

# BMJ Open Cognitive impairment of workers in a large-scale aluminium factory in China: a cross-sectional study

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## ABSTRACT

**Objectives** To investigate the prevalence of mild cognitive impairment and the relationship with plasma aluminium among aluminium workers.

**Design** This was a cross-sectional case-control study in the SH Aluminium Factory, China.

**Setting** The university and affiliated hospital cooperated in the study.

**Participants** There were 910 aluminium workers on duty, among whom 853 participated in our study. Participants, such as those with cerebral vascular disease, epilepsy, brain trauma, Parkinson's and mental diseases, aluminium-containing drug and mental drug use, and any family history of dementia in first-degree relatives were excluded.

**Primary and secondary outcome measures** Blood samples were collected, and plasma aluminium was measured by inductively coupled plasma-mass spectrometry. For each case, four age-matched controls were evaluated to determine the relationship between aluminium exposure and mild cognitive impairment. Conditional logistic regression was used to explore influential factors in mild cognitive impairment.

**Results** Among 910 workers, 93.74% participated in stage 1; 53 cases were finally diagnosed. The crude prevalence of mild cognitive impairment among aluminium workers on duty was 6.21%. There was a significant difference in plasma aluminium concentration between the two groups. In the multivariate analysis, we found that a higher level of plasma aluminium was associated with a high risk of cognitive impairment when compared with a lower aluminium level (AOR=2.24, 95% CI=1.17 to 4.26), and a high education level was a protective factor (AOR=0.36, 95% CI=0.18 to 0.70). No other factor was statistically significant.

**Conclusions** Mild cognitive impairment is no longer a disease specific to elderly people. High plasma aluminium exposure might be associated with an increased risk of cognitive impairment, but a reduced risk was observed with a high education level. The cognitive function of aluminium workers on duty must be considered seriously.

## INTRODUCTION

Alzheimer's disease (AD), the most common neurodegenerative disorder in the world, has tremendous consequences for individuals, families and society.<sup>1 2</sup> With the increasing

## Strengths and limitations of this study

- This investigation was performed using a large sample size.
- This is the first study to evaluate the prevalence of mild cognitive impairment and the relationship with plasma aluminium among aluminium workers on duty in North China.
- Case-control studies were rare among aluminium workers, and neurologists participated in our study.
- This study is limited by its cross-sectional study design, which means our results cannot infer a causal relationship; however, we will continue to observe these workers, and perform a cohort study.

proportion of elderly people, the number of AD cases will grow by up to threefold by 2050.<sup>3</sup> AD is currently considered a continuous disease process that includes mild cognitive impairment (MCI). MCI is the early stage of dementia,<sup>4</sup> and it is associated with an increased risk of developing dementia.<sup>5</sup> However, the aetiology of AD remains unknown after decades of research efforts. The prevalence ratios for black people in different countries clearly vary, indicating that environmental factors may be more important than genetic factors.<sup>6</sup>

Aluminium (Al) is one of the richest elements in the world and is present in every aspect of our life, such as food additives, drugs, cosmetics and industrial production, among others. Al can enter the body through the skin, digestive tract, muscles and respiratory tract, but it is excreted chiefly through the urine and sweat.<sup>7</sup> Increasing environmental pollution leads to acid rain, and subsequently the dissolved silicate in the soil enters the water source, ultimately increasing the Al load in the human body. Al may accumulate in the body after long-term exposure; the skeleton contains approximately 50% and the lungs 25% of the body burden.<sup>8</sup> Al<sup>3+</sup> can enter the nervous system through the



