HHS Public Access

Author manuscript

Sci Total Environ. Author manuscript; available in PMC 2022 January 20.

Published in final edited form as:

Sci Total Environ. 2021 January 20; 753: 142351. doi:10.1016/j.scitotenv.2020.142351.

Evaluation of a portable XRF device for *in vivo* quantification of lead in bone among a US population

Xinxin Zhang[a], **Aaron J. Specht**[b], **Ellen Wells**[a], **Marc G. Weisskopf**[b,1], **Jennifer Weuve**[c,1], **Linda H. Nie**[a,*,1]

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

[b]Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA

[c]Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA

Abstract

Background: Lead (Pb) concentration in bone is a reliable biomarker for cumulative Pb exposure and studying associated health outcomes. However, the standard K-shell fluorescence (KXRF) bone Pb measurement technology has limitations in large-scale population studies.

Objective: We compared measurements from a portable XRF device and a KXRF device.

Methods: We measured bone Pb concentrations *in vivo* using portable XRF and KXRF, each measured at the midtibia bone in 71 people, 38–95 years of age (mean ± SD = 63 ± 11 years) living in or near three Indiana communities, US; 10 participants were occupationally exposed. We estimated the correlation between bone Pb concentrations measured by both devices. We also examined the extent to which the detection limit (DL) of the portable XRF was influenced by scan time and overlying soft tissue thickness. Finally, we quantified the associations of estimated bone Pb concentration with age and age with soft tissue thickness.

Results: The mean bone Pb concentration measured *via* portable XRF was 12.3 ± 16.7 mg Pb/kg dry bone. The uncertainty of a 3-minute (N = 60) *in vivo* portable XRF measurement ranged from 1.8 to 6.3 mg/kg, in the context of soft tissue thickness ranging from 2 to 6 mm. This uncertainty was reduced by a factor of 1.4 with 5-minute measurements (N = 11). Bone Pb measurements *via* portable XRF and KXRF were significantly correlated: r = 0.48 for all participants, and r = 0.73

*Corresponding author at: School of Health Sciences, Purdue University, 550 Stadium Mall Drive, West Lafayette, IN 47906, USA. hnie@purdue.edu (L.H. Nie).

[1]These authors made equal contributions to this project.

CRediT authorship contribution statement

Xinxin Zhang: Conceptualization, Methodology, Validation, Data Analysis, Investigation, Data Curation, Project Administration, Writing– Original Draft, Review and Editing. Aaron J. Specht: Methodology, Validation, Data Analysis, Writing – Review and Editing. Ellen Wells: Data Analysis, Writing – Review and Editing. Marc G. Weisskopf, Jennifer Weuve, and Linda H. Nie: Conceptualization, Supervision, Resources, Project Administration, Methodology, Validation, Investigation, Writing – Review and Editing, Funding Acquisition.

Declaration of competing interest

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.

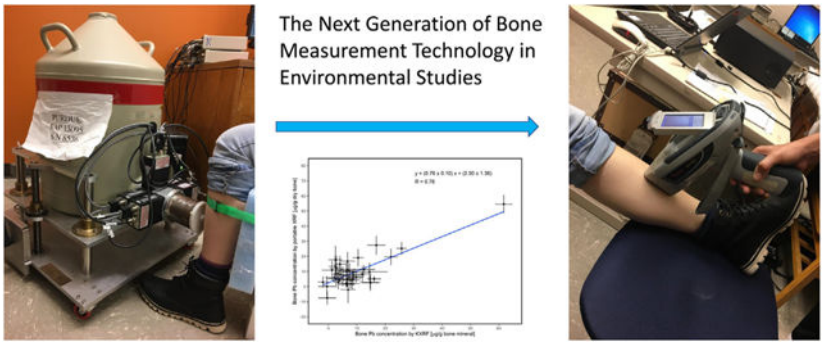
Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2020.142351.

among participants with soft tissue thickness < 6 mm (72% of the sample). Bone Pb concentrations were higher among participants who were older or were occupationally exposed to Pb. Soft tissue thickness decreased with age.

Conclusion: With its ease of use, portability, and comparable sensitivity with conventional KXRF systems, the portable XRF could be a valuable tool for non-invasive quantification of bone Pb *in vivo,* especially for people with thinner soft tissue.

GRAPHICAL ABSTRACT



Keywords

X-ray fluorescence; Biomonitoring; Lead; Bone; *In vivo* quantification

1. Introduction

Lead (Pb) exposure has declined dramatically over the last several decades due to the regulatory actions prompted by numerous scientific findings that Pb is related to many adverse health outcomes (Grosse et al., 2002; Hwang et al., 2019; Pirkle et al., 1994). However, even at the lower exposure levels typical today, there are well-documented health effects (Bellinger and Needleman, 2003; Canfield et al., 2005; Lanphear et al., 2005; Lanphear et al., 2018). Pb remains one of the most common chemical toxicants in the environment and is second, following arsenic, on the substance priority list of the Agency for Toxic Substances and Disease Registry (ATSDR, 2019). Pb exposure is still a significant public concern for many populations, especially some vulnerable populations, including older adults, children, and occupational workers (Centers for Disease and Prevention, 2013; Lanphear et al., 2005; Lanphear et al., 2018). Blood Pb is a commonly used biomarker of Pb exposure. However, the half-life of Pb in the blood is relatively short, approximately 35 days for adults and as low as 7 days for children (Rabinowitz et al., 1976; Specht et al., 2019a). By contrast, Pb in bone has a longer half-life of years to decades (Rabinowitz, 1991), rendering it a more appropriate biomarker of cumulative Pb exposure, especially for populations with long-term Pb exposure or exposure that occurred mostly in the past.

K-shell x-ray fluorescence (KXRF[2]) technology has been used to measure bone Pb *in vivo* and to investigate the adverse health effects of cumulative exposure (Navas-Acien et al.,

[2]XRF X-Ray Fluoresences.

2007; Nie et al., 2006; Shih et al., 2007; Weisskopf et al., 2015; Weuve et al., 2013). However, the system size, long measurement time, and other operational requirements limit such studies to only a few research groups who possess the technology. Furthermore, study participants must visit a central research facility to undergo KXRF measurements, making it impossible to use this technology in field studies. Our group has developed a portable XRF approach that employs an easy-to-use device that can noninvasively quantify metal concentrations *in vivo* in a few minutes (Specht et al., 2014; Specht et al., 2018; Zhang et al., 2018). Thus, this device is more practical for use in large-scale epidemiologic studies and field settings. The portable device may be especially useful among vulnerable and underrepresented populations, whose participation may be limited by physical mobility or proximity to a KXRF system. This study compares the use of portable XRF for bone Pb measurements *in vivo* in adults against the standard KXRF bone Pb measurement.

