HHS Public Access

Author manuscript

J Trace Elem Med Biol. Author manuscript; available in PMC 2021 May 01.

Published in final edited form as:

J Trace Elem Med Biol. 2020 May ; 59: 126469. doi:10.1016/j.jtemb.2020.126469.

Characterization of bone aluminum, a potential biomarker of cumulative exposure, within an occupational population from Zunyi, China

Zainab Hasan[a], **Danelle Rolle-McFarland**[b], **Yingzi Liu**[c], **Jieqiong Zhou**[d], **Farshad Mostafaei**[e], **Yan Li**[f], **Qiyuan Fan**[g], **Yuanzhong Zhou**[f], **Wei Zheng**[a], **Linda H. Nie**[a,#], **Ellen M. Wells**[a,*,#]

[a]School of Health Sciences, Purdue University, West Lafayette, IN, USA

[b]Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

[c]Department of Radiation Oncology, Emory University, Atlanta, GA, USA

[d]School of Public Health, Yale University, New Haven, CT, USA

[e]Department of Radiation Oncology, University of Arizona, Tucson, AZ, USA

[f]School of Public Health, Zunyi Medical University, Zunyi, Guizhou, China

[g]Zunyi Medical and Pharmaceutical College, Zunyi, Guizhou, China

Abstract

Objectives—Aluminum (Al) is a neurotoxicant; however, efforts to understand Al toxicity are limited by the lack of a quantitative biomarker of cumulative exposure. Bone Al measurements may address this need. Here, we describe and compare non-invasive bone Al measurements with fingernail Al and Al cumulative exposure indices (CEIs).

Methods—We completed a cross-sectional study of 43 factory workers in Zunyi, China. Bone Al measurements were taken with a compact *in-vivo* neutron activation analysis system (IVNAA). Fingernail samples were analyzed using inductively coupled plasma mass spectrometry. CEIs,

*Corresponding author: Ellen M. Wells, address: Purdue University, School of Health Sciences, Hampton Hall 1269, 550 Stadium Mall Drive, West Lafayette, IN 47907-2051, wells54@purdue.edu.

#These authors made equal contributions to the work

Author CRediT statement

Zainab Hasan: Conceptualization; Methodology; Formal Analysis; Writing – Original Draft **Danelle Rolle-McFarland:** Investigation; Data Curation **Yingzi Liu:** Methodology; Investigation; Data Curation **Jieqiong Zhou:** Data Curation **Farshad Mostafaei:** Investigation **Yan Li:** Resources; Investigation; Supervision; Project Administration; Funding Acquisition **Qiyuan Fan:** Resources; Supervision; Project Administration **Yuanzhong Zhou:** Resources; Investigation; Supervision **Wei Zheng:** Resources; Supervision; Project Administration; Funding Acquisition **Linda H. Nie:** Conceptualization; Methodology; Validation; Writing – Review and Editing; Supervision; Funding Acquisition **Ellen M. Wells:** Conceptualization; Methodology; Validation; Writing – Review and Editing; Supervision; Funding Acquisition

Declaration of interests

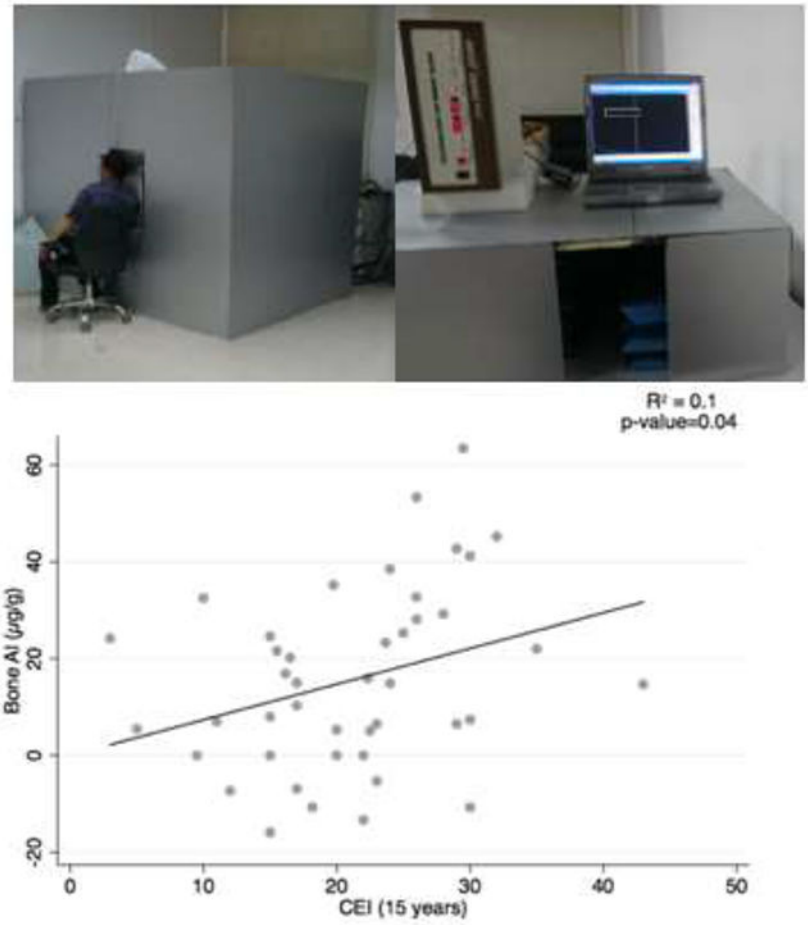
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

based on self-reported work history and prior literature, were calculated for the prior 5, 10, 15, 20 years and lifetime work history. Linear regressions adjusted for age and education compared fingernail Al and Al CEIs with bone Al.

Results—Median (interquartile range (IQR)) Al measurements were: 15 μg/g dry bone (IQR=28) for bone Al; 34.9 μg/g (43.3) for fingernail; and 24 (20) for lifetime CEI. In adjusted regression models, an increase in 15-year CEI was significantly associated with increased bone Al (β=0.91, 95% confidence interval (CI): 0.16, 1.66). Associations of bone Al with 10- and 20-year CEI were approaching statistical significance (β=0.98, 95% CI: −0.14, 2.1; β=0.59, 95% CI: −0.01, 1.18, respectively). Other models were not statistically significant.

Conclusions—Bone Al was significantly associated with 15-year Al CEI, but not other Al CEIs or fingernail Al. Bone Al may be a useful measure of cumulative, rather than short-term, Al exposure. Additional refinement of this method is ongoing.

Graphical abstract



Keywords

biomarker; aluminum; nail; bone; cumulative exposure index; neutron activation analysis

Introduction

Aluminum (Al) is the most abundant metal in the earth's crust and it widely used in a variety of products including cans, siding, foil, food additives, analgesics, antiperspirants, and cosmetics [1]. Several review articles have highlighted research suggesting that exposure to high concentrations of Al is associated with impaired neurological function [2–9]. More specifically, higher Al exposure has been linked with reduced performance on the digit-symbol test [3,10], attention-switching tests [10], visual reaction times and tests of memory [11,12], memory loss and balance issues [13], and motor function [14]. Al has also been suggested as a risk factor for Alzheimer's disease (AD) [8,15,16]. However, the relationship of Al with AD remains highly controversial due in part to concerns that accumulation of Al in the brain in AD patients could be a consequence rather than a cause of the disease [4,5,17].