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blood–brain barrier (BBB). In addition, relatively direct deposition of Al from the air to the brain is also possible via the olfactory paths.<sup>9</sup> Low levels of Al can lead to behavioural and morphological changes associated with AD.<sup>10</sup> Since the 1990s, people have started to pay attention to nervous system damage caused by occupational Al exposure. Hosovski *et al*<sup>11</sup> and White *et al*<sup>12</sup> first reported the cognitive decline of Al foundry workers and smelters. Riihimaki and Aitio<sup>13</sup> found that cognitive function gradually decreases with the increase in blood Al. A meta-analysis<sup>14</sup> performed in 449 Al-exposed workers in Germany reported the dose–response relationship between Al and cognitive dysfunction. Other scholars<sup>15–18</sup> have also reached the same conclusion. In 2014, a case of an occupational Al worker who progressed to AD was reported as direct evidence.<sup>19</sup> Moreover, increased levels of Al have been reported in the brains of AD patients and populations with high Al exposure.<sup>20–22</sup> Due to the inaccessibility of the human brain, plasma Al was used herein as the indicator according to previous studies.<sup>9 23 24</sup> Compared with the environmental exposure level, it can more accurately reflect the actual Al exposure of individuals.

Current studies show that the prevalence of MCI or AD is concentrated in people >60 years of age. The MCI prevalence in Al workers on duty has remained unknown until now. According to statistics from 2013, Al production encompassed close to half of the world, and there were more than 3 million Al workers in China, providing a good choice for large-sample research. In addition, little work has been conducted on the relationship between MCI and Al. Early detection of MCI and progression prevention are necessary.

The mini-mental state examination (MMSE), which was first introduced by Folstein *et al*<sup>25</sup> in 1975, has become a standard tool for cognitive assessment. It examines diverse domains: orientation in time and place, memory, language, calculation skills and visuospatial capacity. The clock drawing test (CDT) is the second most widely used screening tool for cognition detection.<sup>26</sup> Despite appearing simple and easy, it is a complex task that can examine wide scopes of cognition, including planning, executive function, abstract thinking, attention, memory, number order operation, time and space concepts.<sup>27</sup> In this study, we used MMSE and CDT to evaluate cognition in stage 1.

We aimed to identify MCI patients and estimate the prevalence of MCI among Al workers in SH Aluminium Factory, China. Furthermore, we studied the relationship between plasma Al and MCI using case-control methods.

## MATERIALS AND METHODS

### Participants and study design

This study was performed in a large-scale aluminium factory in Hejin, Shanxi Province, North China. Workers on duty in this factory were our target population. Our study was conducted along with the annual health examination in the staff hospital. The workers took work

clothes, masks and gloves during working time. The Al concentration in the drinking water was lower than the national standard (<0.2 mg/L).

A two-stage survey was designed to evaluate workers with cognitive impairment. In stage 1, trained interviewers (doctors and senior medical students) administered a self-designed questionnaire (online supplementary file)<sup>28–31</sup> for subjects in the Al factory staff hospital. Intact demographic and medical information was collected to the extent possible, including age, sex, education, marriage, income, employment history, smoking and drinking habits, health situation and drug use. Education was summarised as junior middle school and below ( $\leq 9$  years) and senior middle school and above ( $> 9$  years). Marital status, household incomes per capita, employment history and type of work were dichotomised as no or yes, <1000 or  $\geq 1000$  yuan per month, <1 or  $\geq 1$  year, and electrolytic or non-electrolytic workers, respectively. Smoking was divided into three categories: never, former and current. Current smokers were defined as subjects who smoke  $\geq 1$  cigarette/day for  $\geq 6$  months; former smokers were defined as subjects who smoke <1 cigarette/day or have quit the habit  $\geq 6$  months; subjects who had never smoked were defined as never. Drinking was also divided into three categories: never, former and current. Current drinkers were defined as subjects who drink at least once a week for  $\geq 6$  months; former drinkers were defined as subjects who drink less than once a week or have quit the habit for  $\geq 6$  months; subjects who had never drunk were defined as never.

After collecting the basic information, the subjects underwent a face-to-face evaluation by the MMSE and CDT scales, both of which were conducted strictly according to the guidelines. The correlation between MMSE and CDT is high, and herein we combined MMSE with CDT<sup>32 33</sup> to increase the sensitivity and specificity. MMSE (illiteracy  $\leq 19$ , primary school  $\leq 22$ , middle school and above  $\leq 26$ ) or CDT  $\leq 2$  was defined as abnormal. Participants whose MMSE or CDT performances were abnormal or who had complaints of memory impairment entered stage 2.

