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ORIGINAL RESEARCH

Relationship between Rare Earth Elements, Lead and Intelligence of Children Aged 6 to 16 years: A Bayesian Structural Equation Modelling Method

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Abstract

Background: The study was to investigate the effect of co-exposure to rare earth elements (REEs) and lead on children's intelligence, and whether there is a certain interactive effect of exposure.

Methods: Exposure to REEs and lead was assessed by analysing the scalp hair samples of children aged 6-16 years who lived in a rare earth mining area, by atomic absorption spectrometry. Intelligence was assessed using Raven's Standard Progressive Matrices. Bayesian Structural Equations were built to explore different patterns of associations between REEs and lead explore and children's intelligence, and the best-fitted one was selected for the most reasonable explanation according to DIC and BIC. In our best-fitted model, which did not contain any interactive item between REEs and lead, age had the greatest effect on IQ with a path coefficient of 0.339. Then came hair lead (-0.166), showing a negative effect on intelligence development. Impact of light REEs and heavy REEs were similar (-0.044 and -0.043, respectively).

Conclusion: Both light and heavy REEs, as well as lead in hair had negative effect on intelligence of children aged 6 to 16-years-old, but interactive effect was not found. Future studies with improved methodologies and focus on mechanisms are expected.

Keywords

Rare earth elements, Lead, Intelligence, Bayesian structural equation model

Introduction

The increased utilization of rare earth elements (REEs) have led to a number of human exposures. Health effects and toxicity mechanisms of rare earth elements were widely reported in past 20 years. including those from both occupational exposure and environmental exposure. People around the mine mainly intake the REE and lead by water, food and air. A small amount of rare earth can affect the function of central nervous system by acting on brain tissue through blood-brain barrier, thus reducing children's cognitive, visual, perceptual and motor behaviour, intelligence quotient (IQ) and memory [1]. The intake of low-dose lead has toxic effects on the nervous system of children during growth and development, which can cause the decrease of children's intelligence quotient and developmental disorder [2]. However, epidemiological studies on its possible effect on children's intelligence was scarcely

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reported [3,4]. Previous studies have shown that REEs are neurotoxicant, which may be associated with redox reactivity, proinflammatory cytokine production, involving ROS formation, lipid peroxidation and modulation of antioxidant activities [3,4]. While there have been some epidemiological studies about REE-related health effect [5-7], reports relating to children's intelligence are scarce. Existing studies showed that exposure to rare earth elements will affect mental development, as well as learning and memory ability of children: A cross-sectional study [8] conducted in South of China suggested that children with higher blood REEs level had relatively lower intelligence quotient. It was also found that children residents near rare earth mining area and with home storage of RE ore had lower test score. Another study [9] conducted in the same area found differences in intelligence in children living in villages with different geological contents of rare earth elements, indicating the effect of REEs exposure to children's intelligence. However, the association between rare earth elements and children's intelligence at individual level cannot be directly confirmed through an ecological study. On the other hand, lead exposure has been proved to have impact on intellectual development in children, with both toxicological and epidemiological findings widely reported [10-16]. Mechanism of lead toxicology involves different biologically significant processes, including metal transport, energy metabolism, apoptosis, ionic conduction, cell adhesion, inter- and intracellular signalling, diverse enzymatic processes, protein maturation, and genetic regulation [17]. It is also clear that young children are particularly susceptible to the toxic effects of lead especially in the development of the brain and nervous system, which can prevent the correct development of cognitive and behavioural functions [15,18,19]. However, to the best of our knowledge, there is no report on the impact of co-exposure to both rare earth elements and lead on children's IQ, as well as potential interactive effect of the two exposures.

Previous detection found that the contents of REE and lead are 2.87 [(%) g/t] and 1.24 [(%) g/t] in rare earth mine, respectively. The concentration of lead is 0.007-0.008 μg/L in the air, 0.020-0.160 mg/kg in the plant and 63.6-229.0 mg/kg in the soil around the mine, while the concentration of lead is 0.007-0.008 μg/L in the air and 153.0 mg/kg in the soil is in the mine zone. Bayesian structural equation model is a multi-disciplinary text ideal used in many areas, including: Biostatistics, medicine, psychology, public health and so on. The method allows the use of prior information resulting in improved parameter estimates, latent variable estimates, and statistics for model comparison, as well as offering more reliable results especially for smaller samples. So, the present study aimed to investigate the effect of co-exposure to REEs and lead on children's intelligence, as well as whether there is any interactive effect of exposures. To explore this interaction, we built up a Bayesian structural equation model using Monte Carlo Markov Chain based on Gibbs' sampling (MCMC BUGS), which is proved to be a very flexible method to investigate complex multivariable analyses especially for those with relative small sample.

Materials and Methods

Study locations

The REE mining area, namely Maoniuping rare-earth deposit, was located in the Mianning City of Sichuan Province, China. Four villages (A, B, C and D) around the mining area of rare earth metals were as the field for research (Figure 1). All of these villages have similar geographic characteristics, socioeconomic status, and distribution of educational level. Populations of those four villages were stable. In addition, residents of the villages can get almost all necessities including vegetables, fruits and drinking water from the local.