Thus, studies are needed that can establish that Al exposure occurred before onset of AD. However, this is challenging, as development of AD occurs over many years or decades [18,19], yet standard quantitative methods to assess Al exposure reflect much shorter time periods. The most commonly used Al biomarkers are Al in serum, plasma or urine; these are considered to be reflective of short-term exposure, i.e., exposure within the past several days or weeks [2,6]. Several recent studies have measured Al in nails (toenail or fingernail) [20–22]. The growth rate of nails and a recent evaluation of other metals in toenail suggest that nail Al might reflect a longer time period, *e.g.*, several months [23,24]. Benefits of nail biomarkers are that their collection is non-invasive and they represent a longer exposure period than blood or urine. However, the time period reflected still falls short of multiple years; thus it may not accurately reflect lifetime work exposure.

Cumulative, or long-term, exposure to Al has traditionally been evaluated using semi-quantitative methods such as cumulative exposure indices (CEIs). CEIs typically incorporate a combination of air sampling and work history data to summarize the total inhaled concentration over time [25,26]. CEIs for Al have been used in several occupational studies, which reported a significant association between cumulative workplace Al exposure with headaches and insomnia [26] as well as reduced balance and coordination [13]. Another study evaluating cumulative occupational Al assessed with CEIs did not observe an association of Al with Alzheimer's disease [27]. An advantage of CEIs is that they can be constructed to reflect different time periods; however, a disadvantage is their reliance on work histories that are often self-reported or collected for purposes other than research.

Bone Al is a potentially useful quantitative biomarker of cumulative exposure as several metals, including aluminum, are stored for long periods in bone tissue. One case study estimated the half-life of cortical bone Al to be up to 29 years [28]. Furthermore, >50% of the body burden of Al is stored in bone [29,30]. Bone tissue collected during iliac crest biopsies have been used to quantify Al concentration among individuals with renal failure [31,32]. However, this highly invasive procedure is not a viable option to assess Al exposure for routine screenings or research studies.

Members of our research team and others have developed and validated the use of *in vivo* neutron activation analysis (IVNAA) as a non-invasive method for quantitative assessment of bone manganese [33,34] and more recently bone Al [35,36]. To date, very few studies have utilized IVNAA to assess bone Al, including: a study of 7 renal failure patients [35], and a small cross-sectional study of 18 healthy participants and 6 Al welders [37].

The availability of a quantitative measure of cumulative Al exposure could help address outstanding questions regarding associations between Al exposure and chronic disease such as Alzheimer's disease or other dementias [38]. The IVNAA technology is a newer, non-invasive method which could address this gap, but research in human populations and research which could establish the time period of exposure reflected by bone Al is lacking. Therefore, in this study we report the distribution of bone Al concentrations measured with IVNAA among Chinese workers and determine the correlation of bone Al with fingernail Al and Al CEIs that reflect exposure over different time periods.

Materials and methods

Study design and population

This cross-sectional study took place in Zunyi, China in collaboration with Zunyi Medical University. Prior publications from this study have focused on studies utilizing bone manganese [39,40]; data on Al exposure were also collected as a secondary part of the study design. Participants signed written informed consent in Chinese prior to their participation. This study was approved by the Purdue University Biomedical Institutional Review Board and the Zunyi Medical University Ethical Review Board.

Adult (≥18 years) males employed at a manufacturing facility or a ferroalloy smelting factory in Zunyi, China were eligible for the study. Figure 1 presents a flowchart depicting selection of study participants. Exclusion criteria included: participation of another research project with procedures involving radiation exposure in the past year; active neurological or psychiatric disease; and cognitive symptoms related to traumatic brain injury. No participants were excluded based on these criteria. A total of 61 workers (30 manufacturing; 31 ferroalloy) were enrolled in the study; however, 18 participants did not have reliable bone Al measurements. One participant did not complete the IVNAA procedure. Five participants were missing the first 5 minutes of the 60 minute decay period (see details on the IVNAA procedure below). Twelve participants had the procedure completed when the gamma ray detector was placed too close to the neutron generator system: the neutron generator produced some Al signal, so when the gamma ray detector was too close to the neutron generator some Al contamination occurred. These 18 participants were excluded from all analyses, leaving a total of N=43. An additional 4 participants did not provide a sufficient quantity of nail sample for laboratory determination of Al; thus, analyses including fingernail Al were limited to N=39.

Participants were asked to come to Zunyi Medical University on a weekday to complete the study; they did not go to work on this day. Participants provided fingernail samples, completed the IVNAA assessment, and completed a 123-item questionnaire to obtain data

on demographics (age and education), lifestyle (body mass index, smoking, drinking), and work history.

Aluminum biomarkers

Details about the fingernail collection and analysis have been reported previously [39]. Briefly, participants were asked to clip all 10 fingernails using a titanium nail clipper. Nails were cleaned with 10 mL of 1% Triton X-100 solution and subsequently placed in an ultrasonic cleaning bath for an hour. Upon completion, samples were rinsed at least five times with distilled deionized water and then moved to a drying oven at 60° C for 24 hours. This process was repeated a second time to reduce the potential for external contamination. Nails were placed in a 2% HNO_3 solution and were placed in a microwave digester in preparation for inductively coupled plasma mass spectrometry (ICP-MS) analysis. ICP-MS analysis was conducted at the Purdue Campuswide Mass Spectrometry Center using an ELEMENT-2 mass spectrometer (ThermoFinnigan, Bremen, Germany). The detection limit for fingernail Al (FnAl) was calculated using previously described methods [41]. Each batch of samples analyzed had different detection limits, therefore; the detection limit ranged from 1.05 to 5.95 μg/g. A total of 2 out of 39 measured samples (5.1%) samples were below the detection limit (DL), these were replaced with the DL/√2.

Bone aluminum (BnAl) measurements were assessed with a compact deuterium-deuterium accelerator-based *in vivo* neutron activation analysis (IVNAA) system [36]. Our research team has developed a transportable version of this technology [33,36,42]. Briefly, participants removed any metal-containing accessories on their right hand and arm. This area was thoroughly washed and then wiped with a 50% alcohol wipe. The participant's right hand was irradiated for 10 minutes followed by a decay period of 5 minutes, and then a 60 minute detection period with the spectrum for the first 5 minutes being saved and used for Al and calcium (Ca) quantifications. The full 60 minute detection period was needed for calculating bone Mn. During the detection period, the participant's hand is placed inside a high-purity germanium (HPGe) detector to quantify γ-rays. The γ-ray spectra were then collected by a digital signal analyzer (Ortec DSPEC Plus) and analyzed by an in-house software [33]. The DL for this method is 11.13 μg Al/g dry bone, which is equivalent to 44.5 μg/g calcium. Measurements in μg/g dry bone can be transformed to μg Al/g calcium by multiplying the results by 4, as explained by Mohseni *et al* (2016) if concentrations apply identical normalization methods they can be readily compared however, when normalization processes differ a rough conversion factor may be used [29]. This method results in some radiation exposure; Purdue's Radiation Safety Committee reviewed the data on potential radiation exposure among participants to ensure that this posed minimal risk to study participants. The estimated radiation exposure from the IVNAA was estimated to be ~11.9 mSv to the hand, which is less than one-tenth the annual limit of radiation dose to the extremities (500 mSv) and the full-body equivalent of this dose is 1/5 of the radiation received from an AP chest x-ray (100 μSv) [36]. Therefore, use of IVNAA was determined to pose minimal risk to study participants.

