The national burden of cardiovascular disease attributable to the dietary lead exposure in adults in China, 2017

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Abstract

Background

Lead is widely used around the world, even though unleaded gasoline has been forced by law for many years. A low level of lead exposure is considered to be associated with a high risk of cardiovascular disease (CVD). However, the contribution of lead exposure, especially lead exposure from the diet for the burden of CVD, has not been quantified in China.

Methods

We adopted a “top-down” approach, combining the pooled blood lead levels (BLLs) published in 2001–2020 about Chinese adults and relative risk (RR) of lead-induced CVD to estimate the burden of disease (BoD) of lead-induced CVD by using disability-adjusted life years (DALYs). The mean observed individual (OIM) model was used to estimate lead exposure from each source (diet, air, water, and soil) and calculate their contribution rates.

Results

The mean BLLs of Chinese adults was 5.23 $\mu\text{g}/\text{dL}$ (standard deviation [SD] = 2.21 $\mu\text{g}/\text{dL}$), which resulted in 3.239 (95% uncertainty interval [UI], 3.034–3.406) million DALYs for CVD. The dietary lead exposure was the major contributor to the BoD of lead-induced CVD, accounting for 67.93%. It resulted in 2.200 (95% UI 2.061–2.313) million DALYs for CVD, including 0.711 (95% UI 0.685–0.737) million DALYs for ischemic heart disease, 1.177 (95% UI 1.113–1.241) million DALYs for stroke, 0.228 (95% UI 0.153–0.253) million DALYs for hypertensive heart disease, and 0.021 (95% UI 0.019–0.024) million DALYs for rheumatic heart disease.

Conclusions

Dietary lead exposure causes high BoD of CVD in Chinese adults. More efforts to clarify the sources of lead contamination and reduce lead exposure in the population are warranted.

1. Background

As a key environmental pollutant, lead is still a global public health issue even the lead gasoline has been banned for many years. Lead could cause various adverse effects; even a low-level lead will also pose a threat to human health (Budtz-Jørgensen et al. 2013; Lanphear et al. 2018). For adults, lead exposure is associated with elevated blood pressure and increases cardiovascular disease (CVD) risk (Chowdhury et al. 2018; Navas-Acien et al. 2007). And a study found that blood lead levels (BLLs) as low as 0.6 $\mu\text{g}/\text{dL}$ may cause temporary or irreversible cardiovascular damage and dysfunction (Kopp et al. 1988). CVD is a

leading cause of death in China. It is estimated that the number of CVD deaths was 3.975 million in China in 2016 (Hu et al. 2019). Since lead is still widely used in China, it is necessary to quantify the impact of lead exposure on CVD.

Humans could ingest lead through many routes. The removal of lead from gasoline over decades had weakened the role of air in the lead exposure sources, but lead exposure from the diet, paint, water, soil/dust, and so on had attracted researchers' attention (Attina and Trasande 2013). Lead paint has been suggested as a major lead exposure source in the United States (Njati and Maguta 2019). Lead exposure from water and soil is significant in Nigeria (Ignatius et al. 2012). In Japan, food and house dust are main sources of lead contamination (Ohtsu et al. 2019). Lead is also reported to be accumulated in the human body through the food chain, and diet may be the primary source of non-occupational lead exposure in China (Pan et al. 2016). To clarify the major sources of lead exposure and their role on health will contribute the evidence for public health policymaking.

Burden of disease (BoD) could be applied to assess the impact of lead exposure on disease in a comparable way. In 2006, WHO launched the Foodborne Disease Burden Assessment Program and established the Foodborne Disease Burden Epidemiological Reference Group (FERG) to implement the program (Torgerson et al. 2015). Some studies have reported the BoD of lead-induced CVD in adults in India and other countries (Ericson et al. 2018; Fuks et al. 2017). Such action and researches could provide practical information for prioritizing action to improve health. However, there are few comprehensive studies on BoD of lead-induced CVD in Chinese, especially on the attributable estimation of various lead exposure sources.

To quantify the BoD of CVD attributable to dietary lead among Chinese adults, we planned to describe the distribution of BLLs in Chinese adults and calculate the population attribution fraction (PAF) based on the methods recommended by WHO (Fewtrell et al. 2004; Gibb et al. 2015). Then, we estimated the BoD of lead-induced CVD by using PAF and the DALYs of all-causes CVD from the Chinese population. Furthermore, we calculated each exposure source's contribution rates by using the exposure assessment model based on the Chinese population parameters, and the DALYs attributed to each exposure source were further estimated. Our study was an extension and refinement of the previous research, aiming to estimate for the national level of BoD for lead-induced CVD and the evidence for public health policymaking to control lead health risk.

