochemical analysis.

(3) Eight highland barley samples were stored in colorless polyethylene plastic bags (about 0.2 kg for each sample). In the laboratory, all samples were cleaned with deionized water three times, dried in a drying oven (60°C), crushed with an agate mill and passed through a 100-mesh nylon sieve for testing.

(4) 44 human hair and 26 human nail samples were stored in colorless polyethylene plastic bags (at least about 20 g for each sample). The Centers for Disease Control and Prevention, Health and Family Planning Commission (CDCP

& HFPC) of Linzhou County assisted in recruitment of KBD and non-KBD patients. All KBD patients were confirmed by CDCP & HFPC of Linzhou County and which has case information for each patient. For in situ sampling, we also visually inspected the condition of the sampled KBD and non-KBD patients (see the supporting information for photos of some KBD patients). In the laboratory, each sample was placed in a clean glass beaker, soaked for 30 minutes in warm 1% detergent and stirred several times. Samples were then rinsed with deionized water until no foam was present, dried in a drying oven (60°C), and cut with poly tetra fluoroethylene (PTFE) scissors to 3 mm.

2.2.2 Sample analysis

All samples were tested at the Laboratory of Analytical and Testing Center of the Institute of Geographic Sciences and Natural Resources Research, Chinese Academy of Sciences (LATC, IGSNRR, CAS) according to the following testing methods:

(1) Drinking water samples: The pH, electrical conductivity (Ec), resistivity (RES), salinity (SAL), total dissolved solids (TDS), temperature (T), and Oxidation Reduction Potential (ORP) were determined using a pH tester (SevenGo SG2, Mettler Toledo, Zurich, Switzerland), Ec tester (SevenGo SG3, Mettler Toledo, Zurich, Switzerland), and ORP tester (SevenGo SG2), in-situ. The alkalinity (HCO_3^- and CO_3^{2-}) was determined using an acid–base titration (MEP, 2002; MH, 2007a). Anions (F^-, Cl^-, SO_4^{2-}, $H_2PO_4^-$, NO_3^-, NO_2^-, and Br^-) were analyzed using ion chromatography (ICS-900, Thermo Fisher Scientific, Massachusetts State, USA, with a limit of detection (LOD): 0.001 mg L^{-1}), following the method 300.0 published by the U.S. Environmental Protection Agency (EPA, 1993). Major cations (Ca, Mg, Na, K, P, Sr, B and SiO_2) were determined using Inductively Coupled Plasma Optical Emission Spectrometry (ICP-OES, Optima 5300 DV, PerkinElmer, Massachusetts State, USA, LOD: 0.001 mg L^{-1}). The concentrations of trace elements (Li, Zn, U, Rb, Ba, Bi, Co, Cs, Ga, In, Ti, V, Ag, Al, Be, Cd, Cr, Cu, Fe, Hg, Mn, Mo, Ni, Pb, and Tl) were determined using Inductively Coupled Plasma Mass Spectrometry (ICP-MS, DRC-e, PerkinElmer, Massachusetts State, USA, LOD: 0.001 μg L^{-1}). Selenium and arsenic (As) concentrations were determined using Hydride Generation Atomic Fluorescence Spectrometry (HG-AFS, AFS-9780, Beijing Haiguang, Beijing, China, LOD: 0.01 μg L^{-1}) (MEP, 2002; MH, 2007a).

(2) Cultivated soil samples: Approximately 0.05 g of cultivated soil was collected for each sample. A 3:3:1 acid mixture of HNO_3, HF, and $HClO_4$ was added and heated at 180 ± 10°C until the solution became transparent when using a PTFE beaker to determine the major and trace elements via ICP-OES and ICP-MS, respectively. A 5:1 acid mixture of HNO_3 and $HClO_4$ was added and heated at 180 ± 10°C until the solution became transparent. After cooling, 5 mL of 6 mol L^{-1} HCl was added and digestion was allowed to continue until white smoke emerged. We then added 1 mL of HCl to determine the Se (by adding 1 mL of 2.5% thiourea and 2.5% ascorbic acid) and As concentrations via HG-AFS.

(3) Highland barley, human hair and nail samples: Approximately 0.5 g of highland barley, human hair, and nail samples were used for analysis. A 5:1 acid mixture of HNO_3 and $HClO_4$ was added and heated at 180 ± 10°C until the solution became transparent to determine the major and trace elements via ICP-OES and ICP-MS, respectively. A 9:1 acid mixture of HNO_3 and $HClO_4$ was added and heated at 180 ± 10°C until the solution became transparent. After cooling, 5 mL of 6 mol L^{-1} HCl was added and digestion was allowed to continue until white smoke appeared. We then added 1 mL of HCl to determine the Se (by adding 1 mL of 2.5% thiourea and 2.5% ascorbic acid) and As concentrations via HG-AFS.

2.2.3 Quality control

Two steps were used for quality control in the chemical analysis.

(1) Drinking water samples: External standard solutions for cations were prepared from Multi-element ICP-MS Calibration Standards (Lot# 15-76JB, Cat# N9300233). External standard solutions for anions were prepared from GBW(E) 080549 (F^-), GBW(E) 080268 (Cl^-), GBW(E) 080266 (SO_4^{2-}), GBW(E) 080435 ($H_2PO_4^-$), GBW(E) 080264 (NO_3^-), GBW(E) 080223 (NO_2^-), and BW 3063 (Br^-), where GB stands for National Standards obtained from the Certified Reference Material Center, China. The percentage relative error of anion and cation concentrations measured in 10 samples ranged from 0.27% to 3.91%, i.e., all were less than 5% so our data are accurate and reliable (Chidambaram et al., 2013).

(2) Cultivated soil, highland barley, human hair and nail samples: The concentrations of major and trace elements, Se and As of the standard reference materials (GBW 10010; rice, GBW 10011; wheat, GBW 07401; soil, GBW 07403; soil, GBW 09101; human hair) were randomly analyzed with each batch of samples. The correlation coefficient was > 0.999 and the relative standard deviation was ±10% for both major elements and trace elements.