Among those with BnAl measurements, 7/43 (16.3%) were negative and an additional 13/43 (30.2%) were positive, but below the DL. Thus, overall, 20/43 (46.5%) of samples were

below the DL. Negative values can be observed using this method when the actual concentrations are close to zero [43].

The most common method to address values <DL is replacement with values such as the DL/√2. However, using this approach is only recommended when 2 conditions are met: if there are a few (<10%) data points below the DL, and if the data points are not exceedingly skewed [44,45]. Otherwise replacement methods may introduce additional bias [45]. Thus, although there is unquestionably substantial variability within values <DL, use of the observed values still allows us characterize relative exposure among those with BnAl <DL, while minimizing potential bias. Similarly, while it is true that values below the DL may have more uncertainty, simply eliminating them from analysis also runs the risk of inducing bias in our analysis due to left-censoring. Previous papers on bone Pb concentrations (with x-ray fluorescence method) showed that retaining all point estimates, including below DL and negative estimates, provides less bias in comparing the mean or median levels of bone lead of different populations [46]. For these reasons, we chose to retain values <DL in statistical analyses has been used previously in studies with bone metal assessments.

Cumulative exposure indices (CEIs)

Cumulative aluminum exposure was estimated by constructing several CEIs representing exposure over the prior 5, 10, 15, 20 years and lifetime exposure. We used a distinct exposure groups approach to determine the magnitude of occupational Al exposure; this method assumes individuals with similar job titles have similar exposures [47]. Prior research documenting air Al concentrations with specific jobs as well as government assessments of job titles which have similar functions were used to develop definitions of which jobs were estimated to be low exposure (assigned a value of 1), moderate exposure (2), and high exposure (3) [48–57]. More details regarding determination of distinct exposure groups are available in the Supplemental Material.

Each worker's CEI is calculated as

$$\mathrm{CEI} = \sum_{i=1}^{n} C_i Y_i \quad (1)$$

where C is the exposure group, Y is the duration (years) of employment in a given position, and i indicates the number of positions held by each participant up to a total of n positions. Since the CEIs are based on distinct exposure groups (ranking exposure) rather than specific measurements, our CEIs have no units. The lifetime CEI included the entire reported work history, whereas the other CEIs were limited summarizing work history over the prior 5, 10, 15, or 20 years, as appropriate.

Statistical analyses

The statistical package Stata 14 (College Station, Texas, USA) was used to organize, analyze, and graph data. A p-value <0.05 was assumed to be statistically significant. FnAl, but not BnAl, was lognormally distributed. Therefore, medians and interquartile ranges are presented for descriptive statistics and natural logarithm transformations for FnAl are used in regression analyses. Bivariate associations between FnAl, BnAl, and all CEI measures

were determined with Spearman correlation coefficients and completing unadjusted regression analyses; the latter are depicted with scatter plots. Demographic variables were identified and controlled for in the multiple linear regression models.

Multiple linear regression models controlling for age and education were used to determine the association between BnAl with FnAl and CEI measures. Age and education were included as continuous variables because our bivariate analyses determined that these were strongly correlated with Al exposure. Model coefficients, 95% confidence intervals, and *p*-values are reported.

Results

Mean age for the 43 workers was 46.7 years (standard deviation (SD)=8); mean education was 9.9 years (4). Mean BnAl was 15.6 μg/g dry bone (SD=18.6); further details about the distribution of BnAl are available in Figure S1 and Table S1 (Supplemental Material). Mean (SD) values for CEIs were 5-year CEI: 9 (2.9); 10-year CEI: 16.6 (5.7); 15-year CEI: 21.2 (8); 20-year CEI 24.1 (10); and lifetime CEI: 28.4 (16.6). Among the 39 participants with FnAl measurements, median (interquartile range) FnAl was 34.9 μg/g (43.3).

Eighteen (41.9%) participants worked at the manufacturing factory; 25 (58.1%) worked at the ferroalloy factory. Aluminum exposure measurements and demographic variables stratified by factory are presented in Table 1. 5-year and 10-year CEIs were significantly higher for ferroalloy workers versus manufacturing workers. There was no evidence of a statistically significant difference in FnAl, BnAl, age, education and other CEI measures by factory.

Scatter plots and unadjusted regression lines comparing BnAl with ln(FnAl) and CEI values are presented in Figure 2. There is no evidence of an unadjusted association between BnAl with ln(FnAl). BnAl had a positive association with all CEI measures. This relationship was statistically significant with 15-year CEI (p=0.04) and approaching statistical significance for 20-year CEI (p=0.07), but was not statistically significant for other CEI time periods. Similar graphs comparing ln(FnAl) with other exposure measures are presented in Figure S2 (Supplemental Material). An increase in ln(FnAl) is associated with increased 5-, 10- or 15-year CEI, whereas an increase in ln(FnAl) is related to a decrease in lifetime CEI. However, none of the associations of CEI with FnAl are statistically significant.

Results from adjusted linear regression models comparing ln(FnAl) and CEI with BnAl are presented in Table 2. An increase in 15-year CEI was significantly associated with higher BnAl (β=0.91, 95% confidence interval (CI) = 0.16, 1.66). Results for 20-year CEI were similar, and approaching significance (p=0.05). Higher 10-year CEI was related to higher BnAl, but it was not statistically significant (p=0.09). We did not observe an association between BnAl with FnAl, 5-year CEI or lifetime CEI.

Discussion and conclusion

This study presented measurements of BnAl, FnAl, and Al CEIs among 43 Chinese workers and determined the correlation of BnAl with FnAl and multiple CEIs representing

cumulative Al exposure. There was a significant association between elevated bone Al with higher 15-year CEI; additionally, the association of BnAl with 20-year CEI was approaching statistical significance. However, we did not observe an association between BnAl and FnAl, or BnAl with the other CEIs.

There is substantial variability in reported median nail Al concentrations. Median FnAl concentration reported in this population was 34.9 μg/g, which is greater than prior reports of median FnAl of 14.9 μg/g among 50 healthy, non-occupationally exposed Canadian adults [22], but substantially lower than the median FnAl reported among 59 Nicaraguans from a gold mining community (135.3 μg/g) [58]. Other studies have measured toenail Al instead of fingernail Al. Bergomi *el al.* (2002) report median Al concentration similar to ours: 34.5 μg/g among Italian ALS patients and 37.5 μg/g in healthy adults [21]. Our median FnAl was greater than the median value for toenail Al reported among Pacific Island children (5.44 μg/g) [20]. The source of the variation between these results is unclear, but it could be attributed to differences in age and ethnic background, the extent of Al contamination or exposure in the different regions, or even differences in cleaning procedures to reduce external contamination.