2. Materials And Methods

By WHO recommended methodology for assessing the BoD of the environmental lead (Fewtrell et al. 2004), we estimated the BoD of CVD attributable to lead exposure from various sources for adults in China. The study process was shown in Fig. 1. Firstly, the PAF was obtained by combining the distribution proportion of BLLs in the population and the RR of lead-induced CVD. Then the BoD attributed to lead can be estimated by the DALYs of all-causes CVD multiplied by the PAF. Secondly, we calculated the uptakes and contribution rates of lead from various exposure sources. In this way, we can estimate the BoD of

CVD attributable to the lead exposure sources and provide the information for effective control of lead exposure by connecting the two parts.

2.1 BLLs of adults in China

2.1.1 Literature retrieval and data selection

We searched the literature reporting the BLLs in Chinese adults from PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), WanFang, and China Biology Medicine disc (CBMdisc) (see Appendix, Table A.1) between Jan 1st, 2001 and July 9th, 2020. Then, the searched articles were assessed by the following inclusion criteria: 1) blood lead level data was from the residents living in China; 2) blood samples came from veins, fingertips, or umbilical cord; 3) subjects included the population ≥ 18 years old; 4) the period of sample collection was after 2000; 5) no lead-related pollution sources were found in or around the residential areas; 6) the results included statistical mean and standard deviation (SD) of the original data; 7) the language was Chinese or English. Literature not meeting one or more of the above criteria will be excluded. Two independent reviewers (YZ. Yan and YL. Li) screened the searched publications to assess conformity with selection criteria, and the disagreement was resolved with a third reviewer (YN. Li). Moreover, we analyzed the potential publication bias for the final included literature.

After screening the literature, the BLL from each study was classified and analyzed according to sex and region. In terms of included studies, if several studies have reported BLLs in the same population, the average of all results was included. If the study was not an epidemiological investigation about the BLLs but a comparative study of population in the lead polluted area and non-polluted area, we choose the BLLs from the control groups.

Besides, the SD of BLLs in Shandong, Guangdong, and Guizhou was not reported in the literature, so we used the method of calculating SD with extreme values recommended in a previous study to estimate the SD of BLLs for these provinces (Hozo et al. 2005).

2.1.2 Pooling of the BLLs

We made a logarithmic transformation of the original BLLs and pooled them by corresponding sample size. Consequently, sample-size weighted geometric mean (GM) and geometric standard deviation (GSD) were calculated as follows:

$$X = \exp\{\sum[\ln(X_i) \times N_i] / \sum N_i\} \quad (1)$$

$$S = \exp\{(\sum[\ln(S_i^2) \times N_i] / \sum N_i)^{1/2}\} \quad (2)$$

In formula (1) and (2), X is the GM, S is the GSD, X_i is the arithmetic mean of BLL in study i , N_i is the sample size of study i , and S_i is the SD of study i . The unit of measurement for blood lead concentration was standardized to $\mu\text{g/dL}$.

2.2 Population distribution proportion of BLLs

We used the pooled results to describe the distribution of BLLs for non-occupationally exposed adults in China. According to the function for calculating the area under log-normal distribution curve in Microsoft Excel, we could obtain the proportion of people exposed to the different BLL intervals (5-10, 10-15, 15-20, and >20µg/dL):

$$N=1-LOGNORMDIST [x, \ln(X), \ln(S)] \quad (3)$$

In formula (3), N is the population distribution proportion, x is the lower limit values of each BLL interval (5, 10, 15, and 20µg/ dL), X is the GM of BLL, and S is the GSD of BLL.

2.3 Calculating the DALYs of CVD attributable to lead exposure

CVD is a series of diseases of the circulatory system. The types involved in this study include ischemic heart disease, stroke, hypertensive heart disease, rheumatic heart disease, and total CVD. We first calculated the PAF based on population distribution proportion in different BLL intervals and corresponding RR of lead-induced CVD. The estimated PAF is then multiplied by the DALYs of all-causes CVD to estimate the DALYs of lead-induced CVD. To this end, we adopted the DALYs of all-causes CVD from a study on the BoD of chronic diseases in China recently published by the China Center for Disease Control and Prevention (Zhou et al. 2019). The PAF was calculated as follows:

$$PAF = \frac{\sum_{i=1}^n P_i (RR_i - 1)}{\sum_{i=1}^n P_i (RR_i - 1) + 1} \quad (4)$$

In formula (4), P_i is the population distribution proportion in the BLL interval i (5-10, 10-15, 15-20, and >20µg/dL), from the formula (3). RR_i is the relative risk of CVD in the BLL interval i (5-10, 10-15, 15-20, and >20µg/dL), its specific calculation process was recommended by GBD 2017 (GBD Risk Factor Collaborators 2018) as follows:

$$RR_i = RR_0 \frac{(i - TMREL)}{10 \text{ mmHg}} \quad (5)$$

In formula (5), RR_0 is the relative risk of CVD corresponding to every 10 mmHg increase in systolic blood pressure (SBP) above the theoretical minimum-risk exposure level (TMREL, 115mmHg) (GBD Risk Factor Collaborators 2018). $(i - TMREL)$ is the increased value of SBP compared with TMREL in BLL interval i (5-10, 10-15, 15-20, and >20µg/dL). (see Appendix, Table A.2)

2.4 Estimating the contribution rate of each lead exposure source

Lead could be taken into the human body through many sources. To clarify each source's role in the process of lead exposure, we estimated the lead uptakes from various sources and further calculated the corresponding contribution rates.