2.3 Data sources

KBD prevalence rate data for Linzhou County was obtained from the 2018 local annual report of the Linzhou Centers for Disease Control and Prevention, Health and Family Planning Commission of Linzhou County.

The mean annual precipitation (PRE) (Fig. 3a) and annual average solar radiation (RAD) (Fig. 3b) data recorded at 55 meteorological monitoring stations in the Qinghai-Tibet Plateau between 1982 and 2015 were interpolated with ANUSPLINE (Version 4.4) software, which was programmed by Hutchinson and Xu (2013), and data for Linzhou

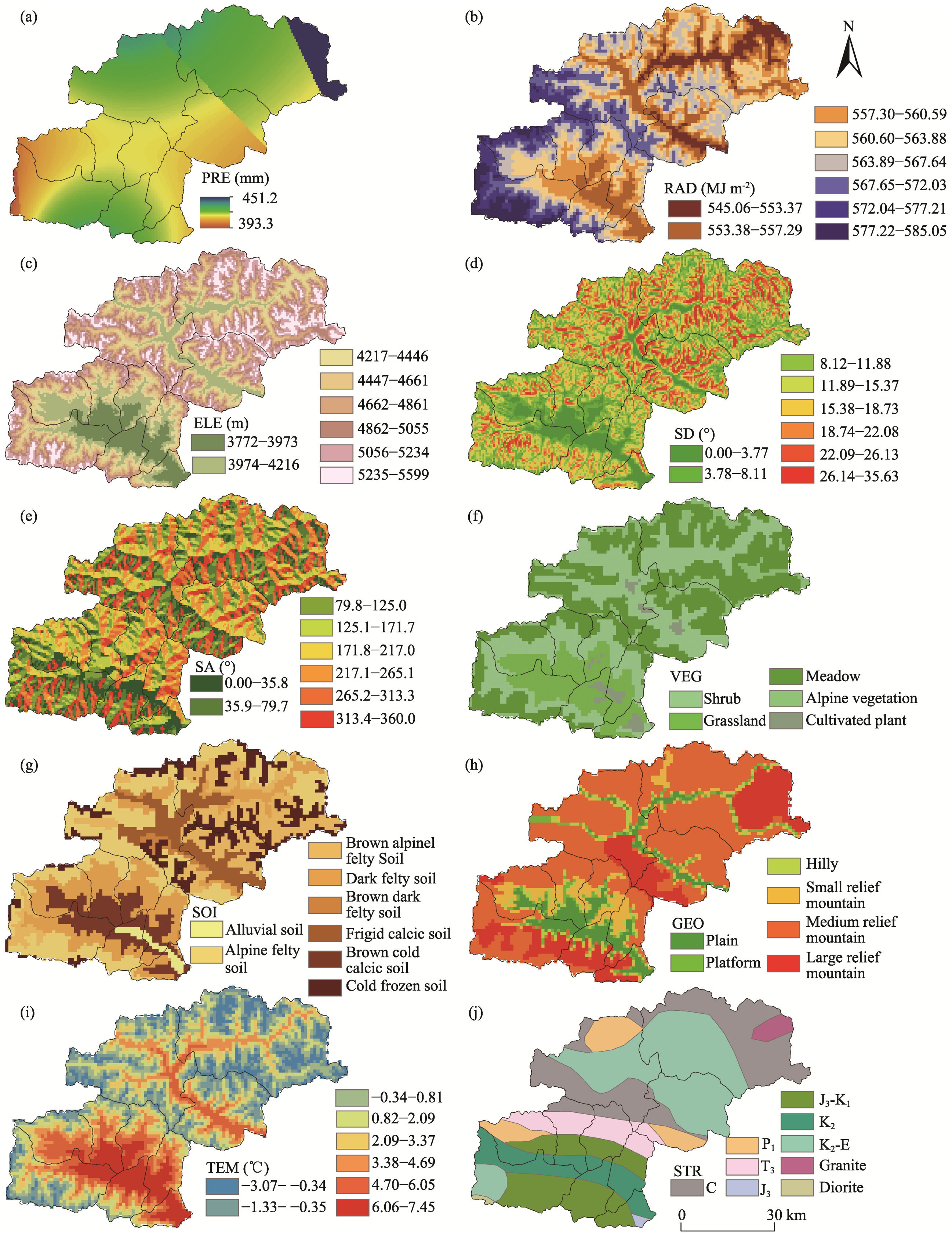

Fig. 3 Spatial distributions of the potential risk factors of KBD in Linzhou County. (a) mean annual precipitation; (b) annual average solar radiation; (c) elevation; (d) slope degree; (e) slope aspect; (f) vegetation type; (g) soil type; (h) geomorphic type; (i) mean annual temperature; and (j) stratum type.

County were extracted with ArcGIS 10.2. The above data were obtained from the China Meteorological Data Network (http://data.cma.cn).

Topographic factors, including the elevation (ELE) (Fig. 3c), slope degree (SD) (Fig. 3d), and slope aspect (SA) (Fig. 3e), were extracted from the 90 m Shuttle Radar Topography Mission (SRTM) digital elevation model (DEM) using ArcGIS 10.2. Vegetation type (VEG) data were available from the vegetation type map of China (1: 1000000) (Fig. 3f). Soil type (SOI) data were digitized from the soil type map of China (1:1000000) (Fig. 3g). Geomorphic type (GEO) data were derived from the geomorphic map of China (1:1000000) (Fig. 3h). Mean annual temperatures (TEM) were corrected by DEM (1:1000000) (Fig. 3i). All of the above data were obtained from the Resource and Environment Data Cloud Platform (http://www.resdc.cn). Stratum data (1:5000000) were drawn by the Ministry of Geology and Mineral Resources of the People's Republic of China (Fig. 3j), and were obtained from the Digital Library of National Geological Archives of China (http://www.ngac.org.cn).

