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Research article

Spatio-temporal distribution of cadmium levels in Chinese population and its potential risk factors

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ABSTRACT

Cadmium (Cd), a ubiquitous heavy metal, exists in numerous environmental matrices and has severe adverse effects on various human organs and tissues. This research evaluates blood and urine Cd levels in the Chinese population through data mining using Monte Carlo simulation (MCS). A total of 168 scientific studies (120 on urine and 48 on blood) published between January 1980 and December 2020, reflecting a population of 109,743 individuals in China, were included in the study. The results indicate that the blood and urine Cd levels in the Chinese population exhibited a peak from 1990 to 1995 and remained stable after 1995, averaging 1.21 μg/L of blood Cd (BCd) and 0.61 μg/L of urine Cd (UCd). The spatial trend of Cd levels varied significantly. Shandong, Zhejiang, Heilongjiang, and Guangdong provinces were identified as the top provinces with high Cd levels, which were related to factors such as tobacco sales, E-waste amounts, and contaminated rice. Additionally, the study highlights that BCd concentrations are highest among preschool-aged individuals, whereas school-age and adolescent groups exhibit the lowest levels. However, no significant difference existed among the different age groups. Males showed significantly higher Cd levels than females in the general population. Moreover, exposure to smoking, drinking, and staple food preferences had an impact on Cd levels. Furthermore, this comprehensive study, using biological monitoring and data mining, provides valuable information on Cd pollution levels in the Chinese population. It presents a statistical analysis that can aid decision-makers in implementing effective measures to control potential Cd pollution and improve the health of vulnerable populations.

1. Introduction

Cadmium (Cd), a Group 1 carcinogen, is recognized by the International Agency for Research on Cancer as one of the most toxic

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heavy metals [1]. Cd can persist in the environment and easily accumulate in the human body, particularly retained in the kidneys, exhibiting a biological life span of 10–30 years. This toxic metal can be released into the environment through natural processes or human activities [2,3]. Due to its long-term accumulative effects, Cd can result in serious health effects with prolonged exposure, even at low levels. Previous studies have shown that Cd burden is associated with adverse health effects on multiple organs and systems, including the renal, bone, lungs, circulatory, and immune systems [4–7].

Currently, Cd is primarily introduced into the human body through ingestion, particularly from grains and vegetables grown in contaminated soils and water sources [8]. As an example, within Hunan Province, the dietary intake of Cd varies from 66.5 to 116 μg/kg BW/month, exceeding the tolerable dietary intake of 25 μg/kg BW/month as recommended by the Joint Food and Agriculture Organization of the United Nations and World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA) by more than 2.7 times [9,10]. Additionally, exposure can also occur via inhalation, including cigarette smoking, contaminated dust, or occupational exposure. In most cases, the concentrations of Cd were notably higher in smokers' urine and blood than in non-smokers [11]. For the non-smoking population, contaminated food and water account for about 90% of Cd exposure; while this is about 50% for smokers, influenced by the accumulation of Cd in tobacco leaves [12–14]. Furthermore, according to the Bulletin of the National Survey of Soil Pollution in 2014, Cd ranked as the No. 1 heavy metal of soil pollution in China. Of greater significance, it is important to note that 7% of soil samples exceeded acceptable levels [15]. Cd production in Asia is specifically increasing due to the rapid expansion of industrial activities [16].

In recent years, the concern for local Cd pollution has led to numerous studies in China have investigated Cd levels in Chinese population, either in blood or urine, in response to increasing attention [17–20]. The majority of the studies were conducted on small groups of residents in particular cities or provinces during specific years. Despite being resource-intensive and time-consuming, a well-designed and nationwide survey involving large-scale sample collection would be the ideal procedure to investigate the Cd levels in the general Chinese population. However, these investigations are sporadic and do not take into account previous Cd exposure in the Chinese population. A comprehensive national study is therefore essential to determine the profile and variances of Cd levels in the Chinese population.