We used the Observed Individual Means (OIM) model for lead exposure assessment, which has been described in detail in a previous study (Boon et al. 2011). The parameters involved in the model, including lead concentration and population consumption of various lead exposure sources, have been localized using information from the Chinese population. Among them, lead concentration was from the literature reported in China (Dong and Hu 2012; Wang et al. 2006); consumption data of each lead exposure source was extracted from the Manual of Exposure Parameters for Chinese Population published by the Ministry of Environmental Protection (Zhao and Duan 2014). Based on the parameters' availability, four major sources of lead exposure were selected, including diet (cereals and vegetables), water, air, and soil. (see Appendix, Table A.3)

Then we calculated the ratio of lead uptake from each source to the total lead uptake from the four sources as the contribution rate of each lead exposure source:

$$\text{Contribution rate (\%)} = \text{Lead uptake of per source} / \text{Lead uptake from all sources} \quad (5)$$

2.5 Estimating the DALYs attributable to each lead exposure source

According to the DALYs of lead-induced CVD and the contribution rates of lead exposure sources estimated in the previous section, the attributable BoD of lead-induced CVD to the various exposure sources could be obtained by multiplying them:

$$\text{Attributable DALYs} = \text{DALYs of lead-induced CVD} \times \text{Contribution rate} \quad (6)$$

2.6 Uncertainty analysis

Our study obtained the sample-size weighted GM and GSD of BLL in Chinese adults based on literature retrieval. However, as studies with a large sample size may have biased the pooled estimates, we recalculated the BLLs after excluding the study with the largest sample size (3404). The results showed that the recalculated BLLs were similar to that before excluding the extensive sample study (5.57 vs. 5.23 µg/dL).

2.7 Statistical analysis

Potential publication bias was assessed with a visual inspection of the funnel plot, Begg correlation test (Begg and Mazumdar 1994) and Egger linear regression test (Egger et al. 1997). All statistical analyses were performed with STATA. 12.0 (Stata Corp, College Station, Texas, USA). All tests were two-sided with a significance level of 0.05.

3. Results

Five databases search yielded 755 studies (see Appendix, Table A.1). After eliminating duplicate publications and judging by inclusion criteria, 42 studies were included, covering 20 Provinces in the mainland of China and of which 22 articles reported BLLs by sex (see Appendix, Table A.4). Furthermore, we conducted a potential publication bias analysis of the included literature, and the results showed that there was no publication bias in our study (Egger, $P=0.911$; Begg, $z=0.063$, $P>0.05$) (see Appendix, Fig. A.1).

Our study eventually included 20,789 cases with mean BLL of 5.23 mg/dL (SD = 2.21 mg/dL), including 7,162 male cases with 5.96 mg/dL (SD =3.81 mg/dL) and 6,867 female cases with 4.90 mg/dL (SD =3.19 mg/dL). The results of time distribution analysis showed that the BLLs of Chinese adults fluctuated significantly in the past 20 years, especially in 2009-2011, which increased greatly (3.52 to 8.77 mg/dL) and then decreased rapidly (8.77 to 4.07 mg/dL) (see Appendix, Fig. A.2). Also, according to the existing literature, we pooled the BLLs of Chinese adults according to regions. The results showed that the three areas with higher BLLs were Guangxi, Shanghai, and Yunnan (9.86, 8.95, and 8.29 mg/dL, respectively), and the three with lower BLLs were Liaoning, Jilin, and Anhui (4.08, 3.03, and 2.88 mg/dL, respectively). (Table 1, Fig. 2)

Table 1 BLLs of the adults in China, 2001-2020			
Groups	Sample size	GM (mg/dL)	GSD (mg/dL)
Sex			
Males	7162	5.96	3.81
Females	6867	4.90	3.19
Both	20789	5.23	2.21
Regions			
Beijing	1167	4.87	2.89
Tianjin	25	4.78	1.41
Shanxi	40	6.37	3.97
Liaoning	1222	4.08	3.93
Jilin	453	3.03	3.20
Heilongjiang	892	6.72	NR
Shanghai	36	8.95	4.66
Jiangsu	260	7.15	3.09
Zhejiang	976	6.81	4.57
Anhui	1098	2.88	3.75
Shandong	312	8.13	5.79
Henan	2209	5.49	3.77
Hubei	1048	4.39	6.22
Hunan	2120	7.89	3.13
Guangdong	109	5.10	0.75
Guangxi	65	9.86	2.41
Chongqing	1486	7.73	2.74
Sichuan	83	7.61	4.77
Guizhou	157	7.44	0.98
Yunnan	233	8.29	6.70

Note: BLLs=Blood Lead Levels. GM=Geometric Mean. GSD=Geometric Standard Deviation. NR=Not Reported.

