Association of arsenic exposure and cognitive impairment: a population-based cross-sectional study in China

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Research

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Abstract

Background: Chronic arsenic exposure is a major public health issue worldwide. Previous studies explored the effects of arsenic exposure on cognitive impairment, but majority of previous studies focused on the effects on school children rather than adults. Moreover, few studies investigated the role of arsenic exposure in cognitive impairment process in a large scale in China.

Methods: Aimed to evaluate the association between long-term exposure to arsenic and cognitive impairment in China, we designed a cross-sectional analytical study in which 1,556 adults from three locations around the Realgar Plant (Heshan Village, Wangyangqiao Community and Baiyangshan Village) were enrolled. Participants' general cognitive function were evaluated by using a Chinese version of Mini-mental state Examination (MMSE). Internal arsenic exposure status of participants (hair arsenic concentrations) was measured by inductively coupled plasma-mass spectroscopy (ICP-MS), and external arsenic exposure status of participants was approximately evaluated by measuring the distance between the participants' location to Realgar Plant.

Results: In our study, we found that the prevalence of cognitive impairment in arsenic-endemic areas was 20.6%, which was significantly higher than the prevalence of cognitive impairment in China (14.5%). Hair arsenic concentrations and prevalence of arsenicosis in cognitive impaired group (CI) was significantly higher than those in cognitive normal group (CN) ($P < 0.05$).

Conclusions: Our analyses revealed that the distance away from Realgar Plant was positively correlated with MMSE scores, while inversely associated with the prevalence of cognitive impairment. In addition, we found that MMSE scores were decreased with the increasing hair arsenic concentrations in a dose-dependent manner. In two-level Logistic regression analysis, arsenicosis was still a risk factor for cognitive impairment (odds ratio (OR) = 1.77, $P < 0.05$) even after adjusting for potential confounding variables. Our results showed that chronic arsenic exposure decreased cognitive function in adults in a dose-dependent manner, and arsenicosis was a risk factor for cognitive impairment.

Background

As global aging population increase dramatically [1], the aging and age-related diseases such as dementia have become the focus of attention. In China, it was estimated that 9.5 million people over age 65 years were suffering from dementia [2]. Dementia imposed a heavy financial burden on patients and their families. The per capita annual cost was US\$19,144.36 and the national annual costs was US\$167.74 billion in China in 2015 [3].

Arsenic (As), a toxic metalloid element widely distributed in nature, has been found to be the risk factor for a variety of diseases including hypertension, atherosclerosis, type-two diabetes, myocardial infarction, keratosis, anemia, skin cancer, bladder cancer, lung cancer, and cognitive impairment [4]. Long-term exposure to air, soil, water and food with high concentration of arsenic leads to a chronic systemic illness called arsenicosis. Arsenicosis is a global public health issue. Tens of millions of people worldwide are at

risk of exposure to arsenic, including the United States, Chile, Bangladesh, Thailand, China, India, Mexico and Hungary [5]. Several epidemiological researches showed the association between chronic arsenic exposure and cognitive impairment [6–9]. However, majority of previous researches of arsenic exposure and cognitive function focused on the effects of arsenic on school children's cognition rather than adults and elders, which led to restriction in the applicability of the findings. Moreover, previous studies used groundwater arsenic concentrations as an indicator of arsenic exposure levels, and lack of appropriate markers for reflecting actual individual arsenic exposure levels precisely.

Realgar Plant, located in Shimen County, Hunan Province of central south China, was known as the largest Realgar Plant in Asia with a mining history of more than 1500 years [10]. It was intensively mined and smelted since the 1950s, until it was shut down by the government due to the serious environmental pollution in 2011 [10, 11]. In 1994, the peak level of arsenic in local drinking water was 14,531 µg/L, and it substantially dropped to 765 µg/L in 2014, which still exceeded the World Health Organization (WHO) standard (0.01 mg/L) [11, 12]. Despite the improvement of local environment under the government's guidance and supervision, the soil and groundwater seriously contaminated by arsenic continually endanger local residents. To investigate the correlation between arsenic exposure and cognition function in a large sample of adults, we conducted a cross-sectional study in the residents around Realgar Plant who had long-term exposure to arsenic.