2. Methods

2.1. Study population

Seventy-six adults were recruited from a community-dwelling population in northwestern Indiana to participate in this study. Data from five participants were excluded from our analysis. Three of those participants had a very thick layer of soft tissue overlying their tibia bone, resulting in unacceptable high uncertainty and unrealistically negative bone Pb concentrations. External Pb contamination on the portable XRF device interfered with the measurements of the other two excluded participants. This contamination was eliminated in subsequent scans by cleaning the surface of the portable XRF. Forty-one participants (22 women and 19 men; ages 43–83 years) were recruited from the vicinity around West Lafayette, Indiana (USA), among whom one was previously occupationally exposed to Pb. Nineteen participants (10 women and 9 men; ages 38–95 years) were recruited from East Chicago, Indiana (USA). East Chicago is the site of intense industrial activity over the past century, including refining Pb ore and recovering Pb from scrap metal and batteries. The East Chicago-based U.S. Smelter and Pb Refinery Superfund site was added to the National Priorities List in 2009 (EPA). All East Chicago participants were residents in the operable unit 1 site, a 322-acre residential area in the Pb superfund site. To cover a broader range of bone Pb concentrations, we recruited eleven participants (2 women and 9 men, ages 45–87 years) with potential moderate to high historical Pb exposure from the vicinity around Muncie, Indiana (USA), among whom nine were occupationally exposed to Pb at some time point of their life.

2.2. Bone Pb exposure assessment

2.2.1. Portable XRF system—The portable XRF used in this study was a customized device from Thermo Fisher Scientific (Thermo Niton XL3t GOLDD+, Billerica, MA). The x-ray tube has an energy span of up to 50 kV and uses a thermoelectric-cooled silicon drift detector with a 25-mm^2 area and a 1-mm thickness. The x-ray tube settings were optimized for Pb measurements with a voltage of 50 kV, a current of 40 μA, and a silver (Ag) and iron (Fe) combination filter. These settings provided the best detection limit (DL)[3] for the

[3]DL Detection Limit.

measurements of bone Pb (Specht et al., 2014). In response to irradiation, Pb atoms in the bone generate Pb L-shell-characteristic x-rays with energies of 10.55 keV (L_α) and 12.61 keV (L_β). However, only the L_β peak was used for estimating bone Pb concentration because of the lower background level under the Pb peak region. The peak fitting with the least-squares algorithm was used to extract the net counts of Pb L_β. A Gaussian distribution was fit to the Pb L_β peak and an exponential function was used to fit the background. The bone Pb concentration was measured in mg/kg dry bone by the portable XRF (Specht et al., 2018).

A 3-minute measurement was performed with the portable XRF for participants from West Lafayette and East Chicago. To determine the extent to which a longer scan time would reduce the DL of the device, the measurement time was extended to 5 min for Muncie participants. The induced whole-body effective radiation dose from the 3-minute scan was about 3.6 μSv (Specht et al., 2016; Specht et al., 2019b), which increased to approximately 6.0 μSv with the 5-minute scan. By contrast, the dose for a standard anteroposterior chest x-ray is 100 μSv, and one day of natural cosmic radiation is equivalent to 10 μSv.

2.2.2. KXRF system—The setup of the ^{109}Cd based KXRF system followed that used in previous studies (Nie et al., 2004; Nie et al., 2006; Specht et al., 2014; Specht et al., 2016). A ^{109}Cd source was mounted in front of the detector, emitting gamma-ray with 88.035 keV energy to irradiate the bone (or bone-equivalent phantoms in calibration procedures). In response, Pb atoms in the bone emit Pb K-shell-characteristic x-rays with energies of 74.97 keV ($K_{\alpha 1}$), 72.80 keV ($K_{\alpha 2}$), and 84.94 keV ($K_{\beta 1}$). The system consists (Specht et al., 2019a) of four high-purified germanium (HpGe) detectors with a dimension of 16 mm in diameter and 10 mm in thickness, four feedback resistance pre-amplifiers, four digital signal analyzers (DSA-1000). This four-detector system is known as a cloverleaf system and has sensitivity about 2–3 times better than the conventional one-unit KXRF systems that are used in most of the labs with bone Pb measurement capability (Nie et al., 2006). An in-house peak fitting program was used to calculate bone Pb concentration and its uncertainty separately with each detector (Nie et al., 2005; Somervaille et al., 1989). The Pb K_α and K_β signals were analyzed independently and normalized to the generated coherent peak signal, and the bone Pb concentration obtained from an individual measurement has a unit of mg Pb/kg bone mineral. The bone Pb concentration was computed as an average of the K_α and K_β signals from all four detectors, with the concentrations weighted by uncertainty according to the inverse variance weighting method (Todd et al., 2002). The whole-body effective dose from a 30-minute measurement was approximately 0.26 μSv with a 135 mCi ^{109}Cd source for this advanced cloverleaf system (Nie et al., 2007a, 2007b).

2.2.3. Calibration of the portable XRF and KXRF systems—The portable XRF system was calibrated using a 100 mg Pb/kg plaster of Paris Pb-doped bone-equivalent phantom. A consequence of the low energy of the Pb L x-ray is that the soft tissue over the bone can attenuate the signal. As the soft tissue thickness increases, the system detects fewer Pb L x-rays and more Compton scattering counts from the soft tissue. Thus, to simulate the soft tissue over bone, Lucite plates of 0 to 5 mm were placed over the 100 mg/kg bone phantom and the phantoms were measured for 15 min to calibrate the portable XRF for bone

Pb. The calibration line was established as the Pb L_β net counts of the 100 mg/kg bone phantom change in relation to the Compton scattering peak counts. The *in vivo* bone Pb concentration was calculated by relating an *in vivo* Pb L_β net count to a known count per concentration from the 100 mg/kg bone phantom.

In a previous study (Nie et al., 2011; Specht et al., 2014), a 0 mg/kg bone phantom was used to estimate the background under the Pb L_β peak, and the Pb net counts were calculated by subtracting the estimated background counts from the gross counts under the peak of interest. However, for *in vivo* measurements, this background subtraction method overestimated the background and resulted in an underestimated Pb signal and higher uncertainty. Instead, the Pb L_β net count was directly extracted through the peak fitting and the count from the 100 mg/kg bone phantom at the corresponding thickness was used to determine concentration.

Because Pb K x-rays have much higher energy than the L x-rays, the KXRF signals were not attenuated as much by the soft tissue over the bone as the portable XRF signals. Hence, the standard calibration for the KXRF calibration uses nine Pb-doped phantoms with concentrations ranging from 0 to 100 mg/kg. The phantoms were positioned in front of a ^{109}Cd source, and a 30-minute measurement was performed. The Pb $K_{\alpha,\beta}$ peaks were normalized to the coherent peak for the correction of the measurement geometry, bone mineral normalization, and soft tissue attenuation. The calibrations lines were plotted as the ratios of Pb K_α and K_β peaks over coherent peak *versus* the bone Pb concentrations.

From the portable XRF calibration data, the relation between Lucite thickness and Compton scattering counts was also determined. Using this relation, the overlying skin thickness for an individual participant was estimated directly from the XRF spectrum of their portable XRF bone Pb measurement. This then allowed us to use the Compton scattering counts from their measurement to correct for the attenuation of the Pb signal caused by overlying tissue.