Note: BJ=Beijing. TJ=Tianjin. HE=Hebei. SX=Shanxi. NM=Inner Mongolia. LN=Liaoning. JL=Jilin. HL=Heilongjiang. SH=Shanghai. JS=Jiangsu. ZJ=Zhejiang. AH=Anhui. FJ=Fujian. JX=Jiangxi. SD=Shandong. HA= Henan. HB=Hubei. HN=Hunan.GD=Guangdong. GX=Guangxi. HI=Hainan. CQ=Chongqing. SC=Sichuan. GZ=Guizhou. YN=Yunnan. XZ=Tibet. SN=Shaanxi. GS=Gansu. QH= Qinghai. NX=Ningxia. XJ=Xinjiang. TW=Taiwan. HK=Hong Kong. MO=Macao. BLLs=Blood Lead Levels. The numbers in parentheses represent the BLL ranking of provinces and cities in descending order.

To evaluate the attributable BoD of CVD caused by lead, we first calculated PAF according to the population distribution proportion of different BLL intervals and the corresponding RRs (see Appendix, Table A.2). Its regional and gender distribution was also described. The results showed that the PAF of hypertensive heart disease was the highest in all regions and genders. And the provinces with higher PAF were Shanghai, Yunnan and Guangxi. (see Appendix, Table A.5; Fig. 3)

After using PAF, CVD caused by lead exposure resulted in about 3.239 (95% uncertainty interval [UI], 3.034-3.406) million DALYs among Chinese adults in 2017. Among them, the BoD attributable to lead exposure for ischemic heart disease was 1.047 (1.008-1.085) million DALYs, for stroke was 1.733 (1.639-1.827) million DALYs, for hypertensive heart disease was 0.336 (0.226-0.372) million DALYs, and for rheumatic heart disease was 0.031 (0.028-0.035) million DALYs. In terms of geographical distribution, for ischemic heart disease, the three provinces with the higher lead-induced age-standardized DALY rate were Shandong, Hunan, and Liaoning (174.74, 147.66, and 135.41 DALYs per 100,000 population, respectively). For stroke, the provinces with the higher lead-induced age-standardized DALY rate were Yunnan, Shandong, and Guizhou (226.59, 225.32, and 224.22 DALYs per 100,000 population, respectively). For hypertensive heart disease, the provinces with the higher lead-induced age-standardized DALY rate were Hunan, Hubei, and Guangxi (87.99, 46.63, and 46.02 DALYs per 100,000 population, respectively). And for rheumatic heart disease, the provinces with the higher lead-induced age-standardized DALY rate were Yunnan, Guizhou, and Sichuan (7.68, 7.50 and 7.46 DALYs per 100,000 population, respectively). (Table 2, Table A.6, Fig. 4)

Table 2 DALY numbers and rates of CVD attributed to lead exposure in China, 2017			
Disease/Sex	Population [#]	Number in thousands (95% UI)	Rate per 100,000 (95% UI)
Ischemic heart disease			
Males	562451675	712.60 (686.56 to 738.65)	126.70 (122.07 to 131.33)
Females	536730805	334.50 (322.28 to 346.73)	62.32 (60.04 to 64.60)
Both	1099182480	1047.11 (1008.84 to 1085.37)	95.26 (91.78 to 98.74)
Stroke			
Males	562451675	1179.57 (1115.66 to 1243.47)	209.72 (198.36 to 221.08)
Females	536730805	553.76 (523.76 to 583.76)	103.17 (97.58 to 108.76)
Both	1099182480	1733.33 (1639.43 to 1827.24)	157.69 (149.15 to 166.24)
Hypertensive heart disease			
Males	562451675	229.04 (153.95 to 253.60)	40.72 (27.37 to 45.09)
Females	536730805	107.67 (72.37 to 119.21)	20.06 (13.48 to 22.21)
Both	1099182480	336.71 (226.33 to 372.81)	30.63 (20.59 to 33.92)
Rheumatic heart disease			
Males	562451675	21.59 (19.44 to 24.09)	3.84 (3.46 to 4.28)
Females	536730805	10.13 (9.12 to 11.31)	1.89 (1.70 to 2.11)
Both	1099182480	31.72 (28.56 to 35.40)	2.89 (2.60 to 3.22)
Other cardiovascular and circulatory diseases			
Males	562451675	61.74 (58.14 to 89.48)	10.98 (10.34 to 15.91)
Females	536730805	28.98 (27.28 to 41.99)	5.40 (5.08 to 7.82)
Both	1099182480	90.72 (85.42 to 131.47)	8.25 (7.77 to 11.96)
Cardiovascular disease			
Males	562451675	2204.54 (2065.10 to 2317.95)	391.95 (367.16 to 412.12)
Females	536730805	1035.04 (969.53 to 1088.29)	192.84 (180.64 to 202.76)
Both	1099182480	3239.59 (3034.63 to 3406.24)	294.73 (276.08 to 309.89)