Aslam *et al.* used IVNAA to assess BnAl concentrations on six Canadian welders [37]. They reported mean BnAl equivalent to 10.3 μg/g dry bone, with a range of 8.6 to 11.2 μg/g [37]. This is lower than our reported mean BnAl of 15.6 μg/g dry bone. This difference might be attributable to differences in factory conditions, such as materials used, or to differences in work history between the two populations. For example, at least one participant in our study reported prior employment in the Al industry. In contrast, BnAl values in this study were lower than most studies which measured BnAl via biopsy in patients with renal failure [35,59,60]. This is consistent with evidence from other Al biomarkers: serum Al was reported to be highest in patients with hemodialysis, followed by individuals with occupational Al exposure, and lowest in healthy non-occupationally exposed individuals [61].

We did not observe an association between BnAl and FnAl. This is consistent with evidence suggesting that nail and bone represent very different time periods with regards to exposure and metal accumulation in the body; the metal in nail presents the prior 2-12 months of exposure for nail [20–22,62] while the metals in bone reflect the past several years exposure [28]. We observed a positive (albeit not statistically significant) relationship between FnAl with 5- and 10-year CEI; this positive association was not apparent at the longer time-periods (Figure S2). This is also consistent with evidence that nails tend to reflect shorter-term exposures.

We observed a statistically significant relationship between increasing BnAl with increasing 15 year CEI after adjusting for age and education (Table 2). Additionally, the relationship of BnAl with 10-year and 20-year CEI, although not statistically significant, appeared stronger than other CEI measurements. This is consistent with prior evidence that metals measured in bone are representative of long term exposure [39,63]. Of note is that we did not observe a significant association between BnAl and lifetime CEI. This is similar to the results we

previously reported with bone manganese [39], and suggests that while the half-life of bone Al is relatively long, it might not reflect multiple decades of exposure.

There are some limitations of this study. Although our sample size for this study is the largest to date which incorporates IVNAA-based BnAl measurements, it is still a relatively small sample. Additionally, our CEI relied on work history to determine relative cumulative Al exposure. It is true that we could have likely added some precision if air sampling data were available for this population. However, the use of work history to compose the CEI is an established method [13] which is sufficiently robust to estimate the relative ranking of exposure within our study population over their working lifetime. While this is not precise enough to estimate thresholds of exposure or determine regulatory guidelines, this precision is sufficient to determine correlations of higher or lower exposure at different time periods with BnAl measurements, which was our goal in this study.

As the IVNAA method to quantify BnAl has been developed relatively recently, the detection limit for BnAl is relatively high, which limits the usefulness of this method in populations without occupational exposure. The detection limit can be reduced in future studies by reconstructing the irradiation cave, rearranging the irradiation/decay/measurement time, and reducing the background with more shielding on the detection system, actions which our group is currently taking.

This study also has several strengths. This is the largest study to date that we are aware of to use INVAA BnAl measurements to quantify long-term aluminum exposures within an occupational population, and the first to compare BnAl with an estimate of cumulative Al exposure. Our results suggest BnAl is significantly associated with the prior 15-years of Al exposure and that IVNAA to assess BnAl can be used in field epidemiology studies. The availability of IVNAA to determine a quantitative measure of cumulative Al exposure has the potential to be highly valuable for studies evaluating the potential association between Al exposure with health outcomes that have a long latency period, such as Alzheimer’s disease.

In conclusion, our data suggest BnAl assessed with IVNAA reflects cumulative Al exposure over the past ~15 years. Future efforts will focus on lowering the detection limit and comparing BnAl with additional biomarkers of exposure in larger populations. Meanwhile, our current results represent an important step forward in the development of a quantitative biomarker of cumulative Al exposure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding This research was funded by the National Natural Science Foundation of China under Grant 81760582; the Natural Science Foundation of Guizhou Provincial Scientific and Technology Department under Grant 2017-1215; the International Scientific and Technology cooperation project of Guizhou Province under Grant G2014-7012; the Innovative Talent Team Training Project of Zunyi City under Grant 2015-42; the United States National Institute of Occupational Safety and Health under Grants R21OH010700 and T03OH008615; and the United States National Institute of Environmental Health Sciences under Grant RO1ES027078.

Abbreviations

Al	Aluminum
BnAl	Bone aluminum
Ca	Calcium
CI	Confidence interval
CEI	Cumulative Exposure Index
DL	Detection limit
FnAl	Fingernail aluminum
HPGe	High purity germanium
IVNAA	In vivo neutron activation analysis
ICP-MS	Inductively coupled plasma mass spectrometry
IQR	Interquartile range
SD	Standard deviation

References:

[1]. ATSDR, Toxicological profile for Aluminum, Agency for Toxic Substances and Disease Registry (ATSDR), U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA, 2008 https://www.atsdr.cdc.gov/toxprofiles/TP.asp?id=191&tid=34 (accessed September 10, 2019).

[2]. Riihimäki V, Aitio A, Occupational exposure to aluminum and its biomonitoring in perspective, Critical Reviews in Toxicology. 42 (2012) 827–853. 10.3109/10408444.2012.725027. [PubMed: 23013241]

[3]. Meyer-Baron M, Schäper M, Knapp G, van Thriel C, Occupational aluminum exposure: evidence in support of its neurobehavioral impact, Neurotoxicology. 28 (2007) 1068–1078. 10.1016/j.neuro.2007.07.001. [PubMed: 17692380]

[4]. Willhite CC, Karyakina NA, Yokel RA, Yenugadhati N, Wisniewski TM, Arnold IMF, Momoli F, Krewski D, Systematic review of potential health risks posed by pharmaceutical, occupational and consumer exposures to metallic and nanoscale aluminum, aluminum oxides, aluminum hydroxide and its soluble salts, Crit. Rev. Toxicol 44 Suppl 4 (2014) 1–80. 10.3109/10408444.2014.934439.

[5]. Klotz K, Weistenhöfer W, Neff F, Hartwig A, van Thriel C, Drexler H, The Health Effects of Aluminum Exposure, Dtsch Arztebl Int. 114 (2017) 653–659. 10.3238/arztebl.2017.0653. [PubMed: 29034866]

[6]. Krewski D, Yokel RA, Nieboer E, Borchelt D, Cohen J, Harry J, Kacew S, Lindsay J, Mahfouz AM, Rondeau V, Human Health Risk Assessment for Aluminium, Aluminium Oxide, and Aluminium Hydroxide, Journal of Toxicology and Environmental Health, Part B. 10 (2007) 1–269. 10.1080/10937400701597766.