To address this main objective, this study used mathematical models to estimate blood and urine Cd levels in the Chinese population by Monte Carlo simulation (MCS), a method that was previously established and validated by our group [21,22]. To investigate the spatial and temporal trend of Chinese Cd levels from 1980 to 2020, the intrinsic factors associated with Cd levels were discussed, and the heavily polluted provinces and relevant sources environmentally were identified. This study provides scientific evidence for Cd bio-monitoring and policy-making regarding Cd pollution control.

2. Materials and methods

2.1. Literature search and selection

PubMed, China National Knowledge Infrastructure (CNKI), VIP Medical Information System (VMIS), and Wanfang Database were systematically searched to identify relevant studies published between January 1, 1980 and December 30, 2020. Literature search was performed using the following keywords: "blood cadmium OR urinary cadmium" AND "China". Duplicate articles were excluded from the four databases.

2.2. Selection criteria

Studies that met the following criteria were collected: (1) Subjects as general populations within China and not belonging to special groups such as having specific diseases or living in Cd polluted areas; (2) For articles mentioning Cd-contaminated areas and occupational Cd exposure, only control group data that match the characteristics of general population were extracted; (3) Studies with strict quality control; (4) Outcomes were reported as either arithmetic mean (AM) and standard deviation (SD), or geometric mean (GM) and geometric standard deviation (GSD), or confidence interval (CI).

2.3. Data extraction

All gathered articles underwent a thorough examination, during which critical information such as article titles, publication years, years of study, sample sizes, age, gender, blood Cd (BCd) or urinary Cd (UCd) levels, and other relevant details were meticulously recorded. It's important to note that for papers lacking information on sample collection or study duration, we assumed the data to be from 2 years prior to the publication date.

Cigarette sales data were sourced from the official website of China Tobacco (http://www.tobacco.gov.cn/). Information about Cd emissions from industrial wastewater was derived from the decade's average statistics (http://www.stats.gov.cn/) (2008–2017). The quantity of E-waste disposal was extracted from seasonal reports provided by the Ministry of Ecology and Environment of the People's Republic of China (www.mee.gov.cn), using data from officially registered factories regarding discarded items like washing machines and air conditioners. Cd content in rice was acquired from scientific literature (Supplementary Table S1). Soil Cd content was largely referenced from a comprehensive review that encompassed 2253 sources on soil Cd published between 2005 and 2017 [15].

2.4. Data analysis

2.4.1. Unit conversion of BCd and UCd levels

In the present study, the uniform unit was μg/L. Other units were converted to μg/L, e.g. 1 μmol/L = 112.4 μg/L, 1 μg/dL = 10 μg/L.

2.4.2. Simulation process

MCS was conducted by using Microsoft Office Excel software. In brief, the procedure used in this method is (1) constructing a mathematical model based on the problem; (2) extracting the simulated stochastic numbers; and (3) deriving the approximate solution to the problem.

For the initial data characterized by normal distribution and logarithmic distribution, the BCd or UCd levels of individuals in each study were calculated using the following functions, respectively:

$$= \mathrm{MAX}\left(\mathrm{LOD}\Big/\sqrt{2}, \mathrm{NORM.INV}\ (\mathrm{RAND}\ (\ ), \mathrm{AM}, \mathrm{SD}\ )\right)$$

$$= \mathrm{MAX}\left(\mathrm{LOD}\Big/\sqrt{2}, \mathrm{LOGNORM.INV}\ (\mathrm{RAND}\ (\ ), \mathrm{LN}_{\mathrm{GM}}, \mathrm{LN}_{\mathrm{GSD}}\ )\right)$$

where NORM. INV and LOGNORM. INV denotes interval points that return a given probability normal distribution or log-normal distribution, respectively. RAND generates randomly generated numbers with a distribution that is greater than or equal to 0 and less than 1. These values were calculated in Excel (Microsoft). Although previous work investigating children blood lead levels using MCS has successfully validated the feasibility and accuracy of simulation of 20 repeat times [21], in this case of BCd or UCd levels, simulation of each sample was repeated 100 times to increase accuracy, due to larger sample sizes and greater variances.