Note: DALYs=Disability Adjusted Life Years. CVD=Cardiovascular Diseases. 95% UI = 95% uncertainty interval.

Data came from China Statistical Yearbook 2018.

By using the lead exposure parameters of the Chinese adults, the lead uptakes of Chinese adults through various exposure sources were estimated. Our results showed that Chinese adults consumed about 6.150 mg of lead per day. Among them, dietary lead uptake was the highest, with an average daily uptake of 4.177 mg, 4.465 mg for males, and 3.890 mg for females. The further calculation showed that dietary lead contributed the most to the total lead uptake, accounting for 67.93% (42.84% for cereals and 25.08% for vegetables), followed by air, soil, and water, contributing 30.38%, 1.57%, and 0.12%, respectively. (Table 3)

Table 3 Uptake and contribution rates of lead exposure from various sources in adults, China				
Sources		Males	Females	Both
Lead uptake (mg/day)	Diet	4.465	3.890	4.177
	Cereal	2.853	2.417	2.635
	Vegetables	1.612	1.473	1.543
	Air	2.142	1.726	1.868
	Soil	0.097	0.097	0.097
	Water	0.008	0.007	0.007
	All	6.712	5.719	6.150
Contribution rates (%)	Diet	66.52	68.01	67.93
	Cereal	42.50	42.26	42.84
	Vegetables	24.02	25.76	25.08
	Air	31.91	30.17	30.38
	Soil	1.44	1.69	1.57
	Water	0.12	0.12	0.12

Based on the lead exposure sources' contribution rates, we estimated the effects of different lead exposure routes in the BoD of CVD. The results showed that dietary lead had the highest attributable BoD for CVD, which was 2.200 (95% uncertainty interval [UI], 2.061-2.313) million DALYs. And the BoD caused by dietary lead for ischemic heart disease, stroke, hypertensive heart disease, and rheumatic heart disease was 0.711 (0.685-0.737) million DALYs, 1.177 (1.113-1.241) million DALYs, 0.228 (0.153-0.253) million DALYs and 0.021 (0.019-0.024) million DALYs, respectively. Also, the BoD caused by lead

exposure in males was higher than that in females in all exposure sources, regardless of ischemic heart disease, stroke, hypertensive heart disease, or rheumatic heart disease. (Table 4)

Table 4 DALY numbers and rates of CVD attributed to lead exposure from various sources			
Disease/Sex	Sources	Number in thousands (95% UI)	Rate per 100,000 (95% UI)
Ischemic heart disease			
Males	Diet	474.06 (456.73 to 491.38)	84.28 (81.20 to 87.36)
	Air	227.42 (219.10 to 235.73)	40.43 (38.96 to 41.91)
	Soil	10.27 (9.90 to 10.65)	1.83 (1.76 to 1.89)
	Water	0.86 (0.83 to 0.89)	0.15 (0.15 to 0.16)
Females	Diet	227.51 (219.20 to 235.82)	42.39 (40.84 to 43.94)
	Air	100.93 (97.24 to 104.62)	18.80 (18.12 to 19.49)
	Soil	5.66 (5.45 to 5.87)	1.05 (1.02 to 1.09)
	Water	0.41 (0.39 to 0.42)	0.08 (0.07 to 0.08)
Both	Diet	711.25 (685.26 to 737.25)	64.71 (62.34 to 67.07)
	Air	318.11 (306.48 to 329.73)	28.94 (27.88 to 30.00)
	Soil	16.47 (15.87 to 17.08)	1.50 (1.44 to 1.55)
	Water	1.28 (1.23 to 1.32)	0.12 (0.11 to 0.12)
Stroke			
Males	Diet	784.70 (742.19 to 827.21)	139.51 (131.96 to 147.07)
	Air	376.44 (356.05 to 396.83)	66.93 (63.30 to 70.55)
	Soil	17.00 (16.08 to 17.92)	3.02 (2.86 to 3.19)
	Water	1.42 (1.35 to 1.50)	0.25 (0.24 to 0.27)
Females	Diet	376.64 (356.23 to 397.04)	70.17 (66.37 to 73.97)
	Air	167.08 (158.03 to 176.14)	31.13 (29.44 to 32.82)
	Soil	9.37 (8.86 to 9.88)	1.75 (1.65 to 1.84)
	Water	0.67 (0.64 to 0.71)	0.13 (0.12 to 0.13)
Both	Diet	1177.38 (1113.59 to 1241.16)	107.11 (101.31 to 112.92)
	Air	526.58 (498.05 to 555.10)	47.91 (45.31 to 50.50)
	Soil	27.27 (25.79 to 28.75)	2.48 (2.35 to 2.62)
	Water	2.11 (2.00 to 2.23)	0.19 (0.18 to 0.20)
Hypertensive heart disease			