2.4 Data processing and statistical analysis

Spatial autocorrelation (i.e., where two closer geographical sites are more similar or more dissimilar than two distant sites) (Tobler, 1970) and spatial stratified heterogeneity (i.e., where the within strata variance is less than the between strata variance) (Wang et al., 2016) are two major features of geological, geographical, ecological, climatic, and economic phenomena (Wang and Xu, 2017). Based on the spatial stratified heterogeneity, the GeoDetector designed by Wang et al. (2010; 2012), can use spatial variance to quantify the relative importance of individual factors and their implicit interactions with response variables. Increasing similarity between the spatial distributions of two variables results in an increased association between the two variables. With respect to spatial distribution, these factors will have greater consistency with changes in geographical phenomena. More details on the GeoDetector can be found in the original publication (Wang et al., 2010), and the free R-GeoDetector can be downloaded from http://www.geodetector.org.

Based on the GeoDetector input requirements, the projections were unified to the Krasovsky-1940-Albers projection coordinate system. As discussed above, the GeoDetector also effectively analyzes the continuous factors by discretizing the continuous data into discrete data. All continuous data were discretized into different categorical zones using optimal classification methods with ArcGIS 10.2. After comparing the q-statistic values from different discretization methods and intervals, all continuous data (mean annual precipitation, elevation, mean annual temperature, slope degree, and slope aspect) were classified into eight intervals using the natural breakpoint method. All data were extracted by grids (1 km × 1 km fishnet) with the intersect analysis tool in ArcGIS 10.2. These data were then input into R-GeoDetector. Test data were statistically analyzed using the SPSS 23.0 software and data were analyzed with the two-tailed t-test.

3 Results and discussion

3.1 Relative influences of risk factors on KBD in Linzhou County

Based on the three major hypotheses for the cause of KBD, we selected 10 ecological environmental impact factors—stratum type (STR), mean annual precipitation (PRE), soil type (SOI), groundwater type (GRO), elevation (ELE), mean annual temperature (TEM), vegetation type (VEG), geomorphic type (GEO), slope degree (SD), and slope aspect (SA)—and examined their individual influences on the prevalence of KBD in Linzhou County (Fig. 4). The factor detector (part of the GeoDetector) quantifies the potential KBD impact factors based on their q-statistic values. The q-statistic ranking for the above factors was as follows: STR (0.175) > TEM (0.172) > RAD (0.148) > ELE (0.135) > SD (0.130) > GEO (0.105) > SA (0.071) > PRE (0.068) > SOI (0.064) > VEG(0.063). Among these factors, the q-statistic values of STR and TEM are larger than those of the other factors. Thus, they are the most important potential risk factors

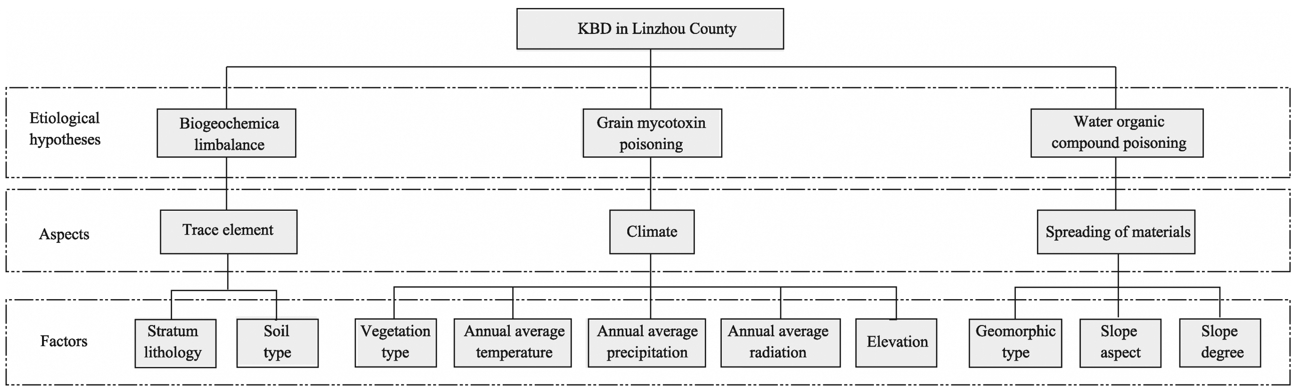

Fig. 4 Selective impact factors and direct influences on KBD in Linzhou County

and they have larger impacts on KBD prevalence in Linzhou County, which can explain the strong spatial distribution. In contrast, the RAD, ELE, SD, GEO, SA, PRE, SOI, and VEG factors may have little impact on KBD prevalence in Linzhou County.

3.2 Differences in drinking water elemental concentrations

The average concentrations of the major and trace elements in drinking water resources in the KBD and non-KBD villages of Linzhou County are listed in Table 2.

According to the Guidelines for Drinking-water Quality (WHO, 2008), Standards for Drinking Water Quality (MH, 2007b), and Drinking Natural Mineral Water (AQSIQ and SAC, 2008), all water samples have the "optimum" or recommended concentrations of the major and trace elements. The strontium (Sr) concentrations measured in non-KBD village drinking water also met Drinking Natural Mineral Water standards.

We can clearly visualize the major ion ratios in water samples with a Piper diagram (Fig. 5), where the percentages of major ions determine the hydrochemical characteristics of the water (Piper, 1944; Chen et al., 2014). All water samples are fresh-soft water (TDS < 1000 mg L^{-1}, TH < 150 mg L^{-1}) and slightly alkaline. Non-KBD village drinking water samples are characterized by Ca-HCO_3 (n=6) and

Table 2 Elemental concentrations of drinking water from Linzhou County KBD villages and non-KBD villages