[7]. Kawahara M, Effects of aluminum on the nervous system and its possible link with neurodegenerative diseases, J. Alzheimers Dis 8 (2005) 171–182; discussion 209-215. [PubMed: 16308486]

[8]. Yokel RA, The toxicology of aluminum in the brain: a review, Neurotoxicology. 21(2000) 813–828. [PubMed: 11130287]

[9]. Zatta P, Lucchini R, van Rensburg SJ, Taylor A, The role of metals in neurodegenerative processes: aluminum, manganese, and zinc., Brain Res Bull. 62 (2003) 15–28. [PubMed: 14596888]

[10]. Buchta A M, Kiesswetter B E, Schäper B M, Zschiesche C W, Schaller D KH, Kuhlmann A A, Letzel A S, Neurotoxicity of exposures to aluminium welding fumes in the truck trailer construction industry, Environ. Toxicol. Pharmacol 19 (2005) 677–685. 10.1016/j.etap.2004.12.036. [PubMed: 21783542]

[11]. Hänninen H, Matikainen E, Kovala T, Valkonen S, Riihimäki V, Internal load of aluminum and the central nervous system function of aluminum welders, Scand J Work Environ Health. 20 (1994) 279–285. [PubMed: 7801073]

[12]. Riihimäki V, Hänninen H, Akila R, Kovala T, Kuosma E, Paakkulainen H, Valkonen S, Engström B, Body burden of aluminum in relation to central nervous system function among metal inert-gas welders, Scand J Work Environ Health. 26 (2000) 118–130. [PubMed: 10817377]

[13]. White DM, Longstreth WT, Rosenstock L, Claypoole KH, Brodkin CA, Townes BD, Neurologic syndrome in 25 workers from an aluminum smelting plant, Arch. Intern. Med 152 (1992) 1443–1448. [PubMed: 1627023]

[14]. Sjögren B, Iregren A, Freeh W, Hagman M, Johansson L, Tesarz M, Wennberg A, Effects on the nervous system among welders exposed to aluminium and manganese, Occup Environ Med. 53 (1996) 32–40. [PubMed: 8563855]

[15]. Tomljenovic L, Aluminum and Alzheimer's disease: after a century of controversy, is there a plausible link?, J. Alzheimers Dis 23 (2011) 567–598. 10.3233/JAD-2010-101494. [PubMed: 21157018]

[16]. Bondy SC, Low levels of aluminum can lead to behavioral and morphological changes associated with Alzheimer's disease and age-related neurodegeneration, Neurotoxicology. 52 (2016) 222–229. 10.1016/j.neuro.2015.12.002. [PubMed: 26687397]

[17]. Caito S, Aschner M, Neurotoxicity of metals, Handb Clin Neurol. 131 (2015) 169–189. 10.1016/B978-0-444-62627-1.00011-1. [PubMed: 26563789]

[18]. Meng X-F, Yu J-T, Wang H-F, Tan M-S, Wang C, Tan C-C, Tan L, Midlife vascular risk factors and the risk of Alzheimer's disease: a systematic review and meta-analysis, J. Alzheimers Dis 42 (2014) 1295–1310. 10.3233/JAD-140954. [PubMed: 25024338]

[19]. Solomon A, Kivipelto M, Wolozin B, Zhou J, Whitmer RA, Midlife serum cholesterol and increased risk of Alzheimer's and vascular dementia three decades later, Dement Geriatr Cogn Disord. 28 (2009) 75–80. 10.1159/000231980. [PubMed: 19648749]

[20]. Karatela S, Ward N, Zeng IS, Paterson J, Status and interrelationship of toenail elements in Pacific children., Journal of Trace Elements in Medicine and Biology : Organ of the Society for Minerals and Trace Elements. 46 (2018) 10–16. 10.1016/jjtemb.2017.11.004.

[21]. Bergomi M, Vinceti M, Nacci G, Pietrini V, Brätter P, Alber D, Ferrari A, Vescovi L, Guidetti D, Sola P, Malagu S, Aramini C, Vivoli G, Environmental exposure to trace elements and risk of amyotrophic lateral sclerosis: a population-based case-control study, Environ. Res 89 (2002) 116–123. 10.1006/enrs.2002.4361. [PubMed: 12123644]

[22]. Goullé JP, Saussereau E, Mahieu L, Bouige D, Groenwont S, Guerbet M, Lacroix C, Application of inductively coupled plasma mass spectrometry multielement analysis in fingernail and toenail as a biomarker of metal exposure, J Anal Toxicol. 33 (2009) 92–98. 10.1093/jat/33.2.92. [PubMed: 19239734]

[23]. Bakri SFZ, Hariri A, Ma'arop NF, Hussin N.S. a. W., Toenail as Non-invasive Biomarker in Metal Toxicity Measurement of Welding Fumes Exposure - A Review, MS&E. 165 (2017) 012019 10.1088/1757-899X/165/1/012019.

[24]. Ward EJ, Edmondson DA, Nour MM, Snyder S, Rosenthal FS, Dydak U, Toenail Manganese: A Sensitive and Specific Biomarker of Exposure to Manganese in Career Welders, Annals of Work Exposures and Health. 62 (2018) 101–111. 10.1093/annweh/wxx091.

[25]. Armstrong BG, Tremblay CG, Cyr D, Thériault GP, Estimating the relationship between exposure to tar volatiles and the incidence of bladder cancer in aluminum smelter workers, Scand J Work Environ Health. 12 (1986) 486–493. 10.5271/sjweh.2109. [PubMed: 3787220]

[26]. Sińczuk-Walczak H, Szymczak M, Raźniewska G, Matczak W, Szymczak W, Effects of occupational exposure to aluminum on nervous system: clinical and electroencephalographic findings, Int J Occup Med Environ Health. 16 (2003) 301–310. [PubMed: 14964639]

[27]. Graves AB, Rosner D, Echeverria D, Mortimer JA, Larson EB, Occupational exposures to solvents and aluminium and estimated risk of Alzheimer's disease, Occup Environ Med. 55 (1998) 627–633. 10.1136/oem.55.9.627. [PubMed: 9861186]

[28]. Priest ND, The biological behaviour and bioavailability of aluminium in man, with special reference to studies employing aluminium-26 as a tracer: review and study update, J Environ Monit. 6 (2004) 375–403. 10.1039/b314329p. [PubMed: 15152306]

[29]. Mohseni HK, Matysiak W, Chettle DR, Byun SH, Priest N, Atanackovic J, Prestwich WV, Optimization of data analysis for the in vivo neutron activation analysis of aluminum in bone, Appl Radiat Isot. 116 (2016) 34–40. 10.1016/j.apradiso.2016.07.004. [PubMed: 27474904]

[30]. Comsa DC, Prestwich WV, McNeill FE, Byun SH, Application of spectral decomposition analysis to in vivo quantification of aluminum by neutron activation analysis, Appl Radiat Isot. 61 (2004) 1353–1360. 10.1016/j.apradiso.2004.03.062. [PubMed: 15388133]