Participants

The study sample were randomly chosen from chil-

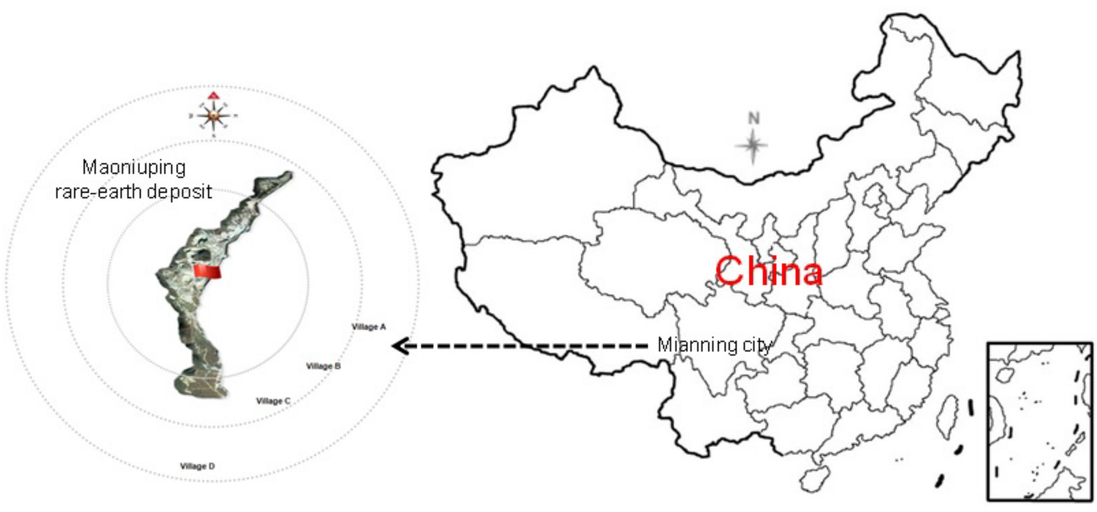

Figure 1: The map of the study area.

dren in the four villages. Inclusion criteria were: (1) Their age ranged from 6 to 16 years, (2) They were born and had been living in the local areas and (3) They must be free of chronic diseases, hereditary diseases and diagnosed mental retardation such as Down's syndrome or iodine deficiency disorders. Of the 122 selected children according to the criteria, 27 children or their parents refused to participate and 95 hair samples were finally collected.

This study was approved by the Ethical Committee of the West China School of Public Health, Sichuan University.

Measurement

Our trained investigators collected hair samples from all participants using stainless steel scissors. Each participant's hair was cut from 1 cm of the occipital scalp, then sealed into a clean polythene bags labelled with information of the participant, including ID, name, sex, age, etc. All visible impurities in each individual scalp hair samples were removed before analysis. Then the hair samples were washed with deionized water and soaked into acetone solution. After rinsed cleanly by deionized water, each hair sample was cut into 1 to 2 mm pieces and dried for further treatment. Microwave-assisted acid digestion method was conducted to decomposition of organisms in hair samples [6,20]. All blank and standard solution must follow the methods above as well.

The standard deviation, linear correlation coefficient and detection limit of 15 REEs and lead were obtained by continuous blank measurement. When ICP-MS was used to determine the samples, the internal standard method and the Chinese standard material human hair (GBW07601a) were used for quality control (Table 1).

Chemicals and reagents

All chemicals and reagents were listed below: (1) Nitric acid (65~68%, GR), (2) Acetone (AR), (3) Standard solution of REEs (GSB 04-1789-2004, contains 100.00 µg/mL, each of La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu, Y, from the National Standard Material Centre of China, GBTC, Beijing), (4) Multi-element calibration standard-2A 8500-6940 (10 mg/L, contains Pb, from Agilent), (5) Standard substance of human hair ingredient (GBW07601a, from Institute of Geophysical and Geochemical Exploration, Chinese Academy of Geological Sciences, Langfang), (6) Standard solution of rhodium (GSB 04-1746-2004, from the National Standard Material Centre of China, GBTC, Beijing), (7) ICP-MS tuning solution 5185-5959 (contains 1 µg/L each of Li, Mg, Y, Ce, Tl and Co, from Agilent) and (8) Nitric acid solutions (2% and 5% of concentration. GR nitric acid diluted by ultrapure water).

Instrumentations: The analysis of Pb and REEs was carried out by Inductively Coupled Plasma Mass Spectrometer (Agilent 7700 Series ICP-MS). And there were other instruments utilized during analysis, they are (1) Type Med-C microwave digestor for gelatine & capsule (PreeKem, Shanghai), (2) Milli-Q® direct water purification system (Merck Millipore, Darmstadt), (3) Type CPA electronic balance (BSA224S, from Sartorius, Beijing) and electric heating oven (Feiyue, Shanghai).