Methods

Selection of study areas and participants

A population-based cross-sectional survey was performed in three locations around Realgar Plant (Heshan Village, Wangyangqiao Community and Baiyangshan Village) between January to March 2019 in Shimen County, Hunan Province of China. Heshan Village, Wangyangqiao Community and Baiyangshan Village is 2 km, 5 km, 10km away from Realgar Plant, respectively (Fig.1). The livelihoods of the residents living in the three locations were approximately similar. Because the lack of data of external arsenic exposure level (arsenic concentrations of atmosphere, soil, water, etc.), the distance from the location to Realgar Plant can be used as representation for the previous level of arsenic exposure approximately. Participants were recruited from a medical examination program approved by the local government at Realgar Plant Hospital. Written informed consent forms were obtained prior to the present study from all participants. The individuals (≥ 18 -year-old) who had lived in these three locations and owning the local household registration were recruited for this study. Individuals with hearing or vision difficulties, neurological conditions, severe mental disorders or end-stage physical diseases (e.g., Parkinson's disease, epilepsy, multiple sclerosis, stroke, schizophrenia, depressive disorder, heart failure, liver failure, respiratory failure, uremia, etc.) were excluded. The demographic characteristics of participants collected by questionnaire included: age, sex, height, weight, location, body mass index (BMI), education, personal medical history, and diastolic blood pressure (DBP), and systolic blood pressure (SBP).

Collection of blood sample and measurement of biochemical index

Fasting blood samples were collected between 8 to 9 a.m. Samples were stored in a cold-chain box and sent to Shimen People's Hospital to test fasting blood glucose and blood lipids. Indices of blood lipids examination included: total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and triglyceride (TG). Among the 1556 participants, 294 participants were unavailable or declined to provide blood samples. The total number of blood samples used for the biochemical index determination was thus 1262.

Cognitive function and sleep assessments

The general cognitive function was evaluated by using a Chinese version of MMSE which ranged from 0 to 30. The higher MMSE scores suggest the better cognitive function. As MMSE scores are susceptible to educational level, the cut-off score indicating cognitive impairment for different education levels are: ≤ 17 points for illiterate participants, ≤ 20 points for participants accepted primary education and ≤ 24 points for participants accepted secondary or higher education [13].

Sleep quality was assessed by Pittsburgh sleep quality index (PSQI). PSQI is a well-validated tool aimed to evaluate subjective sleep quality. It is a questionnaire with 19 self-related items, composed of 7 subsections: subjective sleep quality, sleep duration, sleep latency, sleep efficiency, sleep disturbances, usage of sleeping pills, and daytime dysfunction. Each subsection score ranges from 0 to 3, and the total score of PSQI is 21. A lower PSQI score indicated better sleep quality [14].

All assessments were conducted by trained researchers in the field of neurology according to the protocol. All of the researches were blind to the study areas and cognitive status of participants.

Arsenic exposure status assessment and diagnosis of endemic arseniasis

Previous study suggested that arsenic concentrations in hair samples can be used as an effective marker of arsenic intake [15]. Therefore, in this study, we collected hair samples (approximately 1cm in length) behind the ear and sealed them separately in envelopes. Samples were sent to the local Occupation Disease Prevention and Treatment Center for analyzing. The accurate arsenic concentrations in hair samples were measured by inductively coupled plasma-mass spectroscopy (ICP-MS) [15].

Endemic arsenicosis was diagnosed according on the diagnosis standards of medical and health professions formulated by National Health Commission of the People's Republic of China (PRC) in 2015. Residents of endemic arsenicosis areas can be diagnosed as arsenicosis if they meet one of the following clinical characteristics: (i) existing unexplained papular, nodular or verrucous hyperkeratosis on the skin of palms and soles, or (ii) existing diffuse or scattered pigmentation spots and/or round depigmentation spot of varying sizes with blur edges on the skin of trunk or non-exposed parts. Meanwhile, arsenic concentrations in hair or urine samples were significantly higher than the normal reference values in non-endemic areas can be used as a reference indicator for the diagnosis of arsenicosis [16]. The arseniasis participants were unanimously diagnosed by two dermatologists in

Xiangya Hospital and Centers for Disease Control (CDC) according to the protocol. All of the researchers were blind to the study areas and cognitive status of participants.