Males	Diet	152.37 (102.42 to 168.71)	27.09 (18.21 to 29.99)
	Air	73.09 (49.13 to 80.93)	13.00 (8.74 to 14.39)
	Soil	3.30 (2.22 to 3.66)	0.59 (0.39 to 0.65)
	Water	0.28 (0.19 to 0.31)	0.05 (0.03 to 0.05)
Females	Diet	73.23 (49.22 to 81.08)	13.64 (9.17 to 15.11)
	Air	32.49 (21.84 to 35.97)	6.05 (4.07 to 6.70)
	Soil	1.82 (1.22 to 2.02)	0.34 (0.23 to 0.38)
	Water	0.13 (0.09 to 0.14)	0.02 (0.02 to 0.03)
Both	Diet	228.71 (153.73 to 253.24)	20.81 (13.99 to 23.04)
	Air	102.29 (68.76 to 113.26)	9.31 (6.26 to 10.30)
	Soil	5.30 (3.56 to 5.87)	0.48 (0.32 to 0.53)
	Water	0.41 (0.28 to 0.45)	0.04 (0.03 to 0.04)
Rheumatic heart disease			
Males	Diet	14.36 (12.93 to 16.03)	2.55 (2.30 to 2.85)
	Air	6.89 (6.20 to 7.69)	1.22 (1.10 to 1.37)
	Soil	0.31 (0.28 to 0.35)	0.06 (0.05 to 0.06)
	Water	0.03 (0.02 to 0.03)	0.00 (0.00 to 0.01)
Females	Diet	6.89 (6.21 to 7.69)	1.28 (1.16 to 1.43)
	Air	3.06 (2.75 to 3.41)	0.57 (0.51 to 0.64)
	Soil	0.17 (0.15 to 0.19)	0.03 (0.03 to 0.04)
	Water	0.01 (0.01 to 0.01)	0.00 (0.00 to 0.00)
Both	Diet	21.54 (19.40 to 24.04)	1.96 (1.77 to 2.19)
	Air	9.64 (8.68 to 10.75)	0.88 (0.79 to 0.98)
	Soil	0.50 (0.45 to 0.56)	0.05 (0.04 to 0.05)
	Water	0.04 (0.03 to 0.04)	0.00 (0.00 to 0.00)
Other cardiovascular and circulatory diseases			
Males	Diet	41.07 (38.68 to 59.52)	7.30 (6.88 to 10.58)
	Air	19.70 (10.01 to 15.41)	3.50 (1.78 to 2.74)
	Soil	0.89 (0.71 to 1.09)	0.16 (0.13 to 0.19)

	Water	0.07 (0.04 to 0.05)	0.01 (0.01 to 0.01)
Females	Diet	19.71 (18.56 to 28.56)	3.67 (3.46 to 5.32)
	Air	8.74 (7.42 to 11.42)	1.63 (1.38 to 2.13)
	Soil	0.49 (0.58 to 0.89)	0.09 (0.11 to 0.17)
	Water	0.04 (0.03 to 0.04)	0.01 (0.01 to 0.01)
Both	Diet	61.62 (58.02 to 89.30)	5.61 (5.28 to 8.12)
	Air	27.56 (17.22 to 26.51)	2.51 (1.57 to 2.41)
	Soil	1.43 (1.28 to 1.97)	0.13 (0.12 to 0.18)
	Water	0.11 (0.06 to 0.10)	0.01 (0.01 to 0.01)
Cardiovascular disease			
Males	Diet	1466.56 (1373.80 to 1542.00)	260.74 (244.25 to 274.16)
	Air	703.54 (659.04 to 739.73)	125.09 (117.17 to 131.52)
	Soil	31.78 (29.77 to 33.41)	5.65 (5.29 to 5.94)
	Water	2.66 (2.49 to 2.80)	0.47 (0.44 to 0.50)
Females	Diet	703.98 (659.42 to 740.20)	131.16 (122.86 to 137.91)
	Air	312.30 (292.53 to 328.36)	58.19 (54.50 to 61.18)
	Soil	17.51 (16.40 to 18.41)	3.26 (3.06 to 3.43)
	Water	1.26 (1.18 to 1.32)	0.23 (0.22 to 0.25)
Both	Diet	2200.51 (2061.29 to 2313.71)	200.19 (187.53 to 210.49)
	Air	984.17 (921.90 to 1034.80)	89.54 (83.87 to 94.14)
	Soil	50.97 (47.74 to 53.59)	4.64 (4.34 to 4.88)
	Water	3.95 (3.70 to 4.15)	0.36 (0.34 to 0.38)

Note: DALYs=Disability Adjusted Life Years. CVD=Cardiovascular Diseases. 95% UI = 95% uncertainty interval.