Isotopes of REEs and Pb: The REEs we studied were lanthanum (La), samarium (Sm), europium (Eu), gadolinium (Gd), terbium (Tb), dysprosium (Dy), holmium (Ho), erbium (Er), thulium (Tm), ytterbium (Yb), lutetium (Lu), yttrium (Y), cerium (Ce), praseodymium (Pr), and neodymium (Nd). The selected isotopes should follow the principle of determining the maximum abundance of the elements, avoiding the overlap of polytomy and isotopes. After reference to relevant studies, we chose ^{89}Y, ^{139}La, ^{140}Ce, ^{141}Pr, ^{146}Nd, ^{152}Sm, ^{153}Eu, ^{158}Gd, ^{159}Tb, ^{163}Dy, ^{165}Ho, ^{166}Er, ^{169}Tm, ^{174}Yb, ^{175}Lu, ^{208}Pb as aimed isotopes of detection.

Quality control

The standard solutions were diluted to a series of 100.0 ug/L, 50.0 ug/L, 25.0 ug/L, 12.5 ug/L, 6.25 ug/L and 0 ug/L with ultrapure water. The limits of detection (LODs) were determined by operating the blank solution 11 times in a continuous measurement process, and 3-fold of the standard deviations were set as the LODs. They are 0.0119 (La), 0.0320 (Ce), 0.0039 (Pr), 0.0133 (Nd), 0.0039 (Sm), 0.0022 (Eu), 0.0031 (Gd) 0.0000 (Tb), 0.0030 (Dy), 0.0018 (Ho), 0.0011

Table 1: Parameters of 15 REEs and lead detection methods (ug/g).

Elements	SD	Linear correlation coefficient	Detection limit	Elements	SD	Linear correlation coefficient	Detection limit
La	0.0040	0.9995	0.0119	Dy	0.0010	0.9996	0.0030
Ce	0.0107	0.9994	0.0320	Ho	0.0006	0.9993	0.0018
Pr	0.0013	0.9993	0.0039	Er	0.0004	0.9994	0.0011
Nd	0.0044	0.9998	0.0133	Tm	0.0004	0.9992	0.0012
Sm	0.0013	0.9996	0.0039	Yb	0.0008	0.9993	0.0025
Eu	0.0007	0.9996	0.0022	Lu	0.0006	0.9990	0.0017
Gd	0.0010	0.9996	0.0031	Y	0.0083	0.9993	0.0250
Tb	0.0000	0.9993	0.0000	Pb	0.6696	0.9994	2.0088

(Er), 0.0012 (Tm), 0.0025 (Yb), 0.0017 (Lu) 0.0250 (Y) and 2.0088 (Pb). Internal standard method was used to check the consistency of control blanks, procedural blanks and hair samples with reagent one (GBW07601a) simultaneously. The measured concentrations of 9 elements were consistent with standards, except for lower concentrations of Y, Ce, Eu, Gd, Tb, Lu and higher of Pb. In addition, most elements had stable measurements excluding Sm, Eu, Tm, Lu and Pb (RSD > 10%). That is to say, our measurements had overall accuracy and precision.

IQ measurement

We used Raven's Standard Progressive Matrices (SPM) to test intelligence of participants under similar and partitioned test environment. Our investigators have been rigorously trained and evaluated before testing, and the process was strictly followed in accordance with the procedures and time specified in the instruction manual. Older children (aged 9~16) were tested in groups by investigators companied with local volunteer translators. Younger participants (< 9-years-old) were measured individually. Their IQ scores were adjusted by age. The integrity and formality of materials were asked to be guaranteed, including general characteristics and test results.

Statistical analysis

We used structured equation model to explain associations between REEs and lead explore and children's intelligence. R (version 3.4.1) was used for data management and basic statistical analysis, while Open BUGS (version 3.2.1) was used for model building and estimating. We also use R packages "R2Openbugs" and "CODA" to call Open bugs in R software.

Measurement model

$$u = \Lambda\omega + \mu$$

Where $\boldsymbol{\mu}$ was a 15 by 1 vector of intercept of each rare earth element, $\boldsymbol{\Lambda}$ was a 15 by 2 matrix of factor load in measurement model, $\boldsymbol{\omega}$ was a 2 by 1 vector of explanatory latent variables (ξ_1 and ξ_2) of light REEs and heavy REEs, and $\boldsymbol{u}$ was the matrix of dependent variables of each measurement regression model.

$$\Lambda^T = \begin{bmatrix} \lambda_1 & \lambda_2 & \lambda_3 & \lambda_4 & \lambda_5 & \lambda_6 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \lambda_7 & \lambda_8 & \lambda_9 & \lambda_{10} & \lambda_{11} & \lambda_{12} & \lambda_{13} & \lambda_{14} & \lambda_{15} \end{bmatrix}$$

Structural model

For M_0:

$$\eta = \xi_1\gamma_1 + \xi_2\gamma_2 + \mu_{16}\gamma_3 + \mu_{17}\gamma_4$$

In the basic model, η was the outcome latent variable, μ_{16} and μ_{17} were mean variance of hair Pb and age of children, where γ_3 and γ_4 was their corresponding factor loads.