Statistical Analysis

Data from all questionnaires were processed by SPSS. Characteristics of participants were described using mean ± standard error for normal distributed continuous variables or median (25% quartile, 75% quartile) for skewed distributed continuous variables, and frequency (%) for categorical variables. When the sample distribution conformed to normality, differences between two continuous variables groups were assessed by using Student's t test. For the two categorical variables groups comparisons, Chi-square test was used to analyze the differences. Differences among means of multiple groups were assessed using one-way analysis of variance (ANOVA). For skewed distributed variables, a nonparametric test was used. Two-level Logistic regression analysis was used to determine whether expose to arsenic was a risk factor for cognitive impairment, results were presented as OR and adjusted OR with 95% confidence intervals (CI). We performed linear regression analysis to examine the association of the hair arsenic concentrations and MMSE scores. All analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). Comparisons between groups were considered to be statistically significant when $p<0.05$.

Results

A total of 1556 participants, including 802 males and 754 females, were included in our study. CI prevalence of females was significantly higher than that of males (24.8% vs 16.7%, $P<0.05$). The average age of participants was 57.0 ± 11.5 years. The percentages of participants from Heshan Village, Wangyangqiao Community and Baiyangshan Village were 48.2%, 36.1% and 15.7%, respectively. There were 321 (20.6%) participants in CI and 1235 (79.4%) in CN included in our study. In CI, the proportions of participants without education and with primary education, secondary or higher education were 47.6%, 18.9% and 15.5%, respectively. In CN, the proportions were 52.4%, 81.1% and 84.5%, respectively. There was a statistically significant difference between CI and CN groups in the education levels ($P<0.05$). In other words, the illiteracy participants were most likely prone to cognitive impairment, and participants accepted secondary or higher education had the lowest prevalence of cognitive impairment. MMSE score of CI was significantly lower than that of CN (16.6 ± 5.47 vs. 26.3 ± 2.81 , $P<0.05$), and PSQI score in CI was 6.48 ± 3.89 and in CN was 5.71 ± 3.99 , significantly higher than that of CN ($P<0.05$). Hair arsenic concentrations (HAs) in CI was significantly higher than CN ($0.27(0.14, 0.56)$ mg/kg vs. $0.20(0.10, 0.41)$ mg/kg, $P<0.05$). The prevalence of arsenicosis in all participants was 49.2%. The prevalence of arsenicosis in CI was higher than CN (64.5% vs. 45.3%, $P<0.05$). The demographic characteristics of the subjects was shown in Table 1.

Table 1 Demographic characteristics for participants

	Overall N=1556	CI N=321	CN N=1235	P value
Sex, Female, N (%)	754 (48.5)	187 (24.8)	567 (75.2)	<0.001
Age, year	57.0±11.5	63.4±10.6	55.3±11.1	<0.001
Residence Locations, N (%)				0.012
Heshan Village	750 (48.2)	177 (23.6)	573 (76.4)	
Wangyangqiao Community	561 (36.1)	107 (19.1)	454 (80.9)	
Baiyangshan Village	245 (15.7)	37 (15.1)	208 (84.9)	
BMI	23.9±3.41	23.7±3.20	24.0±3.45	0.164
Education level, N (%)				<0.001
Illiteracy	168 (10.8)	80 (47.6)	88 (52.4)	
Primary	756 (48.6)	143 (18.9)	613 (81.1)	
Secondary or higher	632 (40.6)	98 (15.5)	534 (84.5)	
Medical history, N (%)				
Hypertension	423 (27.2)	110 (34.3)	313 (25.3)	0.001
Myocardial infarction	266 (17.1)	83 (25.9)	183 (14.8)	<0.001
Osteoporosis	76 (4.9)	18 (5.6)	58 (4.7)	0.500
SBP (mmHg)	146±19.9	151±19.6	144±19.7	<0.001
DBP (mmHg)	88.7±12.5	89.1±11.4	88.6±12.7	0.246
Fasting glucose (mmol/L)	6.35±1.90	6.55±1.73	6.29±1.95	<0.001
Blood lipid				
TC (mmol/L)	5.18±1.02	5.20±1.03	5.17±1.02	0.646
HDL-C (mmol/L)	1.41±0.33	1.42±0.32	1.41±0.34	0.652
LDL-C (mmol/L)	3.18±0.86	3.22±0.91	3.17±0.84	0.472
TG (mmol/L)	1.44±1.24	1.50±1.38	1.42±1.19	0.485
MMSE	24.3±5.30	16.6±5.47	26.3±2.81	<0.001
Instant memory	2.64±0.78	1.86±1.17	2.85±0.46	<0.001
Delayed memory	2.00±1.51	0.77±1.04	2.32±0.94	<0.001
Orientation	9.05±1.43	7.45±2.21	9.47±0.68	<0.001

