

Toxic metals, lung function, blood pressure and arterial function in young adults: a multi- ethnic cross-sectional study

Mohammad Talaei

m.talaei@qmul.ac.uk

Wolfson Institute of Population Health, Queen Mary University of London

Alexander Griffiths

King's College London

Piotr Golda

King's College London

Alexis Karamanos

King's College London

J Kennedy Cruickshank

King's College London

Seeromanie Harding

King's College London

Seif O Shaheen

Wolfson Institute of Population Health, Queen Mary University of London

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Abstract

Background

Contemporary population-based studies of toxic metal exposure and health outcomes are lacking in the UK. We aimed to investigate associations between blood lead, cadmium and arsenic concentrations and lung function, blood pressure (BP), and arterial function in young adults.

Methods

In the Determinants of Adolescent Social Well-being and Health study, a multiethnic London cohort, blood lead, cadmium and arsenic concentrations were measured by Inductively Coupled Plasma Quadrupole Mass Spectrometry at 21–24.5 years of age. We analysed cross-sectional associations with lung function [Forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), and forced expiratory flow at 25–75% of FVC (FEF_{25–75})], BP (systolic /diastolic), and arterial function [pulse wave velocity (PWV) and central augmentation index (Aix)] (N = 442–473).

Results

The median (range) of blood lead concentrations was 10.8 (3.39–65.4) µg/L. In multivariable adjusted models, there was a non-linear negative association between blood lead concentrations and FEV₁/FVC and FEF_{25–75}, with the steepest reduction seen at the lowest concentrations; the reduction was – 4.78% (95% CI: -7.97, -1.59) and – 0.45 L/Sec (-0.82, -0.07), respectively, comparing the top with the bottom quintiles of lead. We did not find convincing evidence for associations between cadmium or arsenic and lung function, or between lead or cadmium and BP. However, there was evidence of non-linear positive associations between lead concentration and Aix and PWV, as well as between arsenic concentrations and BP.

Conclusions

Even at low levels of lead exposure, higher blood lead concentrations were associated with obstructive lung function impairment and increased aortic augmentation in young adults.

Background

Recent population-based studies of toxic metal exposure and potential health consequences in the UK are lacking. Consequently, we know little about contemporary exposure to lead, cadmium and arsenic, and whether low-level exposure might be impacting adversely on lung and cardiovascular health. Importantly, for lead exposure, we do not know what proportion of adults has blood lead concentrations $\geq 100\mu\text{g/L}$ ($10\mu\text{g/dL}$), the Public Health Intervention Concentration (PHIC) set by the UK Health Security Agency for non-pregnant adults (UKHSA) (1).

Evidence on the relation of lead and cadmium exposure to adolescent and adult lung function comes from cross-sectional studies in the US, Korea, Taiwan and China. With one exception, which analysed whole blood samples (the optimal biomarker for recent lead exposure measurement in epidemiological studies (2, 3)), other studies either analysed urine samples (4–10) or serum (11, 12) to assess exposure. All but one (7) of these studies found that higher lead and/or cadmium exposure was associated with lower lung function, the majority reporting obstructive lung function deficits. In contrast, a meta-analysis of studies across multiple low-income and middle-income countries (LMICs) found that higher arsenic exposure was associated with restrictive lung function impairment (13). Systematic reviews, mainly of cross-sectional studies, have also reported positive associations between arsenic, lead and cadmium exposure and higher blood pressure and hypertension (14–16). Two cross-sectional studies of adults in the US suggested that higher lead exposure is associated with increased arterial stiffness, although neither had reliable arterial measurements (17, 18).

Limited evidence from the US and UK suggests that certain ethnic groups, and people living in deprived areas, may have higher exposure to toxic metals. For example, Bangladeshis have been found to have higher blood lead concentrations and urinary concentrations of arsenic species, which may reflect exposure to imported spices such as turmeric and a high consumption of rice, respectively (19–22). Children living in older housing in deprived areas are more likely to have higher blood lead concentrations because of leaded paint and lead water pipes (23, 24), and disadvantaged adults are more likely to smoke, which is a major source of lead and especially cadmium exposure (25). This raises the possibility that higher toxic metal exposure might be contributing to ethnic and social health inequalities.

In a cross-sectional study of multi-ethnic young adults in London, we measured blood concentrations of lead, cadmium and arsenic and analysed their associations, firstly with smoking and sociodemographic factors, and secondly with multiple health outcomes, namely, lung function, blood pressure, and arterial function. We then explored whether higher toxic metal concentrations partly explain ethnic and social health inequalities.

Methods

Study population

The Determinants of Adolescent Social well-being and Health (DASH) cohort study is a multi-ethnic cohort which recruited 6,500 11-13 year olds from 51 secondary schools across 10 London boroughs in 2003-04 (26). In 2013/14 a representative 10% subsample (N=665) was followed up (27) (flow diagram in Supplementary **Figure S1**).

Exposure assessment

Whole blood samples were stored at -70°C and analysed at the London Metallomics Facility, King's College London. Samples were digested for 60 minutes at 100 °C in trace metal grade 15-mL polypropylene tubes (Elkay Scientific) using trace metal grade concentrated HNO₃ (67–69% w/w, Fisher Scientific) and H₂O₂ (≥ 30% w/w, Sigma Aldrich). Blood digests were diluted using purified water (resistivity ≥ 18.2 MΩ cm; Merck Millipore) spiked with iridium. Matrix-matched calibration standards were prepared by spiking processed horse blood (TCS Biosciences) with multi-element standard solutions (High-Purity Standards). Blood toxic metal concentration measurements were conducted on a Perkin Elmer NexION 5000 Inductively Coupled Plasma Quadrupole Mass Spectrometer (ICP-QMS) equipped with a CETAC ASX-560 autosampler operating in dynamic reaction cell or kinetic energy discrimination modes with oxygen and helium gas, respectively. Data validation was ensured through repeat analyses of certified reference materials from the National Institute of Standards and Technology (NIST SRM 955d), the Institute for Reference Materials and Measurements (BCR-635), and Recipe (ClinChek). An optimised acid digestion protocol for blood sample preparation, coupled with the latest ICP-MS instrumentation, provided the enhanced sensitivity and low detection limits necessary to quantify toxic metals at sub-ppb concentrations.

We did not find toxic metal values below the limit of detection. Repeat analyses of blood reference materials demonstrated long-term reproducibility of 3–13% RSD for As (0.6–275 µg L⁻¹), 3–18% RSD for Cd (0.25–20 µg L⁻¹), and 2–6% RSD for Pb (5–250 µg L⁻¹). Method performance was validated through repeat analyses of NIST SRM 955d Level I and II (National Institute of Standards and Technology), BCR-635 (Institute for Reference Materials and Measurements), and ClinChek