For M_k, k = 1, 2, 3, 4

$$\eta = \xi_1\gamma_1 + \xi_2\gamma_2 + \mu_{16}\gamma_3 + \mu_{17}\gamma_4 + Int._k\gamma_k(1-t) + Int._{k'}\gamma_{k'}t$$

M_k were a group of extend models adding iterative items (*Int.*) with its own factor loads. Interactive latent variables in different models were showed in table.

Prior distribution and initiation

Prior distribution of the parameters was prescribed as below:

$$\lambda_k \sim N(\lambda_0, \psi_{\varepsilon k})$$
$$\psi_{sk} \sim Gamma(\alpha_{\varepsilon 0}, \beta_{\varepsilon 0})$$
$$\mu_k \sim N(\mu_0, \psi_{\varepsilon k})$$
$$\gamma_i \sim N(\gamma_0, \delta_i)$$
$$\delta_i \sim Gamma(\alpha_{\delta 0}, \beta_{\delta 0})$$
$$\Phi \sim W_{q2}(R_0, \rho_0)$$

Where λ_k was the $\boldsymbol{k}^{th}$ factor load in measurement model, $\boldsymbol{\Psi}_{\varepsilon k}$ was the $\boldsymbol{k}^{th}$ element of the error matrix $\boldsymbol{\Psi}_{\varepsilon}$ of measurement equations, $\boldsymbol{\mu}_k$ was the k^{th} intercept of measurement model, $\boldsymbol{\gamma}_i$ was the $\boldsymbol{i}^{th}$ factor load in structural model, δ_i was the $\boldsymbol{i}^{th}$ error of outcome latent variable, and Φ was the covariance matrix of explanatory latent variables, where $\boldsymbol{W}_{q2}$ was a q_2-dimensional Wishart distribution with a positive definite matrix $\boldsymbol{R}_0$. Other parameters unmentioned were all presupposed parameters or hyperparameters of each distribution. For observed variable vector **y** (15 by 1), we considered $\boldsymbol{y}_k$ was distributed as N ($\boldsymbol{u}_k$, $\boldsymbol{\Psi}_{\varepsilon k}$). And for y_{18} (observed variable of IQ) was distributed as N (η, δ_i). Totally three Monte Carlo Markov chains was generated from different initial values, which were showed in table. Totally 30,000 iterations were conducted, and the first 10,000 was for burn-in. Before iteration, all observed variables were centralized (Figure 2).

Model comparison and checking

Deviance information criteria (DIC) was used for preliminary exploration of the best-fit model. DIC was considered as a Bayesian measure of fit or adequacy. In model comparison, and model with the smaller DIC value would be preferred. As all M_k were nested with M_0, we used a parameter t distributed in U (0,1) produced with interactive latent variable to link up M_0 and M_k (or among different M_k if any M_k fit better than M_0) when comparing different models, as

M_{0k}:

$$\eta = \xi_1\gamma_1 + \xi_2\gamma_2 + \mu_{16}\gamma_3 + \mu_{17}\gamma_4 + Int.\,\gamma_k t$$

When t = 0, $M_{0k} = M_0$, and when t = 1, $M_{0k} = M_k$

$M_{kk'}$:

$$\eta = \xi_1\gamma_1 + \xi_2\gamma_2 + \mu_{16}\gamma_3 + \mu_{17}\gamma_4 + Int._k\gamma_k(1-t) + Int._{k'}\gamma_{k'}t$$