4. Discussion

For the first time, the BoD of lead-induced CVD in adults was estimated in China. Our findings showed that BLLs (5.50 µg/dL) from population-based studies resulted in 3.239 million DALYs of CVD in Chinese adults in 2017, and the 1.733 million DALYs of lead-induced stroke was the highest. Among the various lead exposure sources, dietary lead exposure contributed the most to the BoD of lead-induced CVD

(contribution rate was 67.93%). And it resulted in 2.200, 0.711, 1.177, 0.228, and 0.021 million DALYs for CVD, ischemic heart disease, stroke, hypertensive heart disease, and rheumatic heart disease, respectively.

With the compulsory prohibition of leaded gasoline, BLL in China has steadily decreased in the past decades (Li et al. 2014). A population-based cross-sectional survey in 2014 showed that the BLL was 4.4 $\mu\text{g/dL}$ for males and 3.8 $\mu\text{g/dL}$ for females in Chinese adults (Chen et al. 2017). These results were somewhat lower than that of the BLL pooled by our study (5.96 $\mu\text{g/dL}$ for males and 4.90 $\mu\text{g/dL}$ for females). The possible reason was that our study covered a broader period of lead exposure, which included the stage close to the gasoline lead ban, and lead could be accumulated in the body for a long time (Gómez et al. 2018). Although the results of these two studies were lower than the BLL reported in India (7.52 $\mu\text{g/dL}$) (Ericson et al. 2018), they were still higher than the level of some developed countries, for example, the BLL of American adults was 2.71 $\mu\text{g/dL}$ (Lanphear et al. 2018). These showed that there was still room for the BLL decline in China, after all, some studies have shown that there was no threshold for the toxicity of lead (Kosnett et al. 2007; Lanphear et al. 2018; Menke et al. 2006). The Chinese government was constantly taking relevant measures without hesitation to control and reduce lead pollution, for example, more than 80% of lead battery enterprises were banned or shut down in 2011 (Yu 2012). However, it was reported that more than 70% of lead-acid waste battery was still illegally spilled into the environment in recent years (Yu 2018). This was consistent with the time trend in our study. BLL declined after peaking in 2011 but has risen again in recent years. Therefore, from a social perspective, the current situation of high lead exposure in China has not been fundamentally reversed. Further, greater efforts are required to control the lead exposure in the environment.

Accumulating pieces of evidence indicated that conventional risk factors might not fully explain the booming epidemic of CVD, and the role of environmental factors (heavy metals, etc.) has been paid more and more attention. A population-based study showed that BLL was significantly related to CVD risk and independent of age, smoking, drinking, diabetes, obesity, hypertension, and lipids in Chinese (Chen et al. 2017). Our findings showed that environmental lead exposure resulted in a great BoD in Chinese adults, including 1.047 million DALYs for ischemic heart disease, 1.733 million DALYs for stroke, 0.336 million DALYs for hypertensive heart disease, and 0.031 million DALYs for rheumatic heart disease. Compared with a study in India, the results in China were higher except for ischemic heart disease (Ericson et al. 2018). There may be two reasons to explain our results:

On the one hand, the all-causes BoD of hypertensive heart disease and stroke in Chinese residents was higher in themselves (Zhou et al. 2019), reminding us that the control of epidemic and BoD of CVD was imminent in China. On the other hand, lead exposure played a more important role in Chinese adults. A global study reported that the BoD of CVD related to lead exposure amounted to 3.1 million DALYs, about 2% of the total BoD for CVD (Fewtrell et al. 2004). Compared with the global proportion, our estimated result was higher, and the proportion of BoD for CVD attributable to lead exposure was 3.8% in Chinese. Therefore, lead exposure is significant for the higher lead-induced BoD of CVD in China. For this reason, it is necessary to reduce lead exposure and BLL among Chinese adults effectively.