Elements	Drinking water			GB 5749-2006 (MH, 2007b)	WHO (WHO, 2008)	GB 8537-2008 (AQSIQ and SAC, 2008)
	KBD villages (n=3)	Non-KBD villages (n=7)	Average (n=10)			
pH	7.577	7.890	7.796	6.5–8.5	6.5–9.5	
TDS (mg L^{-1})	50.637	127.221	104.246	<1000	<1000	⩾1000
TH (mg L^{-1})	31.664	103.517	81.961	<450	<500	
F^- (mg L^{-1})	0.236	0.096	0.138			<1.5
Cl^- (mg L^{-1})	3.129	1.092	1.703	<250	<250	
HCO_3^- (mg L^{-1})	28.708	117.757	91.042			⩾250
NO_3^- (mg L^{-1})	5.304	3.689	4.174			<45
SO_4^{2-} (mg L^{-1})	2.879	9.539	7.541	<250	<500	
Al (μg L^{-1})	1.032	10.349	7.554	<200	<200	
As (μg L^{-1})	0.128	1.328	0.968	<10	<10	<10
Ba (μg L^{-1})	2.364	6.815	5.480	<700	<700	<700
Ca (mg L^{-1})	9.929	35.014	27.489			
Cd (μg L^{-1})	0.001	0.001	0.001	<5	<3	<3
Co (μg L^{-1})	0.033	0.051	0.046			
Cr (μg L^{-1})	0.435	1.333	1.064	<50	<50	<50
Cu (μg L^{-1})	0.221	0.185	0.196			
Fe (μg L^{-1})	32.087	88.489	71.568	<300	<300	<1000
Hg (μg L^{-1})	0.002	0.000	0.001	<1	<1	<1
K (mg L^{-1})	0.459	1.186	0.968			
Li (μg L^{-1})	1.535	0.623	0.896			⩾200
Mg (mg L^{-1})	1.642	3.835	3.177			
Mn (μg L^{-1})	0.232	0.046	0.102	<100	<400	<400
Mo (μg L^{-1})	1.048	0.756	0.843	<70	<70	
Na (mg L^{-1})	3.891	3.605	3.691	<200	<200	
Ni (μg L^{-1})	0.267	0.641	0.529	<20	<20	<20
P (μg L^{-1})	0.000	0.006	0.004			
Pb (μg L^{-1})	0.006	0.001	0.002	<10	<10	<10
Se (μg L^{-1})	0.000	0.341	0.239	<10	<10	⩾10 and ＜50
SiO_2 (mg L^{-1})	12.182	12.312	12.273			⩾25
Sr (μg L^{-1})	73.800	214.129	172.030			⩾200
Ti (μg L^{-1})	0.960	0.831	0.869			
Zn (μg L^{-1})	0.164	0.038	0.076	<1000	<3000	⩾200
Na/Ca	0.392	0.103	0.190			

Ca-Mg-HCO_3 (n = 1) water types, whereas the KBD village drinking water samples are characterized by Ca-HCO_3 (n = 1), Ca-Na-HCO_3 (n = 1), and Ca-Na-HCO_3-NO_3 (n = 1) water types. Rock weathering is the main factor controlling the chemical composition of the water samples (Fig. 6), indicating that the elements in these water samples are dissolution products from the rocks and soil, which is consistent with previous studies performed in Tibet (Tian et al., 2016).

Independent sample t-tests show that the concentrations of As, Ba, Ca, Cr, Hg, Mg, Ni, Se, P, Sr, SO_4^{2-} and HCO_3^- in drinking water exhibit significant differences between the KBD and non-KBD villages (P < 0.05). Calcium was the most abundant major cation in drinking water samples, but the Na/Ca ratios show that there is a difference between the KBD and non-KBD villages. Both the pH values and the TDS and TH concentrations in the non-KBD villages were higher than those in the KBD villages, whereas the Li concentrations in the non-KBD villages were lower than in the KBD villages (Table 2).

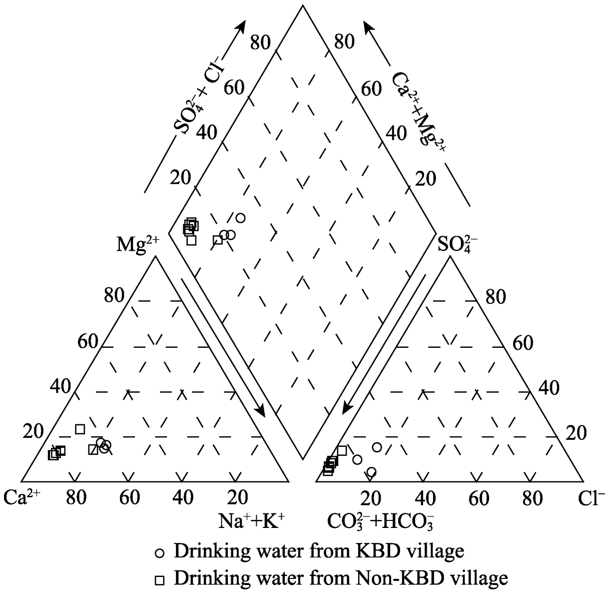

Fig. 5 Piper diagrams for drinking water from Linzhou County KBD villages and non-KBD villages

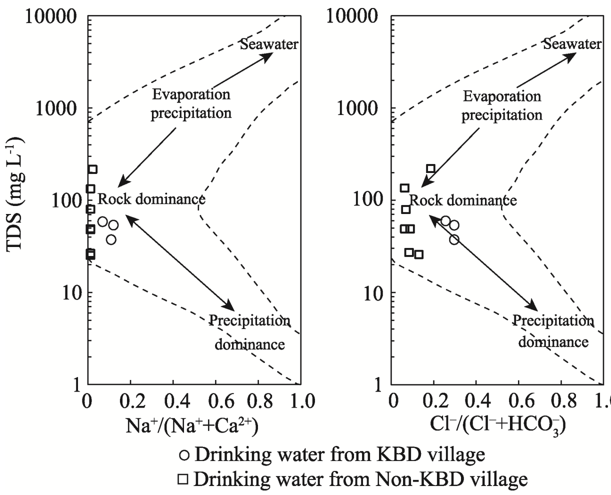

Fig. 6 Plots of the major ions within the Gibbs boomerang envelope (Gibbs, 1970) for water samples, showing TDS values versus the weight ratios of $Na^+/(Na^++Ca^{2+})$ and $Cl^-/(Cl^-+HCO_3^-)$

3.3 Differences in cultivated soil elemental concentrations

Table 3 lists the average major and trace elemental concentrations in cultivated soil from the KBD and non-KBD villages in Linzhou County. Independent sample t-tests show that the concentrations of Co, Fe, Hg, K, Li, Mg, Ni, Se, and Ti in cultivated soil exhibit significant differences between the KBD and non-KBD villages (P < 0.05). More specifically, the concentrations of Co, Fe, Li, Mg, Ni, Se, and Ti in the non-KBD villages are significantly higher than those in the KBD villages, whereas K and Hg in the non-KBD villages are significantly lower than in the KBD villages. Elemental concentrations did not exceed Chinese limitations in either the KBD or non-KBD villages (Table 3). Furthermore, differences in the Na/Ca ratios between the KBD and non-KBD villages are more than 2-fold, which is quite a large difference.