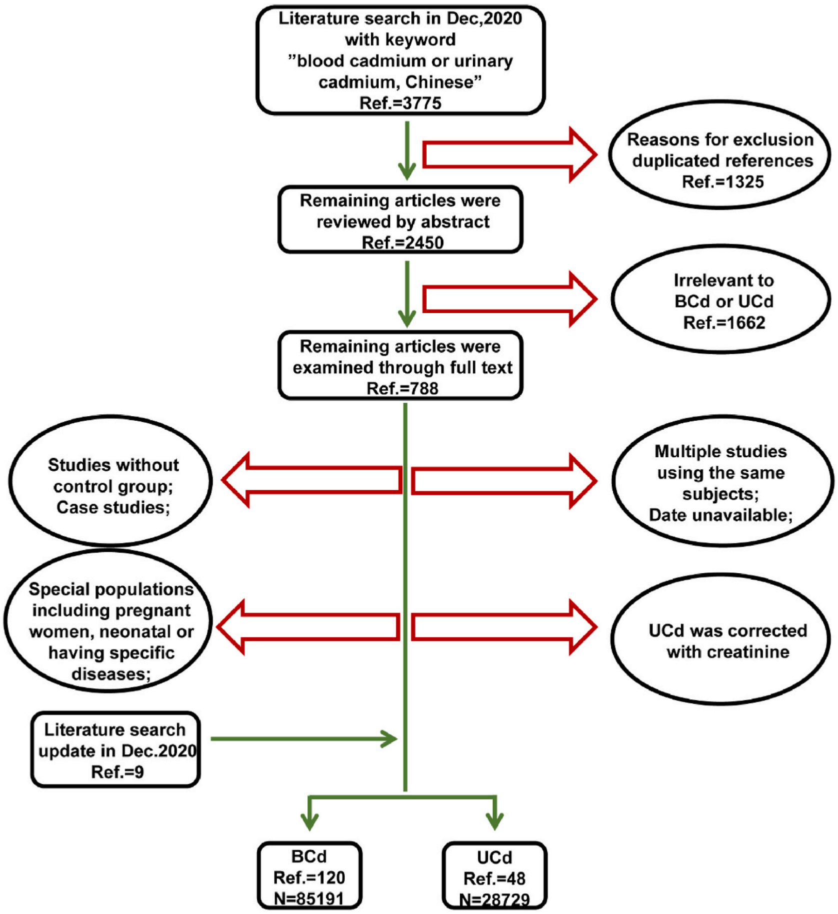

Fig. 1. Flow diagram of the study selection process.

2.5. Statistical analysis

The database resulting from MCS was analyzed using SPSS 25.0 software (IBM, USA). Figures were created using GraphPad Prism 8.3.0 and ArcGIS 10e.6. The differences in subgroups were assessed by T-test and Mann-Whitney *U* Test, with a *p*-value <0.05 indicating a significant difference.

3. Results

3.1. Searching result

A total of 3775 references were gathered from four databases in December 2020 (Fig. 1). References were excluded based on several criteria, such as lack of relevance, absence of control group, involvement of specialized populations, duplication of subject samples across multiple studies, and absence of mean or SD values for MCS of UCd or BCd levels. Studies concerning UCd that solely provided values following creatinine correction were also excluded, as urinary creatinine is considerably influenced by age, gender, body size, and dietary meat intake, which could introduce substantial bias [23]. In the end, a total of 168 articles, comprising 120 on BCd and 48 on UCd, were incorporated into this study (see Supplementary Tables S1 and S2). All the above studies encompassed 109,743 subjects in 28 provinces, autonomous regions, and municipalities.

3.2. The temporal trend of BCd and UCd of Chinese general population from 1980 to 2020

BCd and UCd levels between 1980 and 2020 were simulated and integrated (Fig. 2). The BCd levels exhibited a modest downward trend from 1.08 μg/L during 1980~1984 to 0.49 μg/L during 2015~2020, with variation ranging from 0.49–2.71 μg/L; while the UCd demonstrated a fluctuating trend within the range of 0.95 μg/L and 0.97 μg/L, with variation ranging 0.49–2.27 μg/L. Overall, BCd and UCd trends did not manifest significant changes over time. The simulated GM BCd for the Chinese general population averaged 1.21 μg/L from 1980 to 2020.