When t = 0, $M_{kk'} = M_k$, and when t = 1, $M_{kk'} = M_{k'}$

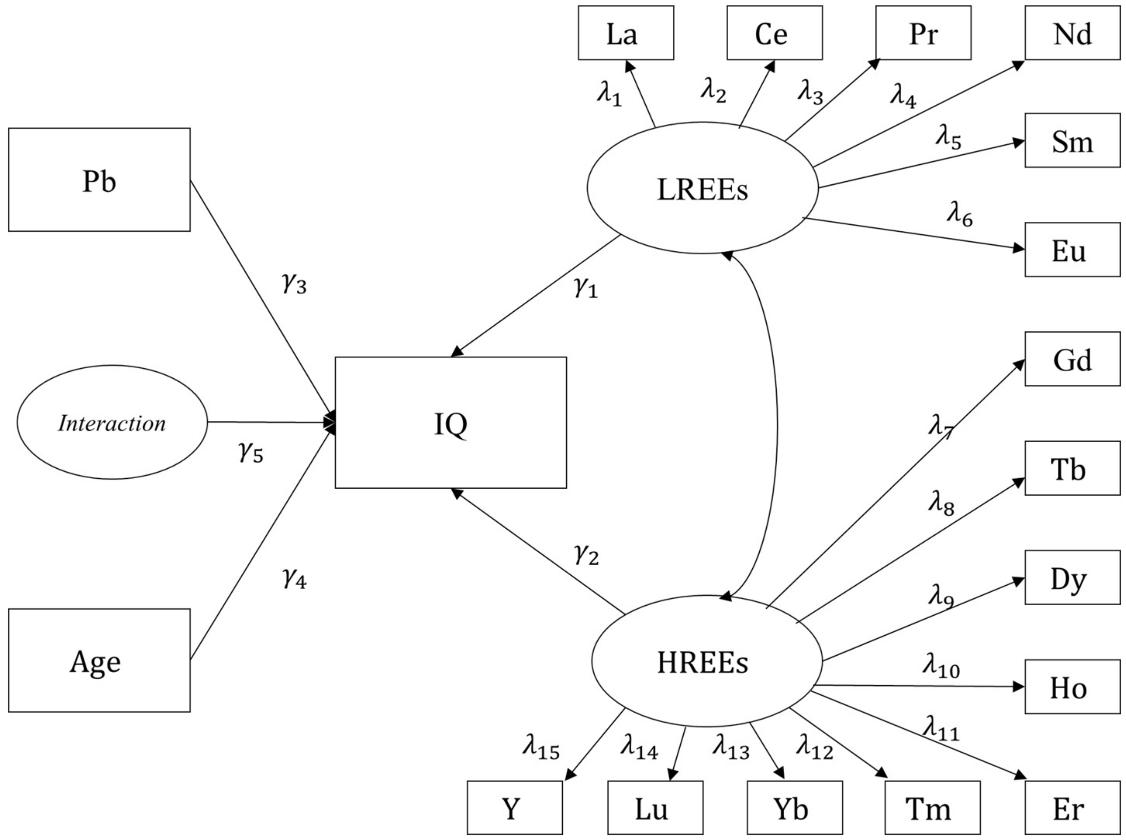

Figure 2: A simplified structural equation model graph.

Note: Only parameters we concerns were demonstrated in the graph, while others omitted.

Table 2: Interactive latent in different interactive models.

Model	Interaction	Interactive latent variable
1	Pb × LREE	$\xi_1\mu_{16}$
2	Pb × HREE	$\xi_2\mu_{16}$
3	LREE × HREE	$\xi_1\xi_2$
4	Pb × (LREE+HREE)	$(\xi_{1+}\xi_2)\mu_{16}$

And we used Bayesian factor (B) to select the best model. If the 2logB of linked-model was more than 2, we consider the alternative model was better, then reject the original model. History plot was used to give information about the convergence of the Gibbs sampler (Table 2).

Results

Information about observed variables

A total of 95 children participated in the study. Their age ranged from 6 to 16 years with an average of about 11 years. Average IQ of all 95 children was 28.8. Based on the guidance of Raven's SPM, 24 of them (33.3%) was considered as lower than expected level of their age. The highest three rare earth element were Ce (46.96%), La (34.48%) and Nd (10.38%). They were all light REEs. Light REEs account for 96.64% of all REEs. The average concentration of hair leads was 26.2 μg/g (Table 3).

Bayesian structural equation model estimation

After 10,000 iterations of burn-in and then 20,00 iterations, main parameters in five different models were estimated (Table 4). According to Deviance Information Criteria, we preferred M_0, which did not contain any interactive latent variable, as the best-fit

Table 3: Rare earth elements and lead concentration in hair of 95 children (μg/g).

Elements	$\bar{x}$	*s*	*M*	P_{25}	P_{75}
La	1.3465	3.4205	0.3907	0.2399	1.1505
Ce	1.8336	4.3124	0.5958	0.3811	1.6591
Pr	0.1393	0.2900	0.0489	0.0337	0.1271
Nd	0.4052	0.7594	0.1646	0.1098	0.3574
Sm	0.0395	0.0527	0.0226	0.0150	0.0364
Eu	0.0090	0.0105	0.0060	0.0042	0.0097
Gd	0.0265	0.0336	0.0184	0.0118	0.0296
Tb	0.0028	0.0043	0.0020	0.0009	0.0030
Dy	0.0149	0.0217	0.0112	0.0066	0.0151
Ho	0.0028	0.0041	0.0020	0.0012	0.0027
Er	0.0073	0.0110	0.0051	0.0028	0.0071
Tm	0.0013	0.0019	0.0009	0.0005	0.0015
Yb	0.0066	0.0088	0.0049	0.0030	0.0064
Lu	0.0010	0.0017	0.0006	0.0003	0.0010
Y	0.0679	0.0969	0.0497	0.0312	0.0672
Pb	26.2245	71.1515	12.3451	6.5210	25.1090

Note: Concentration of all above elements did not distribute as normal.

Table 4: Estimation of main parameters in different model by MCMC BUGS.