2.2.4. In vivo measurement of bone Pb—For portable XRF measurement, the participant sat on a chair with one leg straightened and resting on a chair in front. Before the measurement, the participant's mid-tibia area was cleaned with alcohol swabs to eliminate any extraneous contamination. The portable XRF device was placed in contact with the participant's skin right above the tibia on the medial surface of the anterior crest. Three-minute measurements were taken for West Lafayette and East Chicago participants, and 5-minute measurements for Muncie participants.

The portable XRF measurement was followed by the KXRF measurement, and the same mid-tibial spot was cleaned again. The sitting participant's target leg was immobilized by securing it to the chair leg with Velcro straps and then positioned it about 1–2 mm away from the ^{109}Cd source. The bone was measured with the KXRF system for 30 min. The Muncie participants were measured with a new 135 mCi ^{109}Cd source, which had higher activity than the one used for the West Lafayette and East Chicago participants. This resulted in a lower uncertainty of the bone Pb concentration measured by the KXRF in the Muncie participants.

The Institutional Review Board of Purdue University, Boston University, and Harvard University approved this study. All participants provided their informed consent forms before undergoing the study procedures.

2.3. Data analyses

2.3.1. Detection limit of the XRF systems—The DL of the KXRF system was defined as twice the uncertainty of the measurement of the 0 mg/kg bone phantom. Soft tissue overlying the tibia bone increases the uncertainty and hence the DL of the portable XRF measurement. Thus, the DL of portable XRF was calculated using 3-minute measurements of 0 and 100 mg/kg Pb-doped bone-equivalent phantoms covered with Lucite of thicknesses ranging from 1 to 8 mm. The DL was calculated as

$$DL_{portable\,XRF} = 2 \times \sigma_{0ppm} = 2 \times \sqrt{\frac{1}{\frac{1}{\sigma^2_{\alpha,0ppm}} + \frac{1}{\sigma^2_{\beta,0ppm}}}},$$

where

$$\sigma_{\alpha,\beta,0ppm} = 100ppm \times \frac{\sqrt{BKG_{\alpha,\beta,0ppm}/180s}}{Gross_{\alpha,\beta,100ppm} - BKG_{\alpha,\beta,0ppm}},$$

The DL was estimated from both Pb L_α and Pb L_β peaks. $Gross_{\alpha,\beta,100ppm}$ is the gross count rate under the L_α and L_β area measured with a 100 mg/kg Pb bone phantom in 3 min, and $BKG_{\alpha,\beta,0ppm}$ is the total count rate under the L_α and L_β area measured with a 0 mg/kg bone phantom.

The estimated DL for the phantoms with a given Lucite thickness is the minimum bone Pb concentration that can be reliably detected with that thickness. However, the discrepancy between the Lucite plates and overlying soft tissue *in vivo* can result in slightly lower estimates of the DL for the phantom with Lucite. Hence, the DL for *in vivo* measurement is expected to be slightly higher than that from the phantom. In this study, twice the uncertainty of *in vivo* measurement was used to approximately estimate the DL for an *in vivo* situation.

2.3.2. Statistical analyses—Because the bone Pb concentration estimated by the instruments oscillate around the actual value, negative estimates may occur when a participant's actual *in vivo* bone Pb concentration is close to zero. Hence these negative data points were retained to provide unbiased estimates of the comparison between bone Pb measurements (Kim et al., 1995; Whitcomb and Schisterman, 2008).

The uncertainty of the different measurement times with the portable XRF were compared. The average uncertainty of *in vivo* measurement within 3 min and 5 min, at different soft tissue thickness, were calculated, and the uncertainty reduction factor was determined by simply calculating their ratio.

Estimates of bone Pb concentration generated by the two measurement systems were compared using linear regression models. From these analyses, Pearson correlation coefficients R was computed and the 95% CI based on Fisher R to Z transformation was calculated. Overlying soft tissue tends to increase the uncertainty in the portable XRF estimates. Hence two approaches were taken to evaluate the influence of this uncertainty on the estimated linear regression and Pearson correlation coefficients. First, we repeated our analyses that were progressively restricted to participants with thinner overlying soft tissue. Second, we conducted analyses in which we weighted observations in inverse proportion to their portable XRF measurement uncertainty (Behinaein et al., 2017).

Associations of the portable XRF bone Pb concentrations with two known predictors of cumulative Pb exposure, age and occupational exposure to Pb, were evaluated. Older adults have had more time to accumulate Pb in bone than younger adults, and in the United States, many older adults who are alive today were exposed to a substantial amount of Pb before the ban of leaded gasoline and paint. Hence, bone Pb concentrations estimated by XRF are expected to be higher with older participant age. The association between the portable XRF bone Pb concentrations and the age of the participants were assessed by regressing bone Pb concentration measured by the portable XRF on age. The bone Pb concentrations of occupationally and non-occupationally exposed participants were compared. For this comparison, because the occupationally exposed participants were all male and had a more restricted age range (N = 10; 63 ± 14 years), the comparison was limited to non-occupationally exposed males of similar age distribution (N = 24; 68 ± 8 years). Since the bone Pb concentrations were not normally distributed in these two populations, a two-sample Kolmogorov-Smirnov (K–S) test was used to evaluate the difference and compute the *p*-value. All of these analyses were repeated using KXRF estimates as well.

Finally, to further explore the usefulness of the portable XRF in large-scale studies of older adults, the relation of age to soft tissue thickness was evaluated by regressing soft tissue thickness on age. An inverse association between the two would indicate that soft tissue thickness gets thinner with age, and so would be a less dominant contributor to measurement uncertainty in older adults.

3. Results

3.1. Study population

Table 1 shows selected characteristics of the 71 participants. Ten male participants, ages 45 to 87 years, were occupationally exposed.

3.2. Bone Pb exposure assessment

3.2.1. Calibration of the portable XRF and KXRF systems—Compton scattering counts from the portable XRF increased with thicker Lucite plates (Fig. S1). The Pb L_β net counts decreased with progressively higher Compton scattering counts ($r^2 > 0.99$) due to the signal attenuation from increased Lucite thickness (Fig. S2). Fig. S3a and S3b show the calibration lines for one of the four detectors of the KXRF system for K_α and K_β peaks,

where K_α/coherent and K_β/coherent were plotted against the bone phantom Pb concentrations ($r^2 = 0.99$).

3.2.2. Detection limit of the measurement systems—The attenuation of the net signal caused by soft tissue overlying the bone resulted in a higher DL of bone Pb by the portable XRF than by the KXRF. These tendencies were borne out in both the measurements of bone-equivalent phantoms covered with Lucite and the *in vivo* measurements. With progressively thicker Lucite covering the bone-equivalent phantom, the DL of the 3-minute portable XRF measurements was substantially higher, with DLs ranging from 7.6 to 38.63mg/kg for Lucite thicknesses ranging from 4 to 8 mm (Fig. S4). These results extend those from a previous study, in which DLs calculated with the bone-equivalent phantoms ranged from 1.2 to 11 mg/kg with Lucite thicknesses from 1 to 5 mm (Specht et al., 2014). The mean DL of the bone Pb concentration measured by the KXRF using the phantoms was 2.3 mg/kg and varied little by soft tissue thickness.