[31]. Norris KC, Goodman WG, Howard N, Nugent ME, Coburn JW, Iliac crest bone biopsy for diagnosis of aluminum toxicity and a guide to the use of deferoxamine, Semin. Nephrol 6 (1986) 27–34. [PubMed: 3299590]

[32]. Kriegshauser JS, Swee RG, McCarthy JT, Hauser MF, Aluminum toxicity in patients undergoing dialysis: radiographic findings and prediction of bone biopsy results, Radiology. 164 (1987) 399–403. 10.1148/radiology.164.2.3602376. [PubMed: 3602376]

[33]. Liu Y, Byrne P, Wang H, Koltick D, Zheng W, Nie LH, A compact DD neutron generator-based NAA system to quantify manganese (Mn) in bone in vivo., Physiol Meas. 35 (2014) 1899–1911. 10.1088/0967-3334/35/9/1899. [PubMed: 25154883]

[34]. Liu Y, Mostafaei F, Sowers D, Hsieh M, Zheng W, Nie LH, Customized compact neutron activation analysis system to quantify manganese (Mn) in bone in vivo, Physiological Measurement. 38 (2017) 452–465. 10.1088/1361-6579/aa577b. [PubMed: 28060775]

[35]. Wyatt RM, Ryde SJ, Morgan WD, McNeil EA, Hainsworth IR, Williams AJ, The development of a technique to measure bone aluminium content using neutron activation analysis, Physiol Meas. 14 (1993) 327–335. 10.1088/0967-3334/14/3/011. [PubMed: 8401272]

[36]. Byrne P, Mostafaei F, Liu Y, Blake SP, Koltick D, Nie LH, The study of in vivo quantification of aluminum (Al) in human bone with a compact DD generator-based neutron activation analysis (NAA) system, Physiol Meas. 37 (2016) 649–660. 10.1088/0967-3334/37/5/649. [PubMed: 27093035]

[37]. Aslam K Davis A Pejović-Milić DR Chettle, Noninvasive measurement of aluminium in human bone: preliminary human study and improved system performance, J. Inorg. Biochem 103 (2009) 1585–1590. 10.1016/j.jinorgbio.2009.07.021. [PubMed: 19740544]

[38]. Lukiw WJ, Kruck TPA, Percy ME, Pogue AI, Alexandrov PN, Walsh WJ, Sharfman NM, Jaber VR, Zhao Y, Li W, Bergeron C, Culicchia F, Fang Z, McLachlan DRC, Aluminum in neurological disease - a 36 year multicenter study, J Alzheimers Dis Parkinsonism. 8 (2019). 10.4172/2161-0460.1000457.

[39]. Rolle-McFarland D, Liu Y, Zhou J, Mostafaei F, Zhou Y, Li Y, Fan Q, Zheng W, Nie LH, Wells EM, Development of a Cumulative Exposure Index (CEI) for Manganese and Comparison with Bone Manganese and Other Biomarkers of Manganese Exposure, Int J Environ Res Public Health. 15 (2018). 10.3390/ijerphl5071341.

[40]. Liu Y, Rolle-McFarland D, Mostafaei F, Zhou Y, Li Y, Zheng W, Wells Ellen, Nie LH, In vivo neutron activation analysis of bone manganese in workers, Physiol. Meas 39 (2018) 035003 10.1088/1361-6579/aaa749. [PubMed: 29328060]

[41]. Long GL, Winefordner JD, Limit of Detection A Closer Look at the IUPAC Definition, Anal. Chem 55 (1983) 712A–724A. 10.1021/ac00258a724.

[42]. Mostafaei F, Blake SP, Liu Y, Sowers DA, Nie LH, Compact DD generator-based neutron activation analysis (NAA) system to determine fluorine in human bone in vivo: a feasibility study, Physiol Meas. 36 (2015) 2057–2067. 10.1088/0967-3334/36/10/2057. [PubMed: 26289795]

[43]. van Wijngaarden E, Campbell JR, Cory-Slechta DA, Bone lead levels are associated with measures of memory impairment in older adults., Neurotoxicology. 30 (2009) 572–580. 10.1016/j.neuro.2009.05.007. [PubMed: 19477197]

[44]. Glass DC, Gray CN, Estimating mean exposures from censored data: exposure to benzene in the Australian petroleum industry, Ann Occup Hyg. 45 (2001) 275–282. [PubMed: 11378148]

[45]. Dinse GE, Jusko TA, Ho LA, Annam K, Graubard BI, Hertz-Picciotto I, Miller FW, Gillespie BW, Weinberg CR, Accommodating measurements below a limit of detection: a novel application of Cox regression, Am. J. Epidemiol 179 (2014) 1018–1024. 10.1093/aje/kwu017. [PubMed: 24671072]

[46]. Kim R, Aro A, Rotnitzky A, Amarasiriwardena C, Hu H, K x-ray fluorescence measurements of bone lead concentration: the analysis of low-level data, Phys Med Biol. 40 (1995) 1475–1485. [PubMed: 8532760]

[47]. Noth EM, Dixon-Emst C, Liu S, Cantley L, Tessier-Sherman B, Eisen EA, Cullen MR, Hammond SK, Development of a job-exposure matrix for exposure to total and fine particulate matter in the aluminum industry, J Expo Sci Environ Epidemiol. 24 (2014) 89–99. 10.1038/jes.2013.53. [PubMed: 24022670]

[48]. Chan-Yeung M, Wong R, Maclean L, Tan F, Schulzer M, Enarson D, Martin A, Dennis R, Grzybowski S, Epidemiologic Health Study of Workers in an Aluminum Smelter in British Columbia: Effects on the Respiratory System, American Review of Respiratory Disease. 127 (1983) 465–469. 10.1164/arrd.1983.127.4.465. [PubMed: 6838051]

[49]. Kezunovi CL, Stamatović S, Stamatović B, Jovanović J, ONE-YEAR PREVALENCE OF MUSCULOSKELETAL SYMPTOMS IN ALUMINUM INDUSTRY PORTROOM WORKERS, in: Medicine and Biology, 2004: pp. 148–153. https://pdfs.semanticscholar.org/a033/538e52d0925e8a896bc3c064d43259384732.pdf?_ga=2.196063209.456626857.1575315662-383535074.1575315662.

[50]. Sanitizers and Disinfectants: The Chemicals of Prevention, Food Safety Magazine. (2012). https://www.foodsafetymagazine.com/magazine-archivel/augustseptember-2011/sanitizers-and-disinfectants-the-chemicals-of-prevention/ (accessed September 10, 2019).

[51]. United Nations, ed., International Standard industrial classification of all economic activities (ISIC), Rev. 4, United Nations, New York, 2008.

[52]. van Vuuren B, van Heerden HJ, Zinzen E, Becker P, Meeusen R, Perceptions of work and family assistance and the prevalence of lower back problems in a South African manganese factory, Ind Health. 44 (2006) 645–651. 10.2486/indhealth.44.645. [PubMed: 17085927]

[53]. Quality Control Inspectors : Occupational Outlook Handbook:: U.S. Bureau of Labor Statistics, (n.d.). https://www.bls.gov/ooh/production/quality-control-inspectors.htm (accessed September 10, 2019).