Parameters	$_{M}0$		M_1		M_2		M_3		M_4	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
γ_1	-0.044	0.25	-0.076	0.316	-0.028	0.276	-0.003	0.262	-0.029	0.291
$\gamma 2$	-0.043	0.241	-0.021	0.274	-0.09	0.286	-0.003	0.245	-0.062	0.287
γ_3	-0.116	0.298	-0.117	0.357	-0.315	0.56	-0.099	0.32	-0.17	0.455
γ_4	0.339	0.292	0.344	0.313	0.344	0.313	0.349	0.315	0.338	0.313
γ_5	-	-	-0.161	0.741	0.218	0.501	0.015	0.147	0.055	0.33
λ_1	0.795	0.144	0.829	0.149	0.804	0.15	0.437	0.58	0.815	0.149
λ_2	0.8	0.145	0.834	0.15	0.809	0.151	0.439	0.583	0.82	0.15
λ_3	0.805	0.146	0.838	0.151	0.814	0.152	0.442	0.586	0.825	0.151
λ_4	0.806	0.145	0.84	0.151	0.816	0.152	0.443	0.588	0.827	0.151
λ_5	0.732	0.138	0.763	0.144	0.741	0.144	0.402	0.535	0.751	0.143
λ_6	0.599	0.124	0.624	0.128	0.606	0.128	0.329	0.44	0.614	0.128
λ_7	0.718	0.11	0.716	0.118	0.733	0.117	0.049	0.466	0.727	0.117
λ_8	0.764	0.113	0.762	0.121	0.78	0.12	0.052	0.495	0.773	0.12
λ_9	0.768	0.113	0.767	0.121	0.785	0.121	0.052	0.498	0.778	0.121
λ_{10}	0.769	0.113	0.768	0.122	0.786	0.121	0.053	0.499	0.779	0.121
λ_{11}	0.773	0.113	0.771	0.122	0.79	0.121	0.053	0.501	0.783	0.121
λ_{12}	0.67	0.107	0.668	0.114	0.684	0.113	0.046	0.435	0.678	0.113
λ_{13}	0.767	0.113	0.766	0.122	0.784	0.121	0.052	0.497	0.777	0.121
λ_{14}	0.559	0.1	0.557	0.106	0.571	0.106	0.038	0.364	0.565	0.106
λ_{15}	0.766	0.113	0.764	0.121	0.782	0.12	0.052	0.496	0.775	0.12
Model fitness										
DIC	1580		1593		1593		-8273		1594	
$2logB_{0k}$	-		2651.796		2654.999		-		2650.307	