Likewise, the uncertainty of *in vivo* bone Pb measurements using the portable XRF was higher with progressively thicker overlying soft tissue, whereas the uncertainty of corresponding KXRF measurements was not affected by soft tissue thickness. Sixty participants underwent measurements with the 3-minute portable XRF and the older ^{109}Cd source (all participants from the West Lafayette and East Chicago sites). Among these participants, with a maximum soft tissue thickness of 7.5 mm, the mean uncertainty of portable XRF bone Pb measurement was 10.6 ± 8.2 mg/kg dry bone (Table 2). Among those with soft tissue thicknesses <5 mm (N = 32), the corresponding mean uncertainty was 4.9 ±1.7 mg/kg dry bone. The mean uncertainty of the *in vivo* KXRF measurements was 3.1 ± 1.0 mg/kg bone mineral, and it did not vary meaningfully by soft tissue thickness.

Table 3 shows the mean uncertainty of the 5-minute measurements (all Muncie participants, N = 11) in different soft tissue thickness. Compared with the mean uncertainty of these 3-minute portable XRF measurements, the mean uncertainty of the 5-minute measurements was lower by a factor of 1.4, with soft tissue thicknesses up to a maximum thickness of 6.3 mm. The uncertainty for KXRF measurements among the Muncie participants was approximately 2 mg/kg bone mineral, lower than the 3 mg/kg bone mineral for other participants because of the use of a newer ^{109}Cd source in this group.

3.2.3. Comparison of portable XRF and KXRF bone Pb concentrations—The mean tibia bone Pb concentration in our study population, as measured by the portable XRF, was 12.3 ± 16.7 mg/kg dry bone. As measured by the KXRF system, the mean bone Pb was 7.7 ±8.8 mg/kg bone mineral.

As the uncertainty of *in vivo* bone Pb concentration measured *via* the portable XRF decreased with thinner overlying soft tissue, the correlation between bone Pb concentrations measured by the portable XRF and KXRF systems, in turn, increased when the analyses were restricted to data from persons with thinner overlying tissue (Table 4). The correlation among all participants (N = 71) was r = 0.48, 95% CI (0.27, 0.64) (Table 4; Fig. 1a), but was much higher among participants with soft tissue thicknesses <5 mm (r = 0.78, 95% CI: 0.61, 0.87; N = 40, Table 4; Fig. 1a). The highest bone Pb concentration of 61 mg/kg was obtained

from a gentleman who had been working in a battery factory for many years. If this data was excluded from the linear regression model, the β coefficient would be 1.05 ± 0.30, the correlation coefficient r would be 0.39, and the p-value would be 0.001 for all the participants; for participants with soft tissue thickness less than 5 mm, the β coefficient would be 0.56 ± 0.17, r = 0.48, and p-value <0.001. The regression plots corresponding to Fig. 1a and b, excluding the participant with the highest bone Pb concentration, were shown in Fig. S5a and b in the supplement material. The correlations from inverse-uncertainty-weighted regression models were more consistent across tissue thicknesses, although slightly lower than unweighted correlations at thicknesses <6 mm. Fig. 2 shows the bone Pb concentrations measured by both devices for the participants with soft tissue thickness less than 5 mm, and thicker or equal to 5 mm. All the correlation results presented in Table 4 had p-value <0.001.

3.2.4. Associations of in vivo bone Pb concentration with age and occupational exposure to Pb—

Older age appeared associated with higher estimated bone Pb concentration, as measured by either system. Bone Pb concentrations measured by KXRF was 1.66 mg/kg bone mineral (95% CI: 0.80 to 2.50) higher per five years of age; the corresponding association using the portable XRF was weaker (0.65 mg/kg dry bone higher per five years of age; 95% CI: −1.05 to 2.45) (Table 5). The reduced precision in the portable XRF association likely resulted from the increased measurement uncertainty, which, in turn, resulted from overlying soft tissue. Table 5 shows the mean difference in bone Pb concentrations per five years, estimated from the linear regression model, at different soft tissue thicknesses. The precision of the estimate from portable XRF measurements gets worse at higher tissue thickness.

In the analysis of occupational Pb exposure, the median tibia bone Pb concentration of participants with occupational and non-occupational Pb exposure measured *via* the portable XRF was 16.9 ± 5.2 and 7.7 ±5.9 mg/kg dry bone, respectively. The p-value of the two-sample K–S test was 0.14. The results obtained from the KXRF were 13.2 ± 1.9 mg/kg bone mineral (occupational), 7.6 ± 2.6 mg/kg bone mineral (non-occupational), and p-value of 0.07.

3.2.5. Age and soft tissue thickness—

Older age was inversely associated with the thickness of soft tissue overlying the tibia bone (Fig. 3). The correlation coefficient was r = 0.26 and p-value = 0.028. For each 10-year increase in age, overlying soft tissue was about 0.3 mm thinner, on average (−0.33 mm, 95% CI: −0.03 to −0.63).

4. Discussion

Using the portable XRF method, bone Pb concentrations were quantified in a study population of community-recruited adults, some of whom had been occupationally exposed. The *in vivo* bone Pb concentration measured by the portable XRF was significantly correlated with the concentration measured by KXRF, but the absolute bone Pb concentration measured by these devices differed. This is likely in part because these two devices scan different parts of the bone. The lower energy of L-x-rays detected by the portable XRF allows it to scans about 0.5 mm into the surface, whereas the higher energy of

the K-x-rays detected by KXRF penetrates the bone more than 1 cm beneath the surface; thus the resulting signal is averaged across that span of bone. If Pb concentrations differ slightly in these regions, we would not expect the two methods to generate identical concentration estimates even under ideal conditions.

Because the higher overlying soft tissue thickness leads to higher signal attenuation for the portable XRF, participants with thicker soft tissue had a higher measurement uncertainty. Thus, the correlation of bone Pb measured with the two systems for all the participants (N = 71) was less precise than it was for the participants with soft tissue thinner than 6 mm (72% of the study population). In epidemiologic studies, investigators routinely use bone Pb measurements less than the DL from the conventional KXRF, as they still provide useful information in the distribution of the overall measures (Kim et al., 1995). Hence, the DL, although useful for purposes of determining individual measurement validity, is less useful in population-level diagnostics. The DL of both XRF systems is approximately twice the mean uncertainty of *in vivo* measurements. Nonetheless, while the DL of the portable XRF (~7–10 mg/kg) was higher than that obtained with the cloverleaf KXRF (~4 mg/kg), the portable XRF DL is roughly the same or less than the DL for conventional KXRF systems (~8–10 mg/kg) (Nie et al., 2006) that were used in most of the prior research on health effects of bone Pb, especially if one considers the DL for the portable XRF when tissue thickness is less than 5 mm (~7 mg/kg).