In stage 2, neurologists from the First Hospital of Shanxi Medical University inquired about the participants' history of cognition. Scales with higher specificity were selected, including the digital span, Fuld object-memory examination<sup>34</sup> and rapid verbal retrieve. Cognitive impairment was diagnosed according to the new 2011 National Institute on Aging and Alzheimer's Association (NIA/AA) guidelines.<sup>4</sup>

Exclusion criteria for our study were as follows: (1) any diseases that may cause cognitive impairment including hepatic or renal disorders, brain trauma, cerebrovascular diseases, epilepsy, Parkinson's diseases and mental diseases; (2) any family history of dementia in first-degree relatives; (3) any history of regular drug use (anti-acid drugs containing Al or mental drugs affecting the central nervous system); (4) use of Al cookware in the home or daily consumption of vermicelli or fritters; (5) obviously

poor vision and hearing; (6) workers with missing demographic information and blood samples and (7) dementia defined by impaired daily work and general activity, or poorer life function and execution ability than previously observed, or a condition that could not be explained by delirium or mental illness (as judged by the neurologists).

### Ethical statement

All subjects signed the informed consent.

### Biological sample collection and determination of the plasma Al concentration

Approximately 10 mL of venous blood was collected from each participant in tubes containing EDTA in blood sampling room of the aluminium factory staff hospital in the early morning. The plasma was separated within 30 min by centrifugation (4°C, 5 min, 1500 rpm) into EP tubes. Before use, the tubes, pipette tips and even the bags containing them were all soaked in acid for 3 days and washed adequately with Milli-Q water. The samples were transported by special delivery to the laboratory and stored at -80°C until analysis.

Plasma (0.4 mL) was mixed with 1.6 mL nitric acid (4% v/v) for 24 hours at room temperature and then analysed by inductively coupled plasma mass spectrometry (ICP-MS) (NexION 300D, PerkinElmer, Waltham, MA, USA) to assess the plasma Al concentration. EDTA blanks (Milli-Q water) were measured, and the aluminium concentration was below the detection limit (0.39 µg/L). The specimens were measured in random order by blinded laboratory personnel. Each sample was measured twice. We measured blanks and Al standard liquid (Agilent, Santa Clara, CA, USA) every 10 samples.

In the case-control study, for each case, four controls were matched according to age ( $\pm 2$  years) in a random manner. The plasma Al concentration was categorised into a binary variable according to the median.

### Quality control

All interviewers were trained strictly by neurologists and psychiatrists. Face-to-face interview and cognitive assessments were performed on the same day. The collection and processing of blood samples was handled by a special personnel.

### Statistical analysis

The database was set up using the software EpiData V.3.1, and the double input method was adopted. All data were analysed using SPSS V.22.0. The concentration of plasma Al below the limit of detection (LOD) was assigned a value corresponding to one-half the LOD. Outliers were not removed because of their reasonability. The Student's t-test or Mann-Whitney U test was used to compare continuous variables depending on the distribution types. Differences between categorical variables were calculated using the  $\chi^2$  test. Univariate logistic regression was used to estimate the OR and 95% CI for cognitive impairment. Multivariate logistic regression was used to analyse all the

risk factors. A p value  $<0.05$  was considered statistically significant.

### Patient and public involvement

Patients' priorities, experience and preferences were not involved in our study. The diagnosis of MCI was performed according to the NIA/AA guidelines published in 2011. The measurement results were to be disseminated to the participants after the study by the study team and doctors.

## RESULTS

There were 910 workers in SH Aluminium Factory. Of these, 853 (93.74%) participated in stage 1. They were all men. The mean age and education duration were 44.78 and 10.70 years, respectively. Twenty-two workers were excluded according to the exclusion criteria. Subsequently, 334 (39.16%) workers entered stage 2. In stage 2, 53 (6.21%) workers were finally diagnosed with MCI. Among 53 cases, the chief clinical features were focused on delayed recall (81.13%) and visuospatial executive ability (56.60%).