3.3. The spatial distributions of BCd of Chinese general population

The simulated values were aggregated chronologically and depicted on the Chinese map, corresponding to the 48 cities investigated in the studies (Fig. 3). In cases where studies only specified provinces, they were assumed to have been conducted in the provincial capitals. The BCd levels exhibited substantial variations across different locations, ranging from 0.0145 μg/L (Xiamen Fujian) to 8.99 μg/L (Linyi Shandong).

3.4. The effect of age, gender, smoking, drinking, and dietary preference

Age effects taken into consideration, the BCd of preschool-aged group was the highest (GM: 1.56 μg/L) while the school-age group and adolescence group had the lowest levels (GM: 0.27 μg/L). Conversely, no significant difference was observed among the other age groups (Fig. 4a). Furthermore, BCd of males was significantly higher than those of females in the general population (Fig. 4b). Notably, smokers displayed markedly higher BCd levels in comparison to non-smokers (Fig. 4c). When considering both smoking habits and gender concurrently, BCd levels of either female smokers or female non-smokers surpassed those of males in their respective categories (Fig. 4c). Additionally, individuals who were drinkers exhibited higher BCd levels compared to non-drinkers (Fig. 4d). Furthermore,

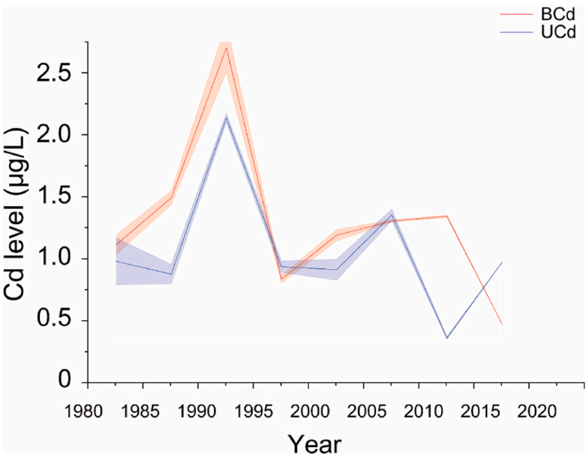

Fig. 2. The temporal trend of BCd and UCd of Chinese general population was based on 105,260 simulated subjects from 148 studies.