Our findings suggested that diet was the primary source of lead exposure and accounted for the most significant proportion of the BoD for lead-induced CVD. Food is highly vulnerable to contamination from both natural and anthropogenic sources, including the process of crop cultivation, food production, and food handling (Hough et al. 2004). It's reported that part of the lead in food comes from the soil where crops are cultivated. And most of the lead in soil originates from the use of higher levels of artificial lead, such as lead arsenate in fungicides and tetraethyl lead in gasoline (Mielke 2016). Besides, when food is stored in lead-containing containers such as earthenware, lead can leach from the surface and enter the food. And the lead in the food handling process cannot be entirely removed by washing or other processing procedures. Like other heavy metals, lead itself does not biodegrade or disappear from the environment over time. Further considerable efforts are required to control lead concentration in the environment, thereby reducing dietary lead uptake and ultimately preventing lead exposure in the population.

Some limitations need to be addressed in our study. Firstly, the BLL may be biased on the pooled data obtained from the literature. However, considering the regional and individual differences of BLLs and various studies' heterogeneity, it is necessary to combine different subsamples into a larger sample to infer the national-level results. And we had conducted a potential publication bias analysis and found that the included literature had no publication bias. Secondly, PAF was calculated by RRs, which were not specified to Chinese. Further studies are needed to analyze the dose-response relationship between lead and CVD in the Chinese population. In general, the consequences of this study were conservative.

5. Conclusions

The dietary lead exposure in our study was estimated to be responsible for over 2.200, 0.711, 1.177, 0.228, and 0.021 million DALYs for CVD, ischemic heart disease, stroke, hypertensive heart disease, and rheumatic heart disease, respectively. Our findings demonstrated that the lead from dietary source is still a great challenge for public health. Such researches on comprehensive attribution analysis for lead exposure have specific implications for clinicians and public health professionals. For clinicians, BLL measurements may be useful in the search for secondary causes of CVD. From the public health perspective, rigorous regulations should be implemented by the Chinese government to reduce adult lead exposure further to mitigate lead-induced risks, including CVD.

Abbreviations

BLLs blood lead levels BoD burden of disease

CVD cardiovascular disease DALYs disability-adjusted life years

GM geometric mean GSD geometric standard deviation

OIM observed individual means PAF population attribution fraction

RR relative risk SD standard deviation

UI uncertainty interval

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YYZ and LYL: Conceptualization, Methodology, Software, Formal analysis, Writing-original draft, Writing-review & editing. Yizhong Yan and Yiling Li contributed equally to this work. **WS and WYBN:** Conceptualization, Supervision, Project administration, Funding acquisition, Writing-review & editing. **LYN, SWJ and HJ:** Methodology, Software, Formal analysis.

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Figures

Figure 1

Framework for establishing attributable DALYs of various lead exposure sources. Note: BLLs=Blood Lead Levels. RR=Relative Risk. PAF=Population Attributable Fraction. DALYs= Disability Adjusted Life Years. OIM= Observed Individual Means.

Figure 2

Geographic distribution of Chinese adults BLLs, 2001–2020. Note: BJ=Beijing. TJ=Tianjin. HE=Hebei. SX=Shanxi. NM=Inner Mongolia. LN=Liaoning. JL=Jilin. HL=Heilongjiang. SH=Shanghai. JS=Jiangsu. ZJ=Zhejiang. AH=Anhui. FJ=Fujian. JX=Jiangxi. SD= Shandong. HA= Henan. HB=Hubei. HN=Hunan. GD=Guangdong. GX=Guangxi. HI=Hainan. CQ= Chongqing. SC=Sichuan. GZ=Guizhou. YN=Yunnan. XZ=Tibet. SN=Shaanxi. GS=Gansu. QH= Qinghai. NX=Ningxia. XJ=Xinjiang. TW=Taiwan. HK=Hong Kong. MO=Macao. BLLs=Blood Lead Levels. The numbers in parentheses represent the BLL ranking of provinces and cities in descending order. 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

The regional and gender distribution of PAF. Note: BJ=Beijing. TJ=Tianjin. SX=Shanxi. LN=Liaoning. JL=Jilin. SH=Shanghai. JS=Jiangsu. ZJ=Zhejiang. AH=Anhui. SD=Shandong. HA=Henan. HB=Hubei. HN=Hunan. GD=Guangdong. GX=Guangxi. CQ=Chongqing. SC=Sichuan. GZ=Guizhou. YN=Yunnan. PAF=Population Attribution Fraction.

Figure 4

Percentage of DALYs for CVD attributed to lead exposure by regions and sex in China, 2017. Note: BJ=Beijing. TJ=Tianjin. SX=Shanxi. LN=Liaoning. JL=Jilin. SH=Shanghai. JS=Jiangsu. ZJ=Zhejiang. AH=Anhui. SD=Shandong. HA=Henan. HB=Hubei. HN=Hunan. GD=Guangdong. GX=Guangxi. CQ=Chongqing. SC=Sichuan. GZ=Guizhou. YN=Yunnan. CVD=Cardiovascular Diseases. DALYs=Disability Adjusted Life Years.

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