For each case, four controls were matched by age ( $\pm 2$  years) in a random manner. The characteristics of the cases and controls are presented in [table 1](#). The mean age of cases and controls were 45.04 and 44.71 years. There were no differences in income, marriage, smoking or drinking between the cases and controls ( $p>0.05$ ). The MCI cases had a lower education level than the controls ( $p=0.001$ ). There was a significant difference in plasma Al between the two groups ( $p=0.001$ ). The proportion of Al working time  $\geq 1$  year, plasma Al  $\geq 13.13$  µg/L and electrolytic workers were higher among the cases than the controls ( $p=0.005$ ,  $p=0.010$ ,  $p<0.001$ ).

In conditional logistic regression analysis, we found that a higher level of plasma Al was associated with a high risk of cognitive impairment (AOR=2.24, 95% CI=1.17 to 4.26,  $p=0.014$ ), and a high education level was a protective factor (AOR=0.36, 95% CI=0.18 to 0.70,  $p=0.003$ ). Smoking and drinking were not associated with cognitive impairment in this population ( $p>0.05$ ) ([table 2](#)).

The combined effect of plasma Al and education is presented in [table 3](#). Compared with workers with low Al exposure, those with high Al exposure and a low education had the highest risk of cognitive impairment. In other words, improving the education level can effectively reduce the risk of cognitive impairment in workers with high Al exposure (AOR=0.36, 95% CI=0.19 to 0.69,  $p=0.002$ ).

## DISCUSSION

Aluminium is widely distributed worldwide, but it is not an essential element for life. Long-term Al exposure can lead to the accumulation of this metal.<sup>8 35</sup> Many studies have indicated that Al is one of the most important environmental factors in cognitive impairment.<sup>36 37</sup>

**Table 1** The characteristics of cases and controls

Variables	Case (n=53)	Control (n=212)	P value
Age, (mean±SD)	45.04±6.15	44.71±6.11	0.729*
Education, n (%)			
Junior middle and below	34 (64.1)	83 (39.1)	0.001†
Senior middle and above	19 (35.9)	128 (60.9)	
Income (RMB)			
<1000	26 (51.0)	82 (40.4)	0.172‡
≥1000	25 (49.0)	121 (59.6)	
Marriage, n (%)			
No	0 (0)	1 (0.5)	0.616†
Yes	53 (100)	211 (99.5)	
Smoking, n (%)			
Never	23 (43.4)	103 (48.6)	0.771†
Former	2 (3.8)	6 (2.8)	
Current	28 (52.8)	103 (48.6)	
Drinking, n (%)			
Never	26 (49.0)	125 (59.0)	0.424†
Former	10 (18.9)	31 (14.6)	
Current	17 (32.1)	56 (26.4)	
AI working time, n(%)			
<1	34 (64.1)	174 (82.1)	0.005†
≥1	19 (35.9)	38 (17.9)	
Plasma AI, Med (25th–75th)	18.17 (10.39, 34.96)	12.02 (6.35, 20.86)	0.001‡
Plasma AI, n (%)			
<13.13	18 (34.0)	114 (53.8)	0.010†
≥13.13	35 (66.0)	98 (46.2)	
Type of work, n (%)			
Non-electrolytic worker	31 (58.5)	173 (81.6)	<0.001†
Electrolytic worker	22 (41.5)	39 (18.4)	

Data were presented as mean ±SD or n (%) or Med (25th–75th).

Missing value: case (income: 2) control (education: 1; income: 9).

The unit for age and AI working time was year; RMB is Chinese money, and the unit is yuan; the unit for plasma AI was µg/L.

\*P value determined by ANOVA.

†P value determined by the X<sup>2</sup> test.

‡P value determined by the Mann-Whitney U test.