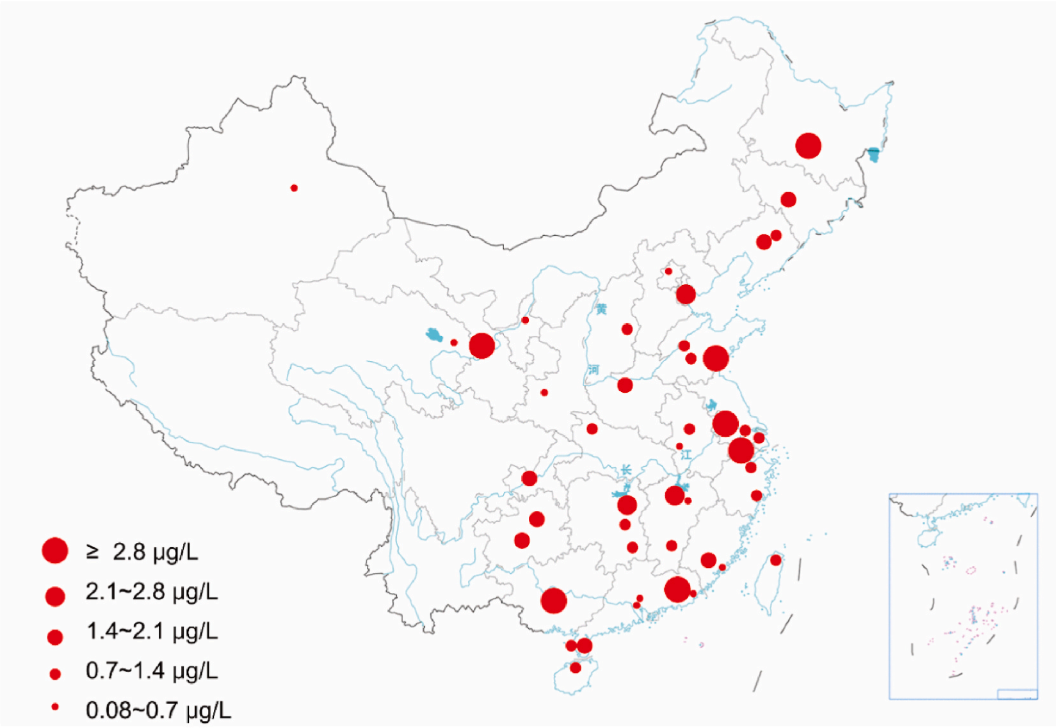

Fig. 3. The spatial distributions of BCd of Chinese general population.

our study divided all examined provinces and cities into two groups based on dietary preferences [24]: The results demonstrated that individuals who preferred rice as staple food showed significantly higher BCd levels than those who preferred wheat (Fig. 4e).

3.5. *Contributing factors of BCd levels of different provinces*

The BCd levels of Chinese provinces, along with contributing factors that were well-recognized as related to Cd pollution were presented in Fig. 5a. Shandong showed the highest BCd levels, which could be linked to factors like substantial annual tobacco sales, relatively high electronic waste disposal capacities, and elevated Cd content in commercial rice within the region. Following Shandong, Zhejiang, Heilongjiang, Guangdong, and Gansu were ranked among the top 5 provinces with elevated BCd levels, each exhibiting a minimum of one contributing factor.

Correlation analysis revealed noteworthy results, showcasing that BCd levels displayed significant positive correlations with tobacco sales ($R = 0.45$), the magnitude of e-waste disposal ($R = 0.26$), and Cd content in rice ($R = 0.52$) (Fig. 5b). A combination of BCd levels of all investigated places and each of the contributing factors drawn on a Chinese map displayed the association clearly (Fig. 5c).

4. Discussion

The primary sources of Cd pollution were primarily attributed to mining and smelting operations, wastewater irrigation, and urban development [15,25]. It is reported that approximately 15 million hectares of agricultural soils have been contaminated with Cd in China [26]. According to the 2014 National Soil Pollution Survey Report, heavy metals and metalloids are present at 16.1% of the investigated sites in China. Cd was the predominant contaminant in soil samples, accounting for 7% of cases [27]. Additionally, incidents of accidental Cd leakage causing water or soil pollution have increased public awareness regarding Cd contamination. Consequently, the issue of Cd pollution and its associated negative health impacts on the Chinese population has emerged as a significant public health concern in the country.

Blood and urine samples are frequently utilized and widely acknowledged matrices for assessing internal xenobiotic exposure for biological monitoring of heavy metal exposure in occupational toxicology [28]. In China, National Human Biomonitoring study demonstrates that the GM of BCd and UCd was 0.48 μg/L and 0.32 μg/L in 2017–2018 [29]. This type of research focuses solely on assessing Cd levels in the Chinese population during a specific timeframe. In contrast, our study, based on comprehensive nationwide data analysis, revealed that BCd GM of Chinese general population was 1.21 μg/L from 1980 to 2020. The finding was very similar to the level reported by Korean National Health and Nutrition Examination Survey (1.37 μg/L) from 1991 to 1998 [30] but was higher than those observed in the United States (median: 0.32–0.40 μg/L in adults) (USCDC, 2019) and in Canada (0.38 μg/L) [31] while lower than that in Japan (1.82 μg/L) [32]. By the end of 2012, China had established more than 50 laws and regulations pertaining to