[54]. Electricians : Occupational Outlook Handbook: : U.S. Bureau of Labor Statistics, (n.d.). https://www.bls.gov/ooh/construction-and-extraction/electricians.htm#tab-8 (accessed September 10, 2019).

[55]. Machinists and Tool and Die Makers : Occupational Outlook Handbook: : U.S. Bureau of Labor Statistics, (n.d.). https://www.bls.gov/ooh/production/machinists-and-tool-and-die-makers.htm (accessed September 10, 2019).

[56]. Water and Wastewater Treatment Plant and System Operators : Occupational Outlook Handbook: : U.S. Bureau of Labor Statistics, (n.d.). https://www.bls.gov/ooh/production/water-and-wastewater-treatment-plant-and-system-operators.htm (accessed September 10, 2019).

[57]. Beach R, Bullock A, Heller K, Domanico J, Muth M, O'Connor A, Spooner R, Lime Production: Industry Profile, Research Triangle Park Institute, Research Triangle Park, NC, 2000 https://www3.epa.gov/ttnecas1/regdata/IPs/Lime%20Manufacturing_IP.pdf (accessed January 19, 2018).

[58]. Saunders JE, Jastrzembski BG, Buckey JC, Enriquez D, MacKenzie TA, Karagas MR, Hearing loss and heavy metal toxicity in a Nicaraguan mining community: audiological results and case reports, Audiol. Neurootol 18 (2013) 101–113. 10.1159/000345470. [PubMed: 23257660]

[59]. Wilhelm M, Passlick J, Busch T, Szydlik M, Ohnesorge FK, Scalp hair as an indicator of aluminium exposure: comparison to bone and plasma, Hum Toxicol. 8 (1989) 5–9. 10.1177/096032718900800102. [PubMed: 2785480]

[60]. Winterberg B, Hair analysis for aluminum monitoring in patients on long-term hemodialysis, Trace Elements in Medicine. (1987).

[61]. Chappuis P, de Vemejoul MC, Paolaggi F, Rousselet F, Relationship between hair, serum and bone aluminium in hemodialyzed patients, Clin. Chim. Acta 179 (1989) 271–278. 10.1016/0009-8981(89)90089-2. [PubMed: 2714000]

[62]. Grashow R, Zhang J, Fang SC, Weisskopf MG, Christiani DC, Cavallari JM, Toenail metal concentration as a biomarker of occupational welding fume exposure., J Occup Environ Hyg. 11 (2014) 397–405. 10.1080/15459624.2013.875182. [PubMed: 24372360]

[63]. Shih RA, Hu H, Weisskopf MG, Schwartz BS, Cumulative lead dose and cognitive function in adults: a review of studies that measured both blood lead and bone lead., Environ Health Perspect. 115 (2007) 483–492. 10.1289/ehp.9786. [PubMed: 17431502]

Highlights

- Occupational aluminum exposure has been associated with neurologic outcomes; however, research in this area is limited by the lack of a quantitative measure of cumulative aluminum exposure.
- *In vivo* neutron activation analysis (IVNAA) has been developed as a non-invasive method to assess bone manganese, and may also be useful to assess bone aluminum.
- We demonstrate the feasibility of using IVNAA in an occupationally exposure population, and provide evidence suggesting that bone aluminum reflects approximately 15 years of aluminum exposure.
- As the detection limit for IVNAA continues to improve, it may serve as an effective tool for measuring cumulative exposures in occupational and clinical settings.

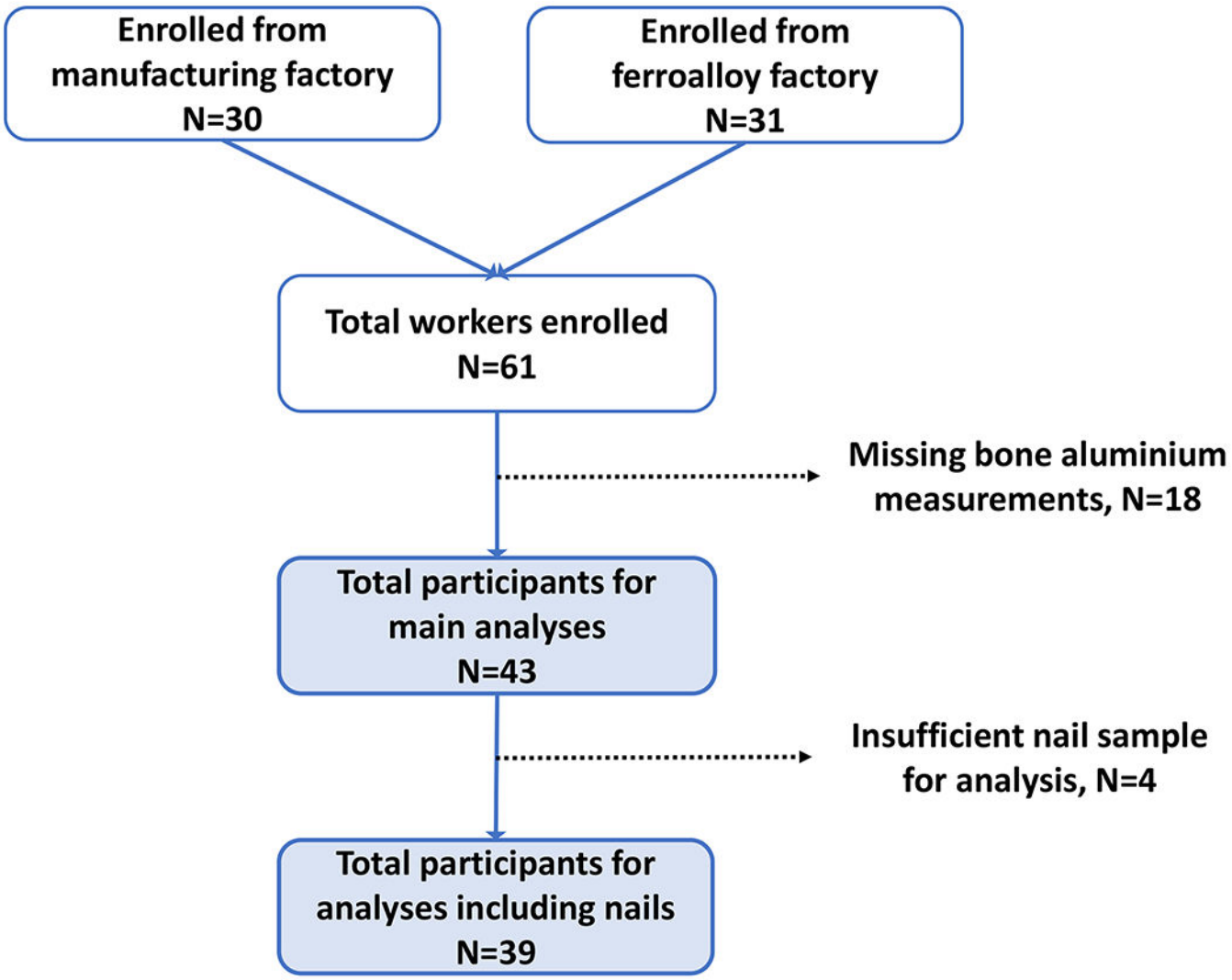


Figure 1:
Flowchart depicting selection of study participants.