MCI is considered to be a transitional stage between normal cognitive ageing and AD.<sup>38</sup> Effective intervention during the MCI phase can prevent progression.<sup>39</sup> Our previous population study<sup>40</sup> showed that retired AI workers had higher plasma AI concentrations and a decline in cognitive functions. Moreover, the detection rate of MCI in retired AI workers was three times greater than the control (18.2% vs 5.7%). Thus, AI workers represent a special group at high risk of developing cognitive decline. There were some limitations to the study. For example, only MMSE was used for retired workers, and the sample size was small. However, AI toxicity was present before the workers retired. There has been a lack of studies with a

large sample size and with data regarding the prevalence of MCI in AI workers on duty.

There are great challenges for the diagnosis of MCI in epidemiological investigations. The prevalence of MCI among the elderly varies in a wide range from approximately 4.3% to 36.8%.<sup>5,41</sup> To a large extent, clinician judgement is necessary. In our cross-sectional study, a two-stage design was used to estimate the prevalence of MCI in the SH Aluminium Factory. MCI can affect a variety of cognitive functions, including memory, language, attention and visuospatial executive abilities, and it is often accompanied by memory impairments. An increasing number of studies have shown that visuospatial executive ability

**Table 2** Univariate and multivariate logistic regression analyses of cognitive impairment and plasma AI

Factors	Univariate		Multivariate	
	OR (95% CI)	P value	AOR (95% CI)	P value
Education				
Junior middle and below	1.0		1.0	
Senior middle and above	0.37 (0.19 to 0.69)	0.002	0.36 (0.18 to 0.70)	0.003
Smoking				
Never	1.0		1.0	
Former	1.50 (0.29 to 7.79)	0.627	0.97 (0.17 to 5.60)	0.975
Current	1.22 (0.66 to 2.25)	0.526	1.15 (0.60 to 2.21)	0.668
Drinking				
Never	1.0		1.0	
Former	1.59 (0.69 to 3.70)	0.278	1.67 (0.68 to 4.11)	0.266
Current	1.49 (0.74 to 2.97)	0.262	1.33 (0.63 to 2.81)	0.451
Plasma AI				
<13.13	1.0		1.0	
≥13.13	2.21 (1.19 to 4.13)	0.013	2.24 (1.17 to 4.26)	0.014

The cut-off for the plasma AI was the median. ORs were adjusted for education, smoking and drinking. The unit for plasma AI was µg/L. AOR, adjusted odds ratio.

impairment occurs in early stages, even before declarative memory impairment.<sup>42 43</sup> MMSE has a wide range of cognitive domains. CDT is commonly used to reflect the function of the parietal lobe, which is closely related to visual space.<sup>44 45</sup> In stage 1, we combined the MMSE with CDT to detect probable MCI patients to avoid missing cases. In stage 2, neurologists adopted the highly specific questionnaire to improve the accuracy of the diagnosis. Finally, 53 cases were ascertained as contracting MCI, thus generating a crude prevalence rate of 6.21%. This rate was higher than the 1% reported among people aged 60–64 years.<sup>46</sup> Investigations concerning the prevalence of MCI are usually conducted among the elderly, and occupational workers may be ignored. The mean age of the cases was much younger than the general MCI population. Thus, cognitive function may be damaged by AI in young people.

Among the cases, delayed recall and visuospatial executive abilities were prominently impaired. Many studies

have described a decline in memory. In Polizzi *et al's* study, a negative relationship was observed between serum AI levels and MMSE and CDT scores.<sup>17</sup> More than half of our cases showed a visual space disorder but without complaints. In recent years, imaging examinations have played an important role in the early diagnosis of AD.<sup>47</sup> Imaging studies on AD patients have become commonplace, but they remain limited for occupational workers. It is necessary to conduct imaging examinations of occupational workers to identify early patients and further study the types of cognitive impairment and even the processes underlying their development.