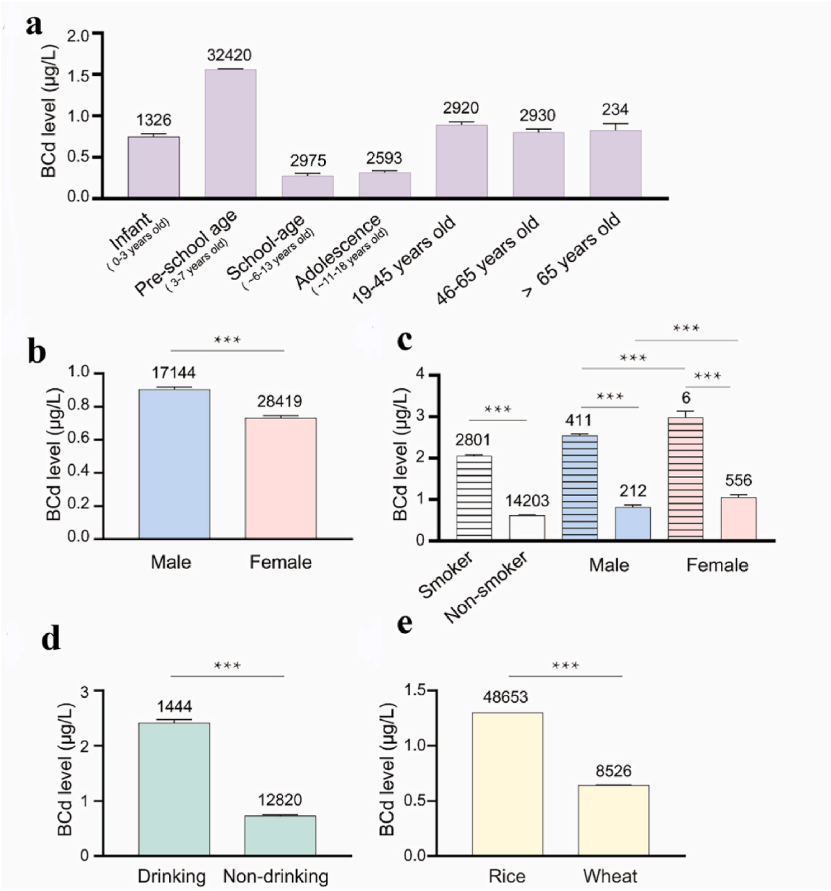

Fig. 4. The BCd levels are in different subgroups according to relevant factors. a: Age; b: Sex; c: Smoking; d: Drinking; e: Dietary preference. The numerical values depicted above the bar chart represent the sample size of each group. ***$P < 0.001$.

environmental pollution. These regulations have, to a certain extent, contributed positively to the mitigation and management of heavy metal pollution [33]. This research was conducted with concern for BCd and UCd levels nationwide. BCd and UCd levels during the 1990s saw an increase when compared to the 1980s, which can likely be attributed to rapid industrial development and the urbanization process. During the 1990s, China had taken a series of actions attempting to prevent and control heavy metal pollution, which may account for declining trend [34]. UCd levels began to increase abruptly from 2015, which appeared contradictory to UCd levels. This could be attributed to the additional increase of about 1128 samples from Gansu Province. Since the UCd levels of Gansu (a province with high Cd levels) had not been observed in any of the other periods, this could introduce a bias in representing the overall simulated GM.

It is widely accepted that Cd levels increase with age [35,36]. In our findings, BCd levels of adults surpassed those below 18 years old, except for the preschool age group which exhibited notably elevated levels (Fig. 4). The results rendered here should be interpreted cautiously: Children may have greater potential exposure to contaminants present in food [37]. EFSA [14] estimates that children have double the relative Cd intake when compared to adults, as toxic elements are more readily absorbed in the intestines of children, while renal excretion is lower than that of adults [37].

Furthermore, preschool-age children might face an increased likelihood of exposure to indoor secondhand smoke. It has been observed that in 2015, the average number of smokers was around 933 million, with over 80% being males [38]. This might explain why males have higher BCd levels compared to females (Fig. 4b).