Visuospatial ability	0.57±0.49	0.26±0.44	0.66±0.48	<0.001
Executive ability	2.52±0.74	1.92±1.02	2.67±0.56	<0.001
Language ability	7.31±1.85	5.12±2.18	7.88±1.23	<0.001
Attention and arithmetic	3.31±1.68	1.36±1.39	3.81±1.34	<0.001
PSQI	5.89±3.98	6.48±3.89	5.71±3.99	0.002
subjective sleep quality	1.09±0.78	1.24±0.72	1.05±0.79	<0.001
sleep latency	2.04±2.10	2.34±2.20	1.96±2.07	0.004
sleep duration	0.35±0.78	0.32±0.72	0.36±0.79	0.582
sleep efficiency	0.71±1.01	0.80±1.02	0.68±1.01	0.060
sleep disturbances	0.77±0.42	0.79±0.41	0.77±0.42	0.386
use of sleeping medicine	0.02±0.21	0.02±0.19	0.02±0.22	0.757
daytime dysfunction	0.90±0.83	0.97±0.77	0.89±0.85	0.022
HAs (M, (P ₂₅ , P ₇₅))	0.21(0.10,0.43)	0.27(0.14,0.56)	0.20(0.10,0.41)	<0.001
Arseniasis, N (%)	766 (49.23)	207 (64.5)	559 (45.3)	<0.001

Arsenic exposure levels and cognitive status of the participants in each village were separately shown in Table 2. We found that prevalence of arseniasis and cognitive impairment were the highest in participants from Heshan Village (58.5%, 23.6%) , followed by Wangyangqiao Community (46.3%, 19.1%) and Baiyangshan Village (27.4%, 15.1%) (Table 2), which were inversely correlated with the distance between the place of residence and the pollution source. There were statistical differences among these three locations in the prevalence of arseniasis and cognitive impairment ($P<0.05$). Additionally, MMSE scores were 24.7 ± 4.50 , 24.3 ± 5.36 and 24.2 ± 5.5 , in participants from Baiyangshan Village, Wangyangqiao Community and Baiyangshan Village, respectively. However, we found that hair arsenic concentrations of participants from Wangyangqiao Community was higher than that of Heshan Village and Baiyangshan Village, which could be explained by introducing survivor effect. Among the three locations, Heshan Village was the most polluted and many residents died of arseniasis in the past few decades [11]. The existing people may be more resistant to absorb arsenic, which was evidenced by the results of our study. In our study, the very low value of hair arsenic concentrations ($<0.01\text{mg/kg}$) was most in Heshan Village (14.9%), while in Wangyangqiao Community and Baiyangshan Village were 0.03% and 1.61%, respectively. On the basis of above, we found that the prevalence of cognitive impairment was the highest in participants from Heshan Village where participants were highest levels of arsenic exposure. Because the lack of data of external arsenic exposure level, we speculated that there was a negative correlated

between the distance away from the Realgar Plant and arsenic external exposure level, which was proved to be correct by these above results.

Table 2 Comparison of cognitive impairment in three locations

Index	locations				P
	Overall	Heshan	Wangyangqiao	Baiyangshan	
Distance		2km	5km	10km	
HAs (M, (P ₂₅ , P ₇₅))	0.21(0.10,0.43)	0.20(0.06,0.47)	0.25(0.14,0.45)	0.20(0.12,0.32)	<0.001
Arseniasis, N (%)	766(49.2)	439(58.5)	260(46.3)	67(27.4)	<0.001
MMSE	24.3±5.30	24.2±5.49	24.3±5.36	24.7±4.50	0.381
Cognitive impairment, N (%)	321(20.6)	177(23.6)	107(19.1)	37(15.1)	0.009

We illustrated the dose-response relationship between arsenic exposure and MMSE scores. We performed linear regression analysis to location-stratified analysis to assess

the association between hair arsenic concentrations and MMSE scores. Results shown that MMSE scores decreased with increasing hair arsenic concentrations (Fig.2).