To help the reader to have a more comprehensive understanding of the characteristics of the KXRF and portable XRF bone Pb measurement systems, a summary of the comparison of these two instruments is made in Table S1 (Nie et al., 2006; Nie et al., 2007b; Specht et al., 2014; Todd et al., 1992). Note that the KXRF system includes both the conventional KXRF which was used for most of the studies that utilized bone Pb, and the newly developed cloverleaf KXRF which has a better sensitivity than the conventional KXRF instrument.

The correlation of age and soft tissue thickness suggests that the portable XRF may be especially suitable for studies among older adults. Our results showed that there was a 0.3 mm decrease in soft tissue thickness per 10 years of age for all the participants with age range from 38 to 95 years. This trend, combined with the minimal logistical barriers of the portable XRF, makes this instrument especially appealing for Pb exposure research among older adults and other populations who may have reduced access to study site visits or less tolerance of the long-measurement times of conventional KXRF.

To further improve the sensitivity of the portable XRF for it to be applied in a large-scale population study, the measurement time was increased from 3 min to 5 min for the Muncie participants. The increase of the measurement time reduced the measurement uncertainty by a factor of 1.4 overall. The improvement factor is higher than the theoretically calculated factor of 1.3. This could be due to the small sample size of population with 5 min measurements. Even though the whole-body effective dose would be increased from 3.6 μSv to 6.0 μSv, it is still negligible compared to the dose for a standard AP chest x-ray of 100 μSv or one day of natural radiation from cosmic sources with a dose of 10 μSv. In addition, as noted above, the DL of the portable XRF is comparable or better than the sensitivity of

conventional KXRF, particularly for participants with soft tissue thickness thinner than 5 mm, which has been extensively used for past bone Pb epidemiology studies.

It is worth to compare the bone Pb concentrations measured at different time period in some other studies. As most of the bone Pb measurements for the other studies were made by KXRF system, the results obtained from KXRF system will be compared. In the current study, the average bone Pb concentrations in the recruited population were estimated to be ~2 mg/kg, which are significantly lower than the bone Pb concentrations reported by some of our previous studies. For example, an average tibia Pb concentration of ~20 mg/kg was reported among an older adult population of over 400 participants (Weisskopf et al., 2004). Another study reported an average tibia Pb concentration of 10 mg/kg among 500 older women (Weuve et al., 2009). In a paper published by our collaborative group several years ago, average tibia Pb was reported to be 7.6 mg/kg for over 100 parkinson's disease (PD) patients and controls (Weuve et al., 2013). The Pb cumulation in bone in general population, especially the older adult population born in or before 1960s, was mainly through the air pollution caused by leaded gasoline. As the other studies were conducted up to 20 years ago, the main reason for a lower bone Pb concentration in the current study is likely the release of Pb from bone during bone resorption process in the absence of external exposures. Moreover, the average age of the participants in the other studies is larger than that in the current study, which partially contributed the higher bone Pb concentrations in the other studies. In addition, the population of the other studies are from east coast while the population in this study is from middle-west, which can also contribute to the difference due to different exposure environment.

Although the project tested a valuable tool for bone Pb measurement, there are at least two limitations associated with the study. First, the sample size of the population is relatively small, which means that the results may not be able to be generized to general population. In addition, the small sample size for the people who had 5-minute measurements and the fact that the 3-min and 5-min measurements were not conducted among the same people may affect the credibility of the improvement made by increasing the measurement time. Second, the number of participants with bone Pb concentrations greater than 20 mg/kg is small (only a couple), which could affect the correlation analysis of the KXRF and portable XRF. The correlation will be more convincing if there were more data points between 20 mg/kg and 60 mg/kg (the highest data point).

In conclusion, in this study of community- and occupationally exposed volunteers, bone Pb concentrations obtained from the portable XRF system were significantly correlated with concentrations measured with a KXRF system. The correlation was greater when the participants with thicker soft tissue were excluded or a weighted least square regression method was used to weigh observations based on soft tissue thickness. However, measuring with the portable XRF for five minutes rather than just three, improved the sensitivity. The portable XRF is a valuable tool for population studies on Pb exposure, avoiding many of the disadvantages of the KXRF measurements, and the method is ready to be used for large-scale population studies where the KXRF is not accessible or not practical.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

This work was supported by the National Institutes of Health [NIH/NIEHS-1R21 ES024700]; the National Institute for Occupational Safety and Health [1K01 OH011648]; and Purdue Bilsland Fellowship. The authors are grateful to the Community Action Group of East Chicago and Debbie Chizewer for their critical outreach to prospective participants in East Chicago.

References

ATSDR, 2019 Agency for toxic substances and disease registry, priority list of hazardous substances. 2019. Available. https://www.atsdr.cdc.gov/spl/index.html#2019spl.

Behinaein S, Chettle DR, Fisher M, Manton WI, Marro L, Fleming DE, et al., 2017 Age and sex influence on bone and blood lead concentrations in a cohort of the general population living in Toronto. Physiol. Meas 38, 431–451. [PubMed: 28067216]

Bellinger DC, Needleman HL, 2003 Intellectual impairment and blood lead levels. N.Engl. J. Med 349, 500–502 (author reply 500–502).

Canfield RL, Jusko TA, Kordas K, 2005 Environmental lead exposure and children's cognitive function. Riv Ital Pediatr 31, 293–300. [PubMed: 26660292]

Centers for Disease C, Prevention, 2013 Very high blood lead levels among adults – United States, 2002–2011. MMWR Morb. Mortal.Wkly Rep 62, 967–971. [PubMed: 24280917]

EPA EPA, d. Uss lead superfund site. Available. https://www.epa.gov/uss-lead-superfund-site.

Grosse SD, Matte TD, Schwartz J, Jackson RJ, 2002 Economic gains resulting from the reduction in children's exposure to lead in the United States. Environ. Health Perspect 110, 563–569. [PubMed: 12055046]

Hwang YH, Hsiao CK, Lin PW, 2019 Globally temporal transitions of blood lead levels of preschool children across countries of different categories of human development index. Sci. Total Environ 659, 1395–1402. [PubMed: 31096350]

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

Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger DC, et al., 2005 Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. Environ. Health Perspect 113, 894–899. [PubMed: 16002379]

Lanphear BP, Rauch S, Auinger P, Allen RW, Hornung RW, 2018 Low-level lead exposure and mortality in us adults: a population-based cohort study. Lancet Public Health 3, e177–e184. [PubMed: 29544878]

Navas-Acien A, Guallar E, Silbergeld EK, Rothenberg SJ, 2007 Lead exposure and cardiovascular disease–a systematic review. Environ. Health Perspect 115, 472–482. [PubMed: 17431501]

Nie H, Chettle DR, McNeill FE, O'Meara JM, 2004 An investigation of the 109cd gamma-ray induced k-x-ray fluorescence (xrf) bone-lead measurement calibration procedure. Phys. Med. Biol 49, N325–N334. [PubMed: 15552425]

Nie H, Chettle DR, Webber CE, Brito JA, O'Meara JM, McNeill FE, 2005 The study of age influence on human bone lead metabolism by using a simplified model and x-ray fluorescence data. J. Environ. Monit 7, 1069–1073. [PubMed: 16252055]

Nie H, Chettle D, Luo L, O'Meara J, 2006 In vivo investigation of a new 109cd gamma-ray induced k-xrf bone lead measurement system. Phys. Med. Biol 51, 351–360. [PubMed: 16394343]

Nie H, C D, Luo L, O'Meara J, 2007a Dosimetry study for a new in vivo x-ray fluorescence (xrf) bone lead measurement system. Nucl. Instrum. Methods Phys. Res., Sect. B 263, 225–230.