Tobacco is a major source of Cd exposure for smokers, given that tobacco can contain Cd concentrations ranging from 0.5 to 5 μg/g or even higher [39]. Smokers generally have a higher level of Cd than non-smokers as shown in Fig. 5B. It has been found that in 2015, the estimated total number of smokers was around 933 million, with over 80% of them being males [38]. This could be the reason why males seemed to have higher BCd level than females (Fig. 5c). Reducing the smoking rate might be an effective way to lower the risk of Cd exposure. Rice, as a predominant staple food choice in southern China, to some extent explained high BCd levels in our study and is consistent with studies in Korea and Japan [40,41].

Until now, studies evaluating the correlation between Cd exposure and the risk of osteoporosis have produced inconsistent results. Our BMD analysis in Supplementary Fig. S1 showed that as BCd rose from 1.26 μg/L to 5.18 μg/L, the prevalence of osteoporosis increased greatly from 1.3 times to 5 times compared to non-polluted area, which suggested that elevated BCd levels are a risk factor

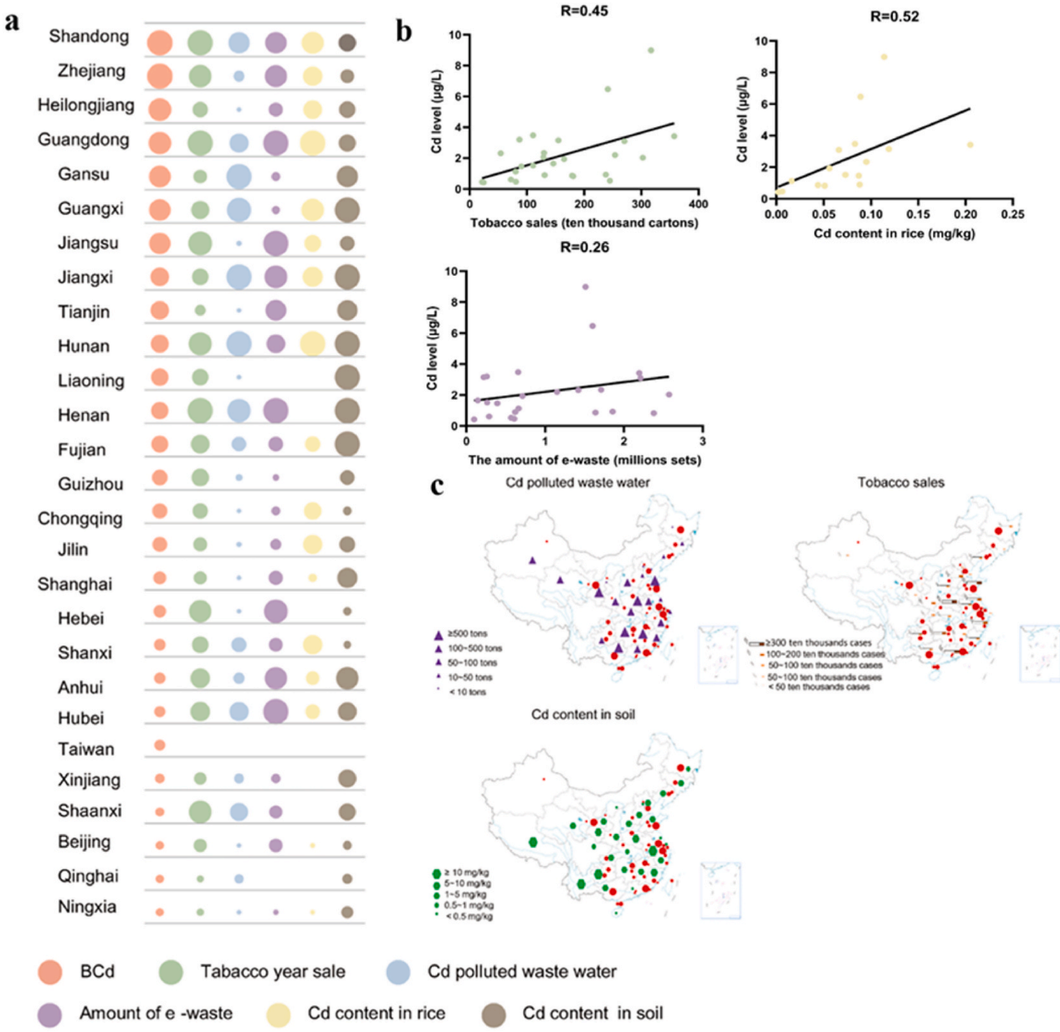

Fig. 5. The population BCd levels and environmental factors associated with Cd pollution in Cd exposed provinces. a: A graphic summary of 27 provinces. b: Correlation analysis between BCd and tobacco sales, Cd pollution waste water, Cd content in soil, Cd content in rice, and the amount of e-waste. c: The spatial distribution of BCd and tobacco sales, Cd polluted waste water, Cd content in soil, Cd content in rice, and the amount of e-waste.

for osteoporosis but also proposed dose-response relationships between disease and BCd. Cd may reduce the normal activation of vitamin D and lead to decreased Ca absorption from the intestines and impaired bone mineralization [42]; this process is thought to be the crucial mechanism of Cd-induced bone effects. Furthermore, recent research conducted in Europe has revealed that Cd might exert a direct impact on bone by influencing the activity and metabolism of bone cells, reducing bone mineralization, and hydroxyapatite formation [43–45]. Studies on osteoclasts suggest that Cd could increase both the quantity and activity of mature osteoclasts [46]. But the mechanism is far from completely understood. However, the precise mechanism remains inadequately understood. As proposed in previous studies that age plays a significant role in bone condition, it's reasonable to assume that older adults with prolonged Cd exposure may face an elevated risk of osteopenia or osteoporosis [47].