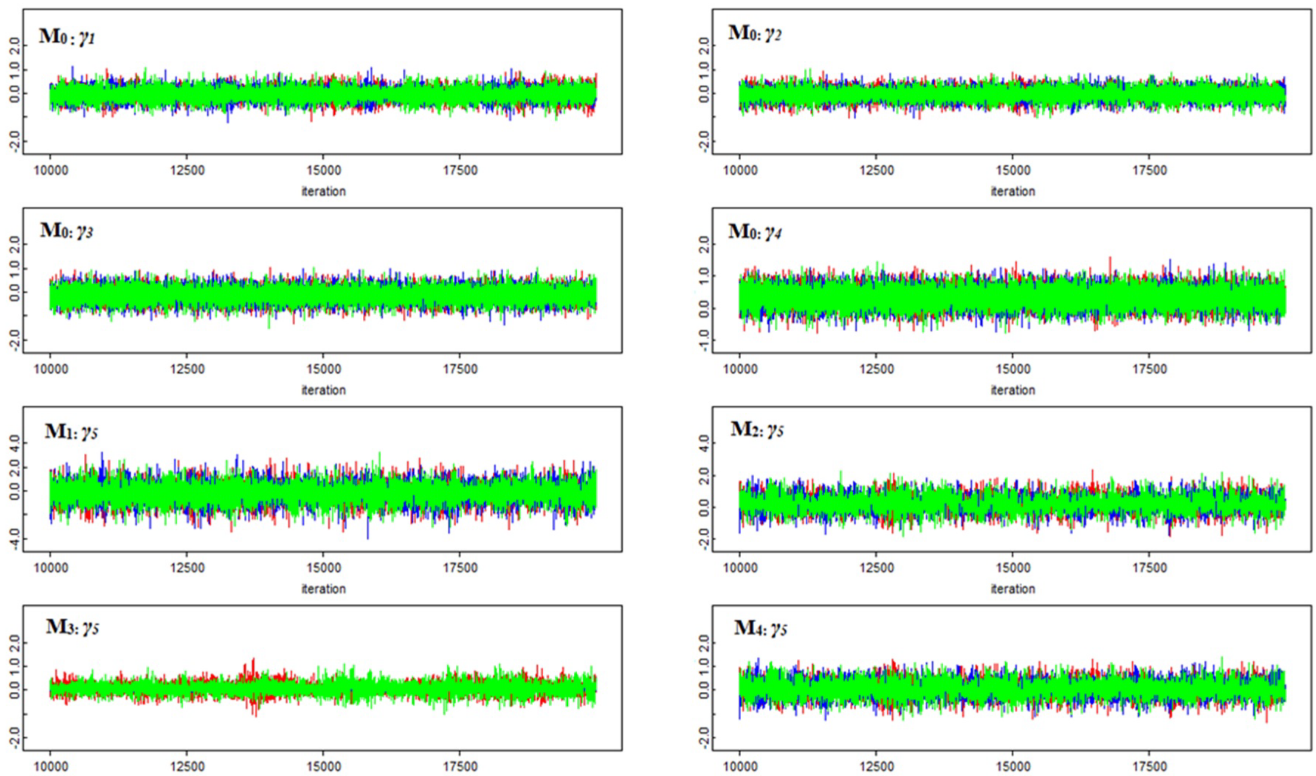

Figure 3: Some of history plots of different three chains by iteration.

model for its lower DIC value. M_3 had a negative DIC, so we discarded this model suspecting bad fitness between data and prior. Then the rest of alternative models was compared with M_0 by Bayesian factor. And $2\log B_{0k}$ showed that the based M_0 was better fitted than those more complex model with different interactive items of lead and REEs (M_1, M_2 and M_4). In Figure 2, history plots of those reserved models showed approximately convergences of there Monte Carlo Markov chains with different initial values. Some of them about main concerned parameters were demonstrated, while there were still some chains of parameters in measurement model showed a snake-like pattern (not demonstrated) (Figure 3).

In M_0, we could find that age has the greatest effect on IQ with its path coefficient of 0.339. It was followed by hair lead (-0.166), showing a negative effect on intelligence development. Impact of light REEs and heavy REEs were similar (-0.044 and -0.043, respectively), which was much lower than that of lead. As for M_1, after adding the interactive item of lead and light REEs, the coefficient of age and lead was barely changed, but the impact of light REEs on IQ was slightly increased while of heavy REEs decreased. The interactive effect of light REEs and lead was -0.161, which should not be omitted, prompting the interaction between lead and light rare earth has a negative effect on intelligence on a certain extent. But in M_2, the interaction between lead and heavy REEs showed a positive effect on intelligence with 0.218. That was much higher than their single negative effect. When considering if there was interaction between lead and both light and heavy rare earth elements, the interaction showed a weak positive effect on IQ, while other path coefficients were similar with those in former models.

As for measurement model in M_0, factor loads of La, Ce, Pr and Nd was observed quite similar and as the highest and Eu was the lowest in light REEs. For heavy REEs, Tb, Dy, Ho, Er, Yb and Y were with more weight and Lu the least. The factor loads did not show consistence with the median concentration of corresponding elements. The same results could be observed in alternative models, even though they were not the best-fit (Figure 4).

Discussion

The process of mining, transportation, screening and refining, REEs and lead are released into the air or washed into the water, as well as the soil itself contains these elements which is harmful to the growing children around mining areas absorbed from breathing air, drinking water and dieting food. The present study was a cross-sectional study about hair lead, rare earth elements and children's intelligence in the south of China. To the best of our knowledge, this was the first study to evaluate the effects of lead and rare earth