Nie H, Chettle DR, Luo L, O'Meara J, 2007b Dosimetry study for a new in vivo x-ray fluorescence (xrf) bone lead measurement system. Nucl. Inst. Methods Phys. Res. B 263, 225–230.

Nie LH, Sanchez S, Newton K, Grodzins L, Cleveland RO, Weisskopf MG, 2011 In vivo quantification of lead in bone with a portable x-ray fluorescence system– methodology and feasibility. Phys. Med. Biol 56, N39–N51. [PubMed: 21242629]

Pirkle JL, Brody DJ, Gunter EW, Kramer RA, Paschal DC, Flegal KM, et al., 1994 The decline in blood lead levels in the United States. The national health and nutrition examination surveys (nhanes). JAMA 272, 284–291. [PubMed: 8028141]

Rabinowitz MB, 1991 Toxicokinetics of bone lead. Environ. Health Perspect 91, 33–37. [PubMed: 2040248]

Rabinowitz MB, Wetherill GW, Kopple JD, 1976 Kinetic analysis of lead metabolism in healthy humans. J. Clin. Invest 58, 260–270. [PubMed: 783195]

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

Somervaille LJ, Nilsson U, Chettle DR, Tell I, Scott MC, Schutz A, et al., 1989 In vivo measurements of bone lead–a comparison of two x-ray fluorescence techniques used at three different bone sites. Phys. Med. Biol 34, 1833–1845. [PubMed: 2616639]

Specht AJ, Weisskopf M, Nie LH, 2014 Portable xrf technology to quantify pb in bone in vivo. Journal of Biomarkers 2014, 398032. [PubMed: 26317033]

Specht AJ, Lin Y, Weisskopf M, Yan C, Hu H, Xu J, et al., 2016 Xrf-measured bone lead (pb) as a biomarker for pb exposure and toxicity among children diagnosed with pb poisoning. Biomarkers : Biochemical Indicators of Exposure, Response, and Susceptibility to Chemicals 21, 347–352.

Specht AJ, Parish CN, Wallens EK, Watson RT, Nie LH, Weisskopf MG, 2018 Feasibility of a portable x-ray fluorescence device for bone lead measurements of condor bones. Sci. Total Environ 615, 398–403. [PubMed: 28988075]

Specht AJ, Weisskopf M, Nie LH, 2019a Childhood lead biokinetics and associations with age among a group of lead-poisoned children in China. Journal of Exposure Science & Environmental Epidemiology 29, 416–423. [PubMed: 29706621]

Specht AJ, Zhang X, Goodman BD, Maher E, Weisskopf MG, Nie LH, 2019b A dosimetry study of portable x-ray fluorescence in vivo metal measurements. Health Phys. 116, 590–598. [PubMed: 30624351]

Todd AC, McNeill FE, Palethorpe JE, Peach DE, Chettle DR, Tobin MJ, et al., 1992 In vivo x-ray fluorescence of lead in bone using k x-ray excitation with 109cd sources: radiation dosimetry studies. Environ. Res 57, 117–132. [PubMed: 1568436]

Todd AC, Carroll S, Geraghty C, Khan FA, Moshier EL, Tang S, et al., 2002 L-shell xray fluorescence measurements of lead in bone: accuracy and precision. Phys. Med. Biol 47, 1399–1419. [PubMed: 12030563]

Weisskopf MG, Wright RO, Schwartz J, Spiro A 3rd, Sparrow D, Aro A, et al., 2004 Cumulative lead exposure and prospective change in cognition among elderly men: the va normative aging study. Am. J. Epidemiol 160, 1184–1193. [PubMed: 15583371]

Weisskopf MG, Sparrow D, Hu H, Power MC, 2015 Biased exposure-health effect estimates from selection in cohort studies: are environmental studies at particular risk? Environ. Health Perspect 123, 1113–1122. [PubMed: 25956004]

Weuve J, Korrick SA, Weisskopf MG, Ryan LM, Schwartz J, Nie H, et al., 2009 Cumulative exposure to lead in relation to cognitive function in older women. Environ. Health Perspect 117, 574–580. [PubMed: 19440496]

Weuve J, Press DZ, Grodstein F, Wright RO, Hu H, Weisskopf MG, 2013 Cumulative exposure to lead and cognition in persons with parkinson's disease. Movement Disorders : Official Journal of the Movement Disorder Society 28, 176–182. [PubMed: 23143985]

Whitcomb BW, Schisterman EF, 2008 Assays with lower detection limits: implications for epidemiological investigations. Paediatr. Perinat. Epidemiol 22, 597–602. [PubMed: 19000298]

Zhang X, Specht AJ, Weisskopf MG, Weuve J, Nie LH, 2018 Quantification of manganese and mercury in toenail in vivo using portable x-ray fluorescence (xrf). Bio-markers : Biochemical Indicators of Exposure, Response, and Susceptibility to Chemicals 23, 154–160.

HIGHLIGHTS

- Portable x-ray fluorescence (XRF) is a valuable tool for non-invasive quantification of lead in bone *in vivo*.
- Lead concentrations in bone measured with the portable XRF were significantly correlated with that measured *via* the KXRF, among a US population.
- Lead concentrations in tibia bone were higher among participants who were older or were occupationally exposed to lead.
- Soft tissue thickness overlying the midtibia bone decreased with age.