Chi-square test was used to calculate the number of participants with cognitive impairment per quartile of hair arsenic concentrations (Table 3). Hair arsenic concentrations and cognitive impairment were included in the binary regression model, and the correlation between the level of arsenic exposure and cognitive impairment was tested. Correlation between the first quartile of hair arsenic concentrations (Q1) and prevalence of cognitive impairment was used as the reference group, and the others quartile of hair arsenic concentrations (Q2-Q4) were estimated, which expressed as OR values. We adjusted age, sex, education and location. The results revealed a positive correlation between hair arsenic concentration and prevalence of cognitive impairment. There was still a dose-response relationship after adjusting for confounding factors.

Table 3 The prevalence of cognitive impairment in arsenic inter-quartile range

HAs	CI, N (%)	OR (95% CI)	P	aOR (95% CI) *	P
Q1	56 (14.4)	1		1	
Q2	76 (19.5)	1.444(0.989,2.107)	0.057	1.454(0.965,2.189)	0.073
Q3	87 (22.7)	1.713(1.183,2.480)	0.004	1.468(0.980,2.199)	0.063
Q4	102 (26.2)	2.113 (1.471,3.036)	0.000	1.582(1.034,2.421)	0.035

*Adjusted for age, sex, education, location

Two-level Logistic regression analysis showed that arseniasis was a risk factor for cognitive impairment (OR=2.20, P< 0.05). After adjusting for age, sex, education, and location, the association attenuated but remained statistically significant (OR=1.77, P <0.05). The results were shown in Table 4.

Table 4 Two-level Logistic regression analysis

Model	b	S _b	Wald χ^2	P	OR (95% CI)
Crude	0.78	0.130	36.671	0.000	2.196(1.702, 2.832)
Adjusted *	0.570	0.156	13.420	0.000	1.768(1.303,2.398)

*Adjusted for age, sex, education, location

Discussion

The major finding of this cross-sectional study was that arsenic exposure was associated with cognitive impairment in adults and arseniasis was an independent risk factor for cognitive impairment. In addition, participants with higher hair arsenic concentrations tend to have lower MMSE scores and higher risks of cognitive impairment. Our analyses showed that the prevalence of cognitive impairment in our study was 20.6%, which was significantly higher than the 14.5% prevalence of cognitive impairment in individuals in China [17]. Therefore, we infer that the arsenic pollution in Shimen country was still serious and had a great impact on the health of local residents. Even after many years of environmental improvement, most of the surrounding villagers still had cognitive impairment.

Environmental exposure to arsenic had been posited to be associated with cognitive impairment in previous studies. Tsai et al examined 49 junior school students living in arsenic exposure area and found that memory and executive functioning were significantly affected by long-term arsenic exposure [6]. In a sample of 80 school children between the ages of 6 to 9 in Mexican, Calderon et al found that arsenic concentration was inversely correlated with verbal comprehension and long-term memory [7]. O'Bryant et al analyzed 434 rural-dwelling adults and elders in a community-based study, found that low-level arsenic exposure can lead to poorer global cognition, including executive function and memory [8]. A cross-sectional study conducted in Bangladesh revealed that arsenic exposure exerted a detrimental impact on intellectual functions in adolescence [9]. In animal studies, Finley and colleagues found that adolescence mice exhibited poorer memory and learning skill after perinatal arsenic exposure [18].

Our analysis shown that cognitive impairment can be considered to be affected by age, sex, education, fasting blood glucose, and SBP. Females was more likely to experience cognitive impairment than males which was consistent with previous studies [19]. Cognitive impairment had tendency to older age, lower education level, which proved that both were the main risk factors for cognitive impairment. CI had higher fasting blood glucose than CN, for hyperglycemia damaged on cognitive function [20–24]. CI had higher SBP than CN in this study. A Meta-analysis showed a correlation between SBP and AD, meanwhile no correlation for DBP [25], which was consistent with our research. Our study found that CI had a higher PSQI score than CN, which represented a worse quality of sleep. There are many studies that linked

cognitive impairment to sleep, and recent article published in Science showed that both A β -amyloid and Tau proteins increased in the brain of healthy adults who did not sleep for one night [26].