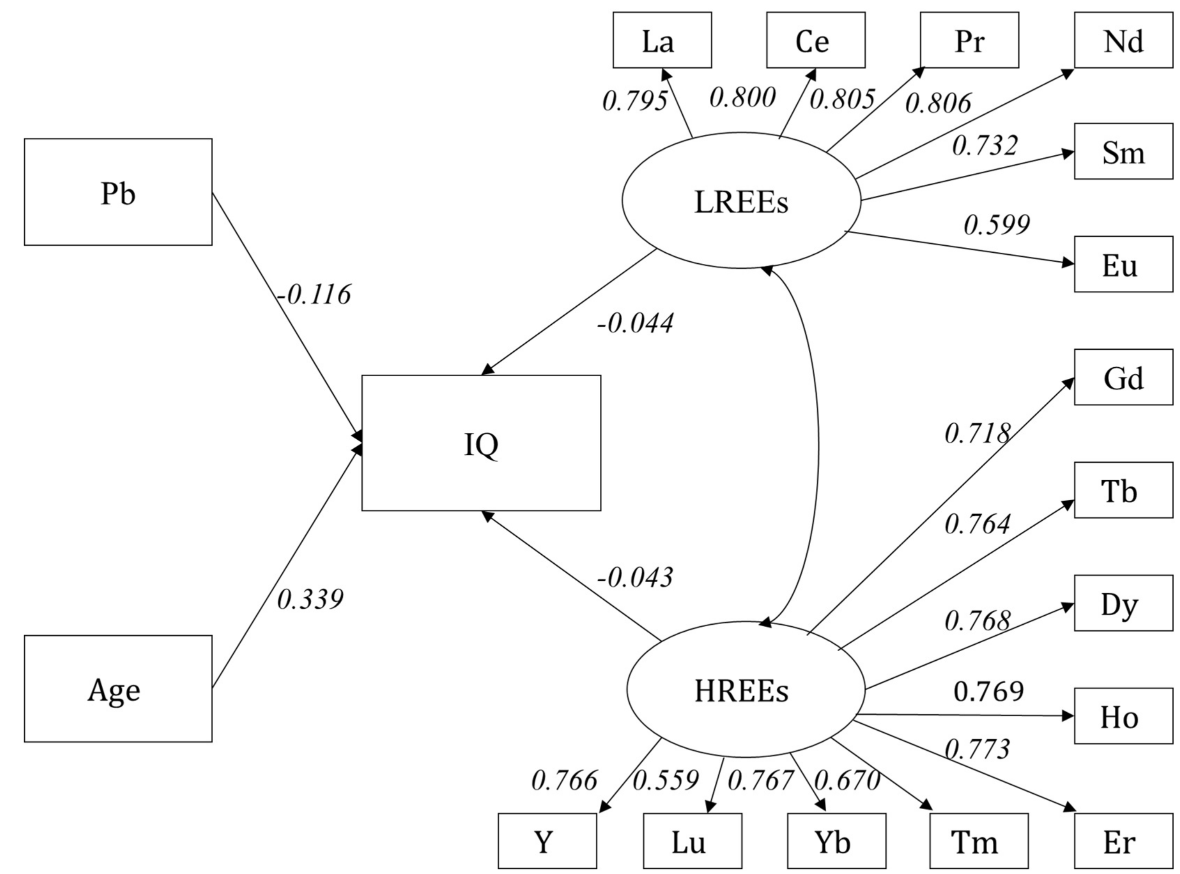

Figure 4: A simplified graph of the best-fitted model (M_0).
Note: Only parameters we concerns were demonstrated in the graph, while others omitted.

exposure simultaneously, and to explore the interaction effects by Bayesian structural equation modelling.

Results of the present study indicated that both light and heavy rare earth elements in hair had negative effect on children aged 6 to 16-years-old, which was quite consistent with previous studies. However, the effect was relatively weaker than that lead, which was reported widely to have significant adverse effects on intelligence development [14]. Still, these kinds of effect should not be omitted, especially for children living in rare earth mining area.

Interaction effect between lead and rare earth elements was not observed based on our selection of the best-fit model. Nevertheless, we cannot simply deny the existence of such interaction entirely, as hormesis of several rare earth elements was reported, by increases or improvements in biological events at low levels [3,4], which might cover up or counteract the adverse effect of lead if interaction did exist. To confirm whether there is any interactive effect on children's intelligence, further mechanism studies under different level of lead and REEs exposure and expanded epidemiological research are needed.

One of the study's advantage is its analytical method, in that structural equation model was widely accepted as an important method in multivariate analysis, especially in relatively complicated context. It was also statistically efficient to build up latent variables of both light and heavy REEs instead of considering single effect of each elements, nor simply sum them all up because their effects on intelligence may be in different weight, which could be seen in our present study, for example, the median concentration of Ce was about five to six times than Pr, but their factor load to latent variable of light REEs were quite similar.

However, there are still some defects of standard SEM. It requires large samples [21], and it is not easy to define an interactive latent variable when the measurement model was too complex or have too many observed variables [22,23]. In Bayesian context, latent variable and parameters could be estimated by a large sample generated by method of Monte Carlo Markov Chain based on Gibbs' Sampling, which is more efficient and flexible when building a relative complex model or estimating unknown parameters [24].

The present study has some limitations. Firstly, even though Bayesian structural equation modelling based on MCMC does not rely on a large sample size, including more research subjects would improve its representativeness and statistical effectiveness. Secondly, our models only estimate effects of age, hair lead and rare earth elements on children's intelligence, although some potential confounders were controlled by random sampling. Ideally, we would expect to build up a more comprehensive model including as many factors as possible, although it was not easy. For model testing and fitting, model with interaction between light and heavy REEs was considered not fit with data because of negative DIC, which was mainly because of a negative p_D [25]. It might be because latent variables of multiplication contain too many observation variables. The convergence of some parameters was observed not ideal and may be due to unsuitable a prior distribution unsuitable. Lastly, Bayesian inference requires sufficient theoretical or empirical bases on prior information [26]. The model we selected in the present study was more theorically than exclusively denying the existence of interaction between hair lead and REEs because it could only demonstrate that the model was better fitted with this specific data. Further epidemiological studies with higher argumentative competence, such as case-control studies, cohort studies, and even empirical studies, are guaranteed in the future.

Conclusion

The health effects and toxicity mechanisms of REEs were widely researched. But the epidemiological evidences of REEs and REEs-lead interaction relating to children's intelligence are scarce. The present study showed that both light and heavy REEs, as well as lead in hair had negative effect on intelligence of children aged 6 to 16-years-old, but interactive effect was not found. Future studies with improved methodologies and focus on mechanisms are expected.

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Conflict of Interest

The authors declared that they have no conflicts of interest to this work.

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