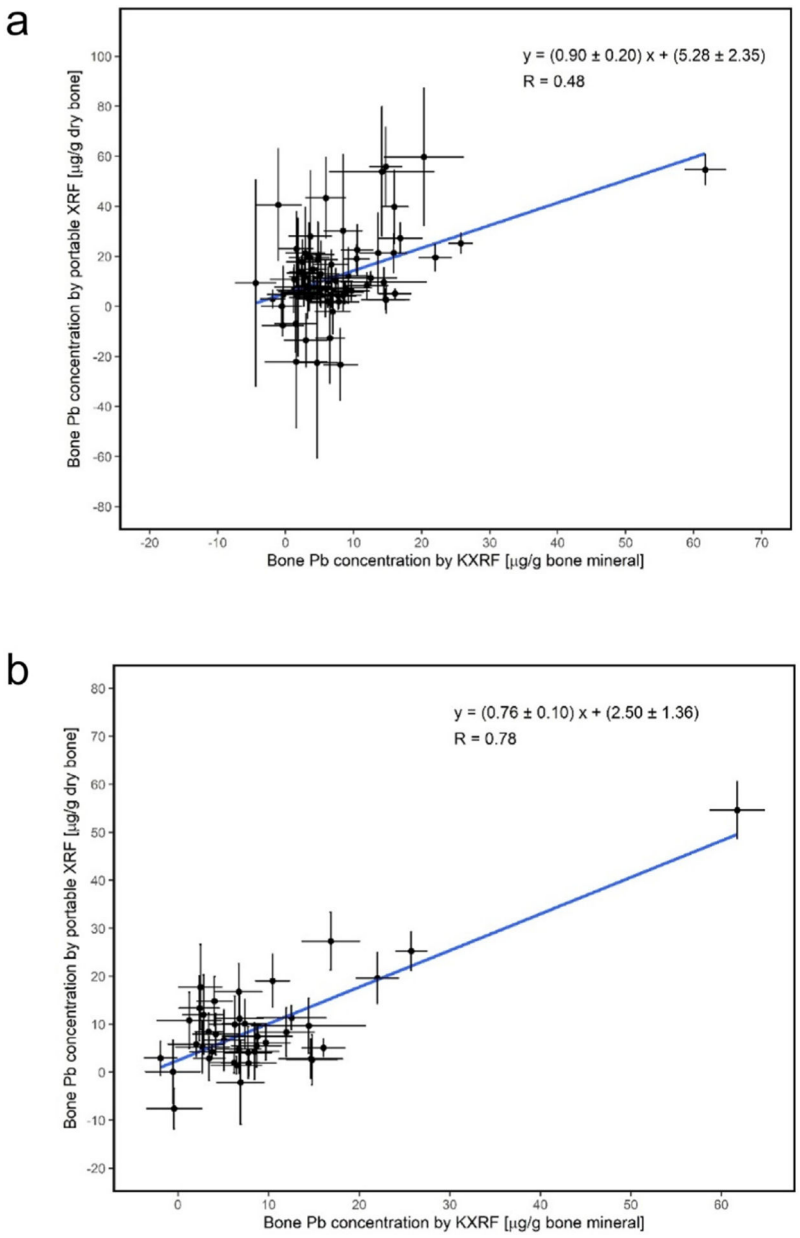


Fig. 1a.

Association of bone Pb measured by the portable XRF and KXRF for all participants. b. Correlation of bone Pb measured by the portable XRF and KXRF for the participants with soft tissue thinner than 5 mm.

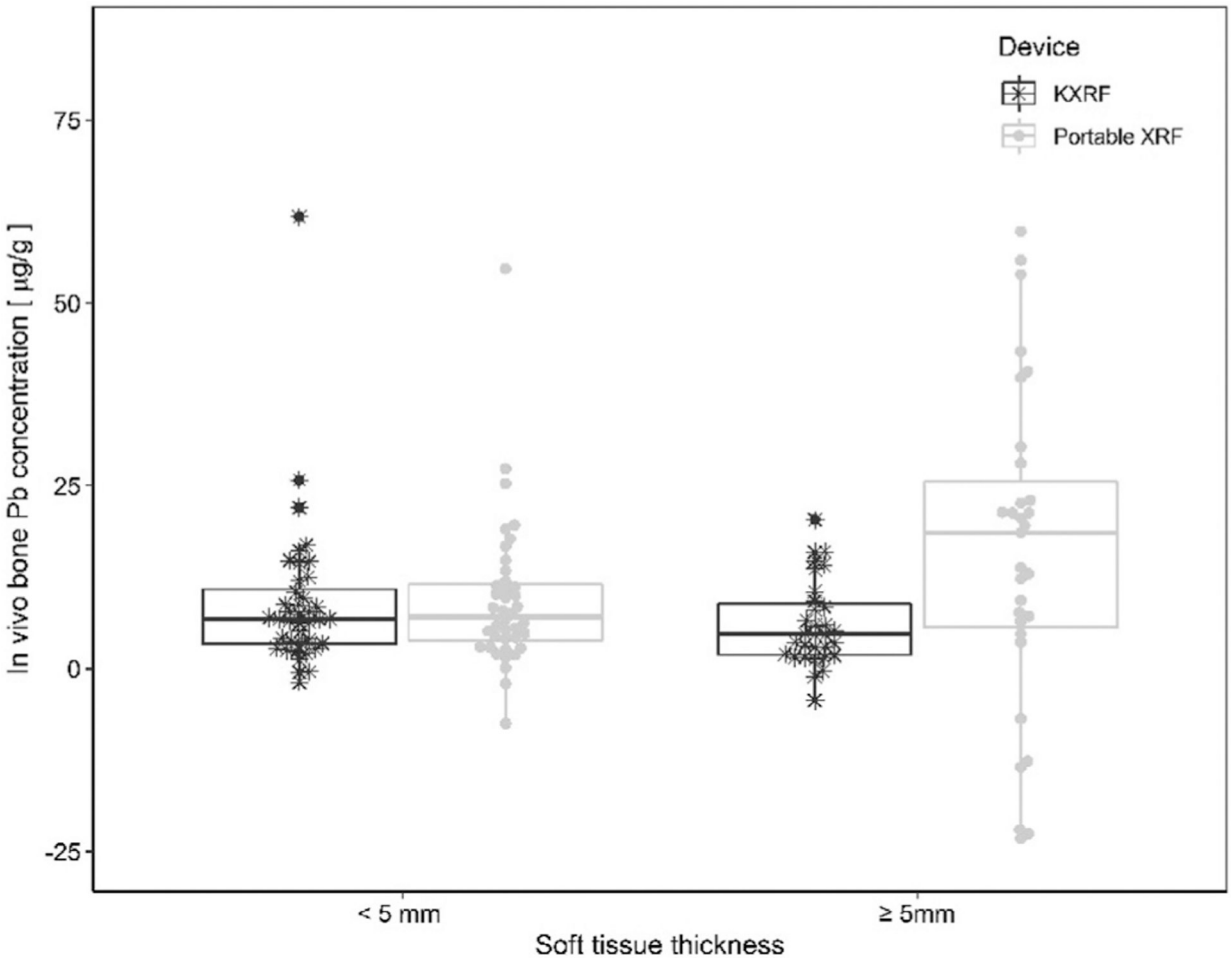


Fig. 2.

Bone Pb measured by the portable XRF and KXRF for the participants with soft tissue thinner than 5 mm and thicker or equal to 5 mm.