The average concentrations of Al, Ba, Cr, Mo, Se, and Zn in cultivated soil from the KBD and non-KBD villages are lower than the Chinese soil elemental background values (MEE, 1990), whereas the average concentrations of As, Cu, Fe, K, Mg, Mn, Na, Pb, and Ti were higher than the Chinese soil elemental background values. The average concentrations of Ca, Cd, Co, Li, Ni, and Sr in cultivated soil were lower than the Chinese soil elemental background values in the KBD villages but higher in the non-KBD villages. The average concentration of Hg in cultivated soil is lower than the Chinese soil elemental background value in the non-KBD villages but higher in the KBD villages.

3.4 Differences in elemental concentrations in highland barley

Table 4 lists the average major and trace elemental concentrations in highland barley from the KBD and non-KBD villages. Independent sample t-tests show that the concentrations of Cu and Mn in highland barley exhibit significant differences between the KBD and non-KBD villages (P < 0.05). More specifically, the concentrations of Cu and Mn in the non-KBD villages are significantly higher than the KBD villages. Neither the KBD nor the non-KBD villages had elemental concentrations that exceeded Chinese limitations (Table 4).

3.5 Differences in elemental concentrations of human hair and nails

The use of hair and nails simplifies the process of testing the

Table 3 Elemental concentrations of cultivated soil from Linzhou County KBD villages and non-KBD villages

Elements	Cultivated soil			GB 15618-2018 (MEE, 2018)	Chinese soil element background value (MEE, 1990)
	KBD villages (n=3)	Non-KBD villages (n =8)	Average (n =11)		
Al_2O_3 (wt%)	11.537	12.458	12.206		6.62
As (mg kg^{-1})	14.964	15.889	15.637	40	11.20
Ba (mg kg^{-1})	421.244	380.222	391.410		469.00
CaO (wt%)	1.220	2.119	1.874		1.54
Cd (mg kg^{-1})	0.091	0.117	0.110	0.3	0.10
Co (mg kg^{-1})	8.795	12.718	11.648		12.70
Cr (mg kg^{-1})	49.586	57.386	55.259	150	61.00
Cu (mg kg^{-1})	28.092	27.232	27.466	50	22.60
Fe_2O_3 (wt%)	3.566	4.946	4.569		2.94
Hg (mg kg^{-1})	0.105	0.059	0.072	1.3	0.07
K_2O (wt%)	3.752	2.735	3.012		1.86
Li (mg kg^{-1})	30.531	35.984	34.497		32.50
MgO (wt%)	0.890	1.440	1.290		0.78
Mn (mg kg^{-1})	672.538	716.462	704.483		583.00
Mo (mg kg^{-1})	1.234	0.751	0.882		2.00
Na_2O (wt%)	1.820	1.573	1.641		1.02
Ni (mg kg^{-1})	20.610	26.938	25.212	60	26.90
P (mg kg^{-1})	993.833	765.575	827.827		
Pb (mg kg^{-1})	33.877	29.833	30.936	70	26.00
S (mg kg^{-1})	223.480	163.085	179.556		
Se (mg kg^{-1})	0.072	0.109	0.099		0.29
Sr (mg kg^{-1})	162.958	187.355	180.701		167.00
Ti (mg kg^{-1})	2932	3586	3407		380
Zn (mg kg^{-1})	51.702	45.436	47.145	200	74.20
Na/Ca	1.492	0.742	0.947		

Table 4 Elemental concentrations of highland barley from Linzhou County KBD villages and non-KBD villages

Elements	Highland barley			NY 861-2004 (MA, 2005)	Elements	Highland barley			NY 861-2004 (MA, 2005)
	KBD villages (n=3)	Non-KBD villages (n=5)	Average (n=8)			KBD villages (n=3)	Non-KBD villages (n=5)	Average (n=8)	
Al (mg kg^{-1})	62.310	80.382	73.605		Mg (mg kg^{-1})	1182.299	1237.991	1217.107	
As (μg kg^{-1})	53.451	69.057	63.204	<700	Mn (mg kg^{-1})	13.222	15.466	14.625	
Ba (mg kg^{-1})	1.405	1.796	1.650		Mo (μg kg^{-1})	658.077	550.724	590.981	
Ca (mg kg^{-1})	399.428	456.841	435.311		Na (mg kg^{-1})	95.420	73.880	81.958	
Cd (μg kg^{-1})	2.640	4.468	3.783	<100	Ni (μg kg^{-1})	153.292	153.330	153.316	
Co (μg kg^{-1})	48.458	60.651	56.078		P (mg kg^{-1})	3300.360	3050.208	3144.015	
Cr (μg kg^{-1})	325.341	265.255	287.788	<1000	Pb (μg kg^{-1})	85.169	81.722	83.014	<400
Cu (mg kg^{-1})	3.610	4.810	4.360	<10	Se (μg kg^{-1})	9.197	10.116	9.772	<300
Fe (mg kg^{-1})	91.660	107.683	101.675		Sr (mg kg^{-1})	2.641	2.576	2.600	
Hg (μg kg^{-1})	0.310	0.152	0.211	<20	Ti (mg kg^{-1})	2.134	2.647	2.455	
K (mg kg^{-1})	4732.670	4420.242	4537.403		Zn (mg kg^{-1})	19.873	22.584	21.568	<50
Li (μg kg^{-1})	146.500	90.080	111.238						

Table 5 Elemental concentrations of human hair and nails from Linzhou County KBD patients and non-KBD patients