There are still some limitations in this study should be acknowledged. Firstly, the number of studies about BCd and UCd levels of Chinese population before 1995 was comparatively small, thus the data from a few provinces may not sufficiently represent the entire country. Differences in the quantity of research across different provinces could introduce certain biases. Secondly, data from various articles lacked uniform stratification based on age, gender, and other variants of population distribution, limiting the establishment of only basic association through ecological study. Therefore, the Cd-exposure database should be continually expanded in the future to acquire adequately stratified data, enabling more comprehensive and in-depth studies. Moreover, there is a possibility of detection bias in this study. UCd and BCd levels were measured using various techniques across the literature referenced in this study, such as atomic absorption spectrometry (AAS) and inductively coupled plasma mass spectrometry (ICP-MS). Nonetheless, it's important to note that any potential detection bias is unlikely to significantly affect data interpretation due to the high level of detection consistency between AAS and ICP-MS, ensured through rigorous quality control measures.

5. Conclusions

The study has contributed to our understanding of the spatial-temporal trend of Cd levels among the general Chinese population through the integration of a literature review, data mining by MCS, and the presentation of detailed GMs and GSD. While the nationwide Cd levels did not significantly change after 1995, significant variations have been observed across different locations. Moreover, our research highlights the influence of personal factors, including gender, age, dietary preferences, and smoking habits, on BCd levels. Furthermore, tobacco sales and e-waste disposal have been identified as vital external environmental indicators reflecting Cd exposure within the Chinese population. The potential repercussions of Cd exposure from polluted rice, a prevalent dietary source, are also deserving of concern. It is recommended that government authorities implement regular monitoring of BCd levels and associated environmental pollution indicators to further reduce the burden of Cd exposure in Chinese populations.

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Additional information

Supplementary data associated with this article can be found in the online version.

CRediT authorship contribution statement

Xinglin Zhang: Writing – original draft, Validation, Investigation, Data curation. **Tsendmaa Bold:** Writing – original draft, Data curation. **Wenjing Zhang:** Formal analysis, Data curation. **Qianwen Zhao:** Methodology, Investigation. **Yanting Li:** Formal analysis, Data curation. **Jianzhong Zhang:** Methodology, Investigation. **Lin Lu:** Validation, Investigation. **Xiaoya Ji:** Formal analysis, Data curation. **Lin Zhang:** Writing – review & editing, Resources. **Yuan Jin:** Writing – review & editing, Supervision, Conceptualization. **Jinglong Tang:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28879.

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