Next, an age-matched case-control study was conducted. Our findings showed that income, marriage, smoking and drinking were evenly balanced between the two groups. However, the plasma AI concentration was higher in the cases than in the controls. A meta analyses<sup>48</sup> also demonstrated that AI levels in AD cases were significantly elevated in the brain, serum and CSF, particularly in the

**Table 3** Joint effects of plasma AI and education on cognitive impairment

Variables			Case (%) (n=53)	Control (%) (n=211)	AOR (95% CI)
Plasma AI	Education	N			
Low exposure	Junior middle and below	54	9 (17.0)	45 (21.3)	1
	Senior middle and above	77	9 (17.0)	68 (32.2)	0.64 (0.18 to 2.27)
High exposure	Junior middle and below	63	25 (47.2)	38 (18.0)	1
	Senior middle and above	70	10 (18.8)	60 (28.5)	0.36 (0.19 to 0.69)

ORs were adjusted for smoking and drinking. Missing value: low exposure control (senior middle and above: 1). AOR, adjusted odds ratio.

serum, which may serve as an early marker of AD. The plasma Al concentration was much higher in our cases than in the AD cases assessed in the above study. The general population is primarily exposed to Al through the consumption of food items, taking in antacids, ingestion of Al in drinking water and inhalation of ambient air, though the latter two exposure ways are believed as only minor parts. Workers in Al industries can be occupationally exposed to airborne Al particulate at concentrations exceeding the general population exposure.<sup>49</sup> These results support the existing evidence linking chronic aluminium exposure and the development of AD. Some early studies<sup>50 51</sup> did not find an association between Al and AD, but those studies have severe limitations related to their retrospective design and sole investigation of the occupational history of AD patients without plasma Al measurements. Our controls also had higher plasma Al concentrations than the normal range, as they live in the region of the aluminium factory where the air may have been polluted. ICP-MS is a leading technique for elemental trace analysis due to its great sensitivity, speed and accuracy, even at lower LOD levels (0.39 µg/L for Al in our study). Contamination can be easily identified, which is important in Al research. Moreover, in our study, we found that electrolysis workers were prone to cognitive impairment. Electrolysis is the last process in Al production, where the workers are mainly exposed to aluminium oxide dust, which is more harmful due to a higher bioavailability.<sup>52 53</sup>

In the multivariate analysis, higher plasma Al was associated with an increased risk of cognitive impairment. Education was found to be a protective factor for MCI, which has been widely accepted. In the case group, 64.1% had a low education level, suggesting that the risk of cognitive impairment in Al workers might be improved through continuing education. For Al workers with high plasma Al levels, the role of education was more prominent. Smoking and drinking were not associated with MCI in our study. The above results indicated that Al played an important role in the pathogenesis of cognitive impairment. Our animal experiments<sup>54–56</sup> and other research<sup>57 58</sup> have confirmed this point.

We investigated, for the first time, the crude prevalence of MCI among on-duty Al workers. Moreover, we provided data supporting the relationship between the plasma Al level and cognitive impairment, proposing valuable interventions. There were some limitations to our study. First, our study may not fully assess the temporal relationship between risk factors and cognitive outcome, and a longitudinal follow-up study is needed to clarify this issue. Second, recall bias may occur in the collection of general demographic data, which may exaggerate or minimise the association between exposure and outcome. Third, the number of cases was still limited. Finally, there were no women in the factory, and consequently data for women are lacking.

## CONCLUSIONS

In conclusion, cognitive impairment is no longer a specific disease of elderly people, electrolytic workers may be at more risk. We observed a significant association between the plasma Al concentration and cognitive impairment in a Chinese aluminium factory population, and the result of our study imply plasma Al concentration is a significant risk. The workers with higher education level may understand more about the impairment of aluminium on health, and more successful protective measures, thus indicating that high education level could decrease the risk in our study. Our findings require confirmation in other regions, but they may have important implications for public health. Given the large sample of Al workers in China, the cognitive function of Al workers must be seriously considered.

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**Contributors** QN and HM: study design; HM, JG and YZ: questionnaire training and diagnosis; SSW, SZ and YZ: data input and sorting; HM and SSW: experiment and data analyses; HM: manuscript writing; QN: revision.

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