Elements	Human hair			Human nail		
	KBD patients (*n*=18)	Non-KBD patients (*n*=5)	Average (*n*=23)	KBD patients (*n*=19)	Non-KBD patients (*n*=7)	Average (*n*=26)
Al (mg kg^{-1})	43.249	32.668	40.949	229.818	156.446	210.064
As (mg kg^{-1})	0.150	0.075	0.133	2.172	1.010	1.859
Ba (mg kg^{-1})	25.925	3.384	21.025	6.430	3.871	5.741
Ca (mg kg^{-1})	1504.861	2194.720	1654.830	2418.368	2612.143	2470.538
Cd (mg kg^{-1})	0.174	0.034	0.144	0.206	0.056	0.165
Co (mg kg^{-1})	0.026	0.019	0.024	0.082	0.121	0.092
Cr (mg kg^{-1})	0.247	0.263	0.251	0.965	0.541	0.851
Cu (mg kg^{-1})	13.180	10.553	12.609	12.473	14.730	13.080
Fe (mg kg^{-1})	75.710	52.962	70.765	206.385	185.329	200.716
Hg (μg kg^{-1})	3.958	4.000	3.967	4.079	14.167	6.795
K (mg kg^{-1})	44.922	22.974	40.151	363.795	280.314	341.319
Li (mg kg^{-1})	0.093	0.066	0.087	0.615	0.421	0.563
Mg (mg kg^{-1})	151.208	117.096	143.793	225.600	209.586	221.288
Mn (mg kg^{-1})	11.068	5.038	9.757	8.576	6.510	8.020
Mo (mg kg^{-1})	0.066	0.057	0.064	0.053	0.049	0.052
Na (mg kg^{-1})	164.144	105.400	151.373	1580.893	747.807	1356.600
Ni (mg kg^{-1})	0.212	0.149	0.198	7.990	43.341	17.507
P (mg kg^{-1})	124.806	131.620	126.287	534.816	447.757	511.377
Pb (mg kg^{-1})	3.855	2.233	3.502	1.973	1.252	1.779
Se (mg kg^{-1})	0.251	0.321	0.266	0.470	0.509	0.481
Sr (mg kg^{-1})	5.509	8.638	6.189	1.558	2.130	1.712
Ti (mg kg^{-1})	2.373	1.329	2.146	9.685	8.429	9.347
Zn (mg kg^{-1})	203.061	176.700	197.330	193.932	185.014	191.531

trace element concentrations in human beings and, for this reason, such sample types are used extensively in trace element studies (Hopps, 1977). Hair and nails are unique biological tissues in the sense that they accumulate trace elements, form in relatively short time periods and remain isolated from metabolic events in the body. These characteristics allow these tissues to reflect the metabolic trace elemental levels in humans over certain time periods and they can be used as an evaluation index of the human Se nutrition status (Takagi et al., 1986; Aguiar and Saiki, 2001). Table 5 lists the average major and trace elemental concentrations in human hair and nails from KBD and non-KBD villages in Linzhou County.

Independent sample t-tests show that the concentrations of As, Mn, and Se in human hair and the Mo and Pb concentrations in human nails exhibit significant differences between the KBD and non-KBD villages ($P < 0.05$). More specifically, Se concentrations in the non-KBD villages are significantly higher than in the KBD villages, whereas As, Mn, Mo, and Pb in the non-KBD villages are significantly lower than in the KBD villages.

3.6 Essential trace elements and relationships between potentially toxic elemental concentrations in drinking water, cultivated soil, highland barley, and humans

In the soil-water-grain-human ecosystem, soil is the most basic element and its Se concentration can ultimately affect human health through the food chain (Tan et al., 2002). According to Uchida et al. (2007), elemental transfer factors (TFs) are calculated based on the proportion of elements taken up from the ingested substances. For example, the TF of an element consumed by a plant from the soil is equal to the elemental concentration in the plant divided by the elemental concentration in the soil. Table 6 lists the soil- water-grain TFs in the KBD and non-KBD villages, which includes the TFs of each pair-wise permutation (soil-water, soil-grain, and water-grain) to illustrate the tendencies of different media to absorb and accumulate these elements. Based on the data in Table 6, the average transfer factor of each element is less than 1, which indicates that in both the KBD and non-KBD villages, transfer of these elements from

Table 6 Transfer factors (TFs) of some essential trace elements and potentially toxic elements in the soil–water–highland barley system

Element	Water/Soil			Grain/Soil			Water/Grain		
	KBD	Non-KBD	All	KBD	Non-KBD	All	KBD	Non-KBD	All
As	8.53E–06	8.36E–05	6.19E–05	3.57E–03	4.35E–03	4.04E–03	2.39E–03	1.92E–02	1.53E–02
Cd	1.10E–05	6.11E–06	7.27E–06	2.90E–02	3.82E–02	3.44E–02	3.79E–04	1.60E–04	2.11E–04
Co	3.79E–06	4.01E–06	3.92E–06	5.51E–03	4.77E–03	4.81E–03	6.88E–04	8.41E–04	8.15E–04
Cr	8.78E–06	2.32E–05	1.93E–05	6.56E–03	4.62E–03	5.21E–03	1.34E–03	5.03E–03	3.70E–03
Cu	7.86E–06	6.80E–06	7.13E–06	1.28E–01	1.77E–01	1.59E–01	6.11E–05	3.85E–05	4.49E–05
Fe	1.29E–06	2.56E–06	2.24E–06	3.67E–06	3.11E–06	3.18E–06	3.50E–01	8.22E–01	7.04E–01
Hg	1.90E–05	7.26E–06	1.25E–05	2.96E–03	2.57E–03	2.93E–03	6.45E–03	2.83E–03	4.26E–03
Mn	3.45E–07	6.36E–08	1.44E–07	1.97E–02	2.16E–02	2.08E–02	1.75E–05	2.95E–06	6.94E–06
Mo	8.49E–04	1.01E–03	9.56E–04	5.33E–01	7.33E–01	6.70E–01	1.59E–03	1.37E–03	1.43E–03
Ni	1.30E–05	2.38E–05	2.10E–05	7.44E–03	5.69E–03	6.08E–03	1.74E–03	4.18E–03	3.45E–03
Pb	1.77E–07	2.39E–08	7.43E–08	2.51E–03	2.74E–03	2.68E–03	7.04E–05	8.74E–06	2.77E–05
Se	n.d.	3.13E–03	2.41E–03	1.28E–01	9.28E–02	9.87E–02	n.d.	3.37E–02	2.44E–02
Sr	4.53E–04	1.14E–03	9.52E–04	1.62E–05	1.37E–05	1.44E–05	2.79E–02	8.31E–02	6.62E–02
Zn	3.18E–06	8.36E–07	1.61E–06	3.84E–04	4.97E–04	4.57E–04	8.27E–03	1.68E–03	3.52E–03

Note: n.d. means not detected

soil to water, soil to grain, or water to grain is difficult.