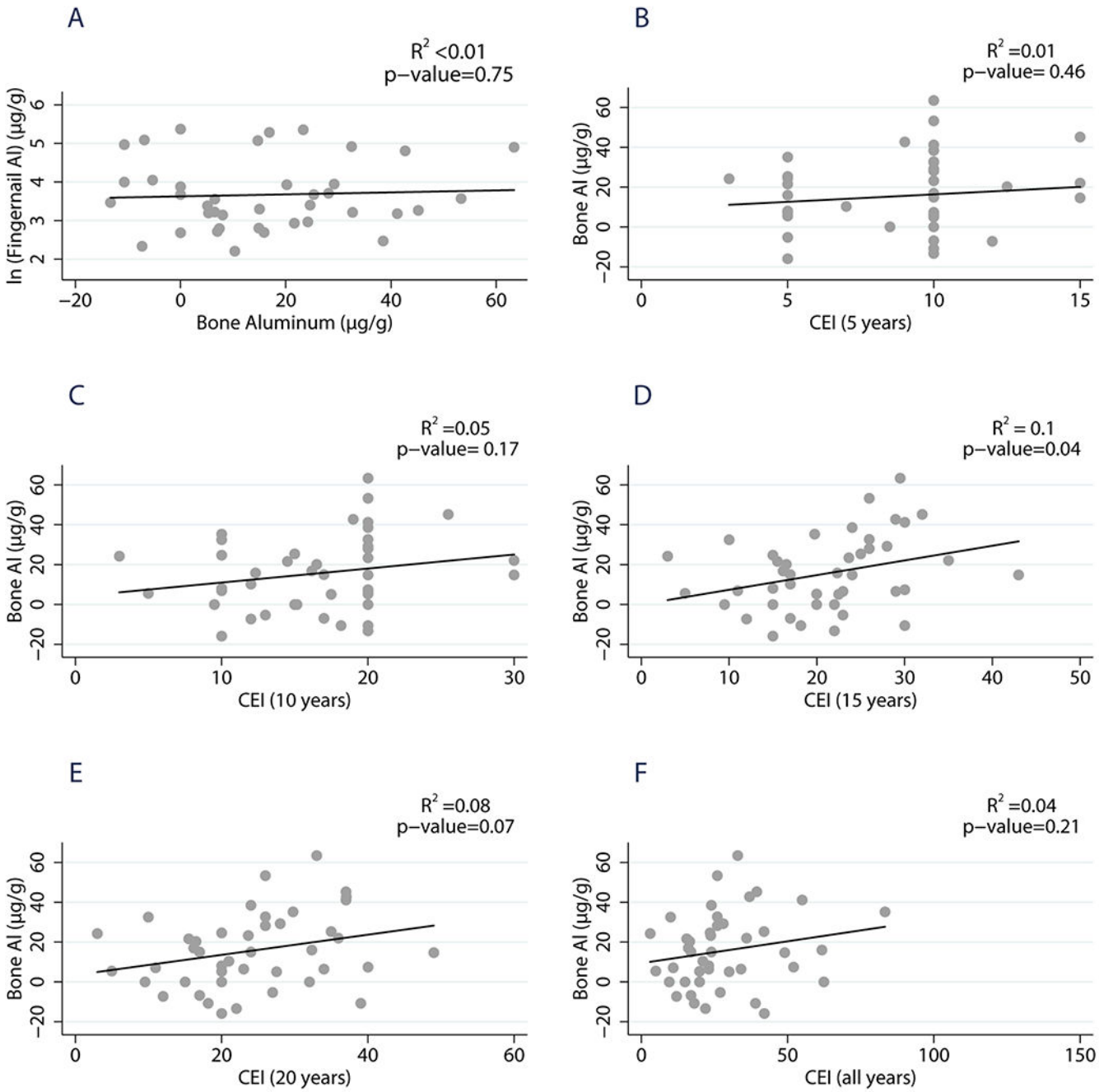


Figure 2.

Scatter plot and unadjusted regression line for bone aluminum (µg/g dry bone) with A: ln(FnAl) (µg/g); B: 5 year CEI; C: 10 year CEI; D: 15 year CEI; E: 20 year CEI; F: lifetime CEI.

Table 1.

Population characteristics and aluminium measurements, stratified by factory.

Variable	Manufacturing Facility			Ferroalloy Facility			*p*-value[a]
	N	Mean (SD)	Median (IQR)	N	Mean (SD)	Median (IQR)	
FnAl, μg/g	15	52.06 (50.5)	26.2 (47.6)	24	67.56 (66.72)	37.32 (63.58)	0.35
BnAl, μg/g dry bone	18	17.02 (20.95)	13.10 (27.00)	25	14.63 (17.14)	14.90 (24.60)	0.68
5-year CEI	18	7.33 (3.29)	5.00 (5.00)	25	10.20 (1.87)	10.00 (0)	<0.01
10-year CEI	18	13.30 (5.61)	12.17 (7.01)	25	18.96 (4.46)	20.00 (3.00)	<0.01
15-year CEI	18	18.39 (8.60)	17.00 (13.00)	25	23.26 (7.10)	23.00 (7.83)	<0.05
20-year CEI	18	22.20 (11.29)	20.50 (21.00)	25	25.42 (9.17)	24.00 (8.00)	0.31
Lifetime CEI	18	29.73 (21.47)	25.01 (30.02)	25	27.36 (12.47)	24.00 (10.02)	0.65
Education, years	18	10.94 (4.28)	10.50 (8.00)	25	9.16 (3.70)	9.00 (5.00)	0.15
Age, years	18	47.39 (10.22)	49.50 (20.00)	25	46.24 (6.11)	45.00 (8.00)	0.65

IQR=interquartile range, Al=aluminum, BnAl=bone Al, 95% CI= 95% confidence interval, FnAl=fingemail Al, CEI=cumulative exposure index. CEI measures have no units.

[a]Student's t test (comparing means).

J Trace Elem Med Biol. Author manuscript; available in PMC 2021 May 01.

Table 2.

Results from adjusted linear regression models predicting bone aluminium concentrations.

Variable	N	β	95% CI	*p*-value
FnAl, μg/g [a]	39	−0.02	−0.14, 0.10	0.79
5-year CEI	43	1.27	−1.10, 3.63	0.29
10-year CEI	43	0.98	−0.14, 2.10	0.09
15-year CEI	43	0.91	0.16, 1.66	0.02
20-year CEI	43	0.59	−0.01, 1.18	0.05
Lifetime CEI	43	0.22	−0.16, 0.61	0.25

All models are adjusted for age (continuous) and education (continuous). CI=confidence interval, FnAl=fingemail aluminum, CEI=cumulative exposure index.

[a]Natural logarithm of FnAl used in analysis.