Many literatures described the mechanisms of arsenicosis causing cognitive impairment in detail. First, arsenic inhibited the excitatory synaptic transmission in hippocampal slices of rats [27]. Second, arsenic may evoke inflammatory responses and oxidative stress via up-regulation of a range of inflammatory signaling molecules, such as tumor necrosis factor- α (TNF- α), interleukins (ILs) – IL-6, IL-8, IL-12 and nuclear factor- κ B (NF- κ B) [28], and impair the ubiquitin-proteasomal protein degradation system, all of which played a key roles in Alzheimer's disease (AD) [29]. Third, arsenic exposure increased tau hyperphosphorylation levels [30], interfered the expression and processing of amyloid precursor protein (APP) in neuronal cells [31], and induced the neuronal apoptosis and necrosis [28, 32, 33]. All of these supported that arsenic exposure could increase the risk of cognitive impairment.

Our research was consistent with and extend previous work to adults living in arsenic exposed areas, and the first large-scale population study explored the correlation between arsenic exposure and cognitive function in arsenic-exposed area in China. Cognitive impairment may be an important symptom of neglect in people exposed to arsenic. Our current research differed from previous studies in the impact of arsenic exposure on cognitive function in adults and elders living in three arsenic exposure communities rather than school children. Our study demonstrated that arseniasis was associated with poorer cognitive function. We showed that arseniasis was an independent risk factor of cognitive impairment. There were still some limitations in this present study. First, this study was a cross-sectional study that lacked longitudinal data, which means that we cannot infer the temporal relationship of arsenic exposure with cognitive function. Second, diagnosis of cognitive impairment was mainly based on MMSE. Although MMSE is a well-validated screening tool for cognitive impairment, it can be influenced by external factors such as age, sex, education, and cultural background. Therefore, we used a Chinese version of MMSE, and the researchers were well trained. Third, this study lacked data about external arsenic exposure levels (atmospheric, soil, water). However, we used the distance between the participants' location and Realgar Plant as a marker of external arsenic exposure status approximately.

Conclusions

In summary, our study was a large population-based study showed that arsenic exposure was associated with cognitive impairment, and hair arsenic concentrations were inversely associated with MMSE scores in a dose-dependent manner. Cognitive impairment may be an important symptom of neglect in people exposed to arsenic. As prevention was critical for dementia, our finding that arseniasis is an independent risk factor for cognitive impairment, can help prevent and delay the onset of dementia.

Abbreviations

MMSE: Mini-mental state Examination; ICP-MS: inductively coupled plasma-mass spectroscopy; CI: cognitive impaired group; CN: cognitive normal group; OR: odds ratio; WHO: World Health Organization;

BMI: body mass index; DBP: diastolic blood pressure; SBP: systolic blood pressure; TC: total cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TG: triglyceride; PSQI: Pittsburgh sleep quality index; PRC: the People's Republic of China; CDC: Centers for Disease Control; ANOVA: one-way analysis of variance; TNF- α : tumor necrosis factor- α ; ILs: interleukins; NF- κ B: nuclear factor- κ B; AD: Alzheimer's disease; APP: amyloid precursor protein

Declarations

Ethics approval and consent to participate: All procedures were approved by the Ethics Committee of Xiangya Hospital, Center South of University, and performed in accordance with Helsinki Declaration.

Consent for publication: All participants had given consent for their data to be used for research purposes.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: All authors declare that they have no competing interests.

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Authors' contributions: W.X, H.X.Y collected and analyzed the data, wrote the manuscript. W.X, H.X.Y, Z.L, C.J, Z.X.X, X.K, H.Z.J collected participants data from different locations. H.M.A performed the data analysis. S.M.X, C.X, T.B.S. and S.L discussed the results and commented on the manuscript. Z.Y.F conceived the project, designed research, supervised the data collection and analysis, and revised the manuscript.

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Figures

Figure 2

Geographical distribution of study locations. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

Figure 3

Correlation between hair arsenic concentration and MMSE in three locations