By selecting the essential and potentially toxic elements (i.e., As, Co, Cr, Cu, Fe, Hg, Mn, Mo, Ni, Pb, Se, and Sr) in the soil-water-grain-human ecosystem which exhibit significant differences between the KBD and non-KBD villages, we can calculate the intake of these elements by local residents. Several varieties of agricultural products grow in the agricultural areas of the Tibet Autonomous Region (Cheng and Min, 2002), and highland dominate the agricultural industry. Most residents in the KBD high-risk area predominantly consume highland barley as their main diet, with less meat and protein intake (Basangzhuoma et al., 2012). Therefore, local residents mainly consume trace elements through drinking water and by eating highland barley. We determined the doses of elements received through individual routes using equations modified from the US Environmental Protection Agency's Human Health Assessment Manual (EPA, 2001):

$$\mathrm{ADD} = \mathrm{C_g} \times \mathrm{IR_g} \times \mathrm{GD} \times \mathrm{GAF} + \mathrm{C_w} \times \mathrm{IR_w} \times \mathrm{GAF} \qquad (1)$$

where *ADD* is the average daily dose by ingestion (μg d^{-1}); C_g is the average concentration of element in grain (μg g^{-1}); IR_g is the ingestion rate of grain (g d^{-1}); *GD* is the gastrointestinal digestibility (no dimension); *GAF*, the gastrointestinal absorption factor (no dimension); C_W is the average concentration of the element in water (μg L^{-1}); and IR_w is the ingestion rate of water (L d^{-1}). Approximate standard values for each variable are found in some references as: IR_f = 690 g d^{-1} (Tang and Li, 2012), IR_w = 2 L d^{-1} (EPA, 2004), *GD* = 70% (Lintas and Mariani-Costantini, 1991), and the *GAF* of each element is shown in Table 7. The *ADD* of each element of the local population is calculated by using the average concentration of each element in the drinking water and highland barley in the KBD villages and the non-KBD villages of Linzhou County, and comparing the *ADD* with the WHO lower intake level (LL), the WHO tolerable upper intake level (UL), and the Chinese Nutrition Society (CNS) recommended nutrient intake (RNI) (Table 7).

By calculating the *ADD* of the selected elements in the KBD and non-KBD villages and comparing the adult intake values recommended by the WHO and CNS, we find that: 1) The *ADD* of As, Co, Cr, Cu, Fe, Mn, Mo, Ni, Pb, and Se are lower than the UL, which indicates that the average intake of these elements by local residents does not exceed the human dietary intake tolerance, i.e., these elements will not yield toxic side effects in the local residents. 2) The *ADD* of As, Co, and Cu in non-KBD females are higher than the LL, and the *ADD* of Fe and Mo in both village types for males and females are higher than the LL, which indicates that the average intake of these elements by local residents is within the safe intake range. 3) The *ADD* of Cr and Cu in KBD and non-KBD males and the ADD of Se in both village types for males and females are lower than the LL. Chromium is only 12% and 10% of the LL in the KBD and non-KBD villages, respectively. Male Cu intake is 74% and 98% of the LL in the KBD and non-KBD villages, respectively, and female Cu intake in the KBD villages is 86% of the LL. Male Se intake is 3.3% and 4.2% of the LL in the KBD and non-KBD villages, respectively, and female Se intake is 4.4% and 5.6% of the LL in the KBD and non-KBD villages, respectively. These results indicate that the local population suffers from serious deficiencies based on the average

Table 7 *GAF*, *ADD* and adult recommended intakes of some essential trace elements and potentially toxic elements

Element	*GAF*	Village type	C_f (μg g^{-1})	C_w (μg mL^{-1})	*ADD* (μg)	Adult average intake reference value		
						LL (WHO, 1996)	RNI (CNS, 2014)	UL (WHO, 1996)
As	0.95 (EPA, 2004)	KBD	0.053	0.128	24.768	20 μg d^{-1}	12–25 μg d^{-1}	M:139.3 μg d^{-1}
		Non-KBD	0.069	1.328	34.210			F: 117.9 μg d^{-1}
Co	0.85 (Underwood, 1956)	KBD	0.048	0.033	19.951	2 μg d^{-1}	60 μg d^{-1}	1 mg d^{-1}
		Non-KBD	0.061	0.051	24.987			
Cr	0.025 (EPA, 2004)	KBD	0.325	0.435	3.950	33 μg d^{-1}	30 μg d^{-1}	250 μg d^{-1}
		Non-KBD	0.265	1.333	3.270			
Cu	0.57 (EPA, 2004)	KBD	3.610	0.221	994.029	M: 1.35 mg d^{-1}	0.8 mg d^{-1}	M: 12 mg d^{-1}
		Non-KBD	4.810	0.185	1324.562	F: 1.15 mg d^{-1}		F: 10 mg d^{-1}
Fe	0.1 (Underwood, 1956)	KBD	91.660	32.087	4433.595	M: 1.20 mg d^{-1}	M: 12 mg d^{-1}	50 mg d^{-1}
		Non-KBD	107.683	88.489	5218.796	F: 1.69 mg d^{-1}	F: 20 mg d^{-1}	
Hg	0.95 (EPA, 2004)	KBD	0.000	0.002	0.146	–	–	–
		Non-KBD	0.000	0.000	0.070			
Mn	0.04 (EPA, 2004)	KBD	13.222	0.232	255.468	–	4.5 mg d^{-1}	10 mg d^{-1}
		Non-KBD	15.466	0.046	298.807			
Mo	0.95 (Suttle, 2010)	KBD	0.658	1.048	303.949	M: 13 μg d^{-1}	100 μg d^{-1}	M: 845 μg d^{-1}
		Non-KBD	0.551	0.756	254.135	F: 7.7 μg d^{-1}		F: 423.5 μg d^{-1}
Ni	0.04 (EPA, 2004)	KBD	0.153	0.267	2.983	–	25-35 μg d^{-1}	600 μg d^{-1}
		Non-KBD	0.153	0.641	3.014			
Pb	0.14 (Watson et al., 1986)	KBD	0.085	0.006	5.761	–	–	M: 232.1 μg d^{-1}
		Non-KBD	0.082	0.001	5.526			F: 196.4 μg d^{-1}
Se	0.3 (EPA, 2004)	KBD	0.009	0.000	1.333	M: 40 μg d^{-1}	60 μg d^{-1}	400 μg d^{-1}
		Non-KBD	0.010	0.341	1.671	F: 30 μg d^{-1}		
Sr	0.3 (Höllriegl et al., 2006)	KBD	9.197	73.800	1376.981	–	3.6 mg d^{-1}	–
		Non-KBD	10.116	214.129	1594.354			