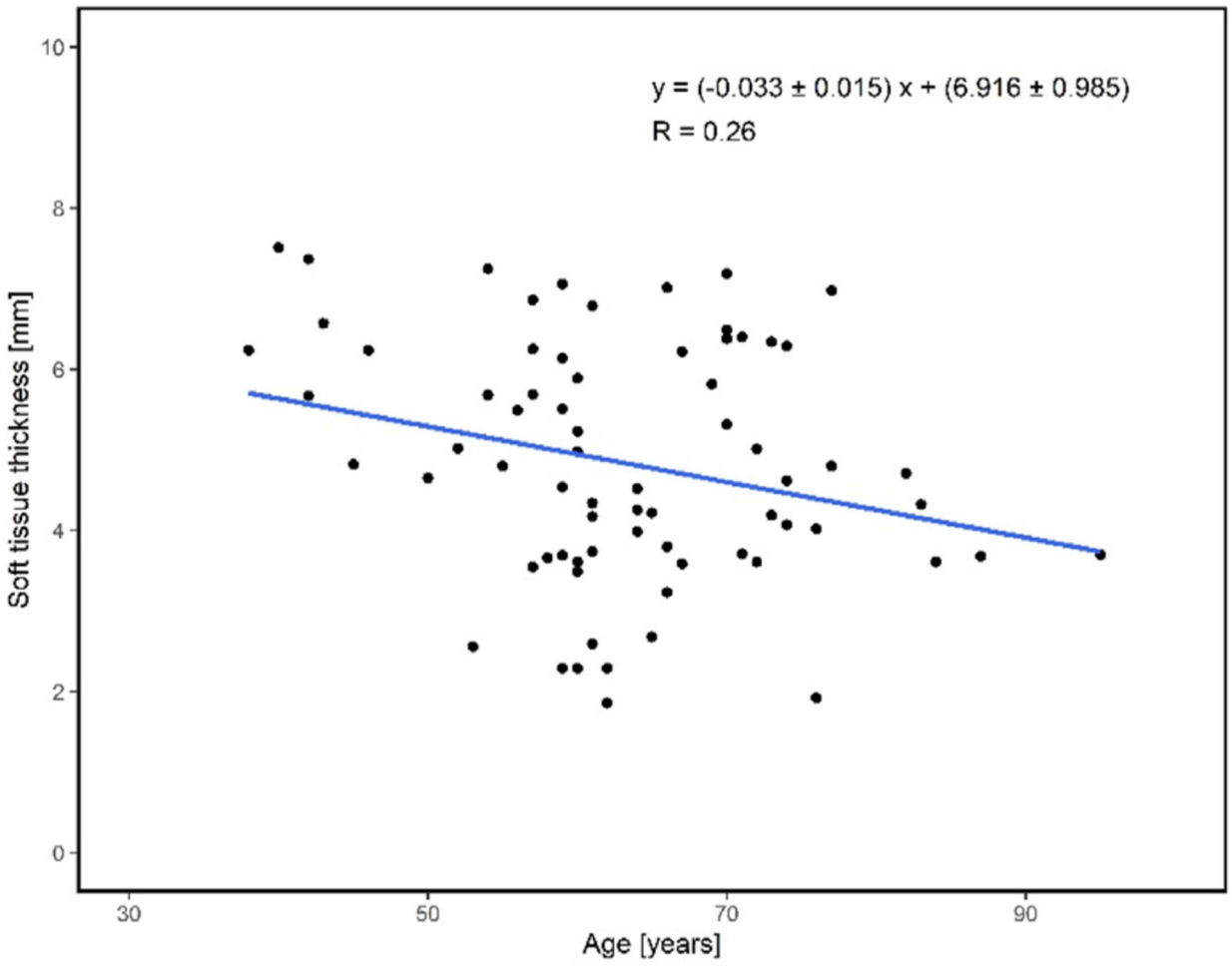


Fig. 3.
Correlation of soft tissue thickness over bone and age of participants.

Table 1

Characteristics of study participants, by site, and previous occupational exposure to Pb.

	West Lafayette	East Chicago	Muncie	Occupational exposure to Pb	No occupational to Pb	Total
Participants, N	41	19	11	10	61	71
Male, N (%)[a]	19 (46%)	9 (47%)	9 (82%)	10 (100%)	27 (44%)	37 (52%)
Age (Mean ± SD,years)	64 ± 8	62 ± 17	62 ± 12	63 ± 14	63 ± 11	63 ± 11
Soft tissue thickness (Mean ± SD, mm)	4.7 ± 1.4	5.5 ± 1.5	4.2 ± 1.2	4.4 ± 1.0	4.9 ± 1.5	4.8 ± 1.5
Soft tissue thickness <5 mm, N (%)	25 (61%)	7 (34%)	8 (73%)	7 (70%)	33 (54%)	40 (56%)

[a]All other participants were female.

Table 2

Mean uncertainty[a], by overlying soft tissue thickness, of 3-minute *in vivo* bone Pb measurements using the portable XRF and KXRF systems (N = 60).

Soft tissue thickness	<5 mm	<6 mm	<7 mm	<8 mm
N (% of study population) Portable XRF measurements	32 (53%)	41 (68%)	54 (90%)	60 (100%)
Mean uncertainty ± SD (mg/kg dry bone)	4.9 ± 1.7	6.1 ± 2.8	8.6 ± 5.4	10.6 ± 8.2
% of observations >2*uncertainty KXRF measurements	28%	24%	22%	23%
Mean uncertainty ± SD (mg/kg bone mineral)	3.0 ± 0.7	2.9 ± 0.7	2.9 ± 0.6	3.1 ± 1.0
% of observations >2*uncertainty	72%	63%	56%	53%

[a]The DL of the XRF systems is approximately twice the mean uncertainty.

Table 3

Mean uncertainty[a], by overlying soft tissue thickness, of 5 min *in vivo* bone Pb measurements using the portable XRF and KXRF systems (N = 11).

Soft tissue thickness	<5 mm	<6 mm	<7 mm
N (% of study population)	8 (73%)	10 (91%)	11(100%)
Portable XRF measurements Mean uncertainty ± SD (mg/kg dry bone)	3.7 ± 1.5	4.3 ± 1.8	5.2 ± 3.6
% of observations >2* uncertainty	75%	80%	82%
KXRF measurements Mean uncertainty ± SD (mg/kg bone mineral)	2.0 ± 0.3	1.9 ± 0.3	1.9 ± 0.3
% of observations >2*uncertainty	64%	60%	63%

[a]The DL of the XRF systems is approximately twice the mean uncertainty.

Table 4

Correlation between *in vivo* bone Pb measurements *via* portable XRF and KXRF (N = 71).

Soft tissue thickness	**<5 mm**	**<6 mm**	**<7 mm**	**<8 mm**
Participant, N	40	51	65	71
Male, N (%)[a]	27 (68%)	32 (63%)	36 (55%)	37 (52%)
Correlation between bone Pb concentrations estimated by portable XRF and KXRF				
Unweighted	0.78	0.73	0.46	0.48
Uncertainty-weighted[b]	0.71	0.68	0.63	0.62

[a]All other participants were female.

[b]Observations weighted in inverse proportion to the uncertainty of portable XRF bone Pb estimate.

Table 5

Mean difference in bone Pb concentration per 5 years in age, as estimated with bone Pb measured *via* the portable XRF and KXRF, by soft tissue thickness.

Soft tissue thickness	<5 mm (N = 40)	≥5 mm (N = 31)	All (N = 71)
Age (years, Mean ± SD)	66 ± 12	60 ± 11	63 ± 11
Portable XRF measurements (mg/kg dry bone per 5 years in age)	0.87 (−0.50, 2.50)	1.60 (−2.10, 5.25)	0.65 (−1.05, 2.45)
KXRF measurements (mg/kg bone mineral per 5 years in age)	1.87 (0.40, 3.30)	1.30 (0.45, 2.15)	1.66 (0.80, 2.50)