Note: M means male and F means female.

intakes of Cr and Se, and there may be cases of endemic or degenerative diseases due to the lack of these elements. 4) The *ADD* of Co, Fe, Mn, Ni, and Sr are lower than the RNI of the CNS but higher than the LL, which indicates that local residents may be at risk of insufficient intakes of Co, Fe, Mn, Ni, and Sr.

3.7 Preliminary discussion of KDB causes

The investigation of KBD in the KBD and non-KBD villages based on factor detectors from the GeoDetector showed that STR was the first major factor that affects KBD pathogenesis (q-statistic = 0.175). Through the analysis of elemental concentrations in the soil-water-grain-human ecosystem, the calculation of the *ADD* values associated with the local population, and a comparison with the WHO and CNS recommended values of adult element intakes (Table 7), we found that the average Se and Cr intakes in the local population were seriously deficient (especially Se in the KBD villages). Previous studies have identified a lack of essential trace elements in the human body as the causes of KBD and Keshan disease, and indicated that they may also increase the risk of degenerative diseases, such as cancer, cardiovascular disease, and cerebral thrombosis (FAO and WHO, 2013; WHO, 1996). Impaired glucose tolerance or hyperglycemia, with impaired glycosuria and a refractory response to insulin, are the definitive symptoms of chromium deficiency (WHO, 1996), but there is no evidence of the effects on KBD. The removal of Se from local strata can lead to the loss of Se in the soil, which, in turn, yields a low Se nutritional status in the population and leads to KBD (Malaisse and Mathieu, 2008; Peng et al., 1992; Tan et al., 2002). The analysis and comparison of Se concentrations further confirmed that the Se concentrations in each environmental medium and human tissues in the KBD villages were lower than those in the non-KBD villages (Tables 1–4). Furthermore, we confirmed that local biogeochemical Se deficiency is an important factor that leads to KBD in local populations.

TEM appeared to be the second most important KBD controlling factor, with an individual q-statistic value of 0.172. This could be a good explanation for the food fungal toxin poisoning hypothesis (since food is contaminated by fungi in wet conditions during the drying and storage processes). Other factors (such as RAD, ELE, SD, and GEO) had relatively high q-statistic values for KBD in Linzhou County. All these factors nonlinearly or bivariately enhanced each other, and the interactions of these factors can enhance the prevalence rate of KBD. Therefore, it can be inferred that KBD in Linzhou County is caused by a set of multiple and interrelated potential risk factors.

4 Conclusions

In summary, based on the spatial analysis of a set of multiple and interrelated environmental factors in the KBD villages of Linzhou County and a comprehensive study of the soil-water-grain-human biogeochemical cycle in the endemic KBD and non-KBD villages, we can reach several conclusions. 1) KBD in Linzhou County occurs due to a set of multiple and interrelated environmental factors, the most important of which is the stratum factor. 2) The concentrations of Se in all environmental media (soil, water, and grain) and human tissues in the KBD villages of Linzhou County are lower than those of the non-KBD villages. 3) Local resident intakes of Se and Cr are seriously deficient, especially since the *ADD* of Se in the KBD villages is only approximately 4% of the WHO recommended lower limit for adult intake. 4) We speculate that the main cause of the endemic KBD epidemic is a lack of Se in the stratum, which leads to a serious Se shortage in the local population via the migration and transformation through the ecosystem, which eventually leads to a shortage of endemic biogeochemical Se. To some extent, this study may provide an improved understanding of the migration and biogeochemical cycles for local trace elements in ecosystems, as well as the ability to explore the main causes of KBD among local residents via spatial analysis and environmental chemistry. There are, however, still several issues that must be addressed. For example, due to the complexity of KBD pathogenesis, future studies will require the use of other research methods to further quantify the impacts that the factors operating in the other two disease factors may have on local residents suffering from KBD.

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空间分析与生物地球化学循环：西藏林周县大骨节病患病村与非患病村的比较研究

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摘　要：西藏林周县是我国大骨节病（KBD）患病较为严重的地区之一，本文将林周县作为研究区，通过使用地理探测器（GeoDetector）量化分析 KBD 患病率风险因子的影响，并使用环境化学方法验证空间分析结果。通过对 10 个潜在影响因子的分析以及对当地 KBD 患病村和非患病村的土壤–水–粮食–人这一生物地球化学循环的环境化学分析，结果表明:（1）林周县 KBD 由一组多重且交互作用的环境影响因子共同作用影响，其中最重要的控制因子是地层因子;（2）所有环境介质（土壤、水、谷物）及人体组织中的硒元素浓度在 KBD 患病区均低于非患病区;（3）当地居民对硒和铬的摄入严重不足，尤其是 KBD 患病村中居民硒元素平均日摄入量（ADD）大约仅为世界卫生组织（WHO）建议的成人基本摄入量下限的 4%;（4）我们推测，当地居民患病主要是由于地层这一影响因子，这是由于通过生态系统的迁移转化导致当地人口严重硒缺乏，最终导致地方性生物地球化学硒缺乏。

关键词：大骨节病；西藏；空间分析；生物地球化学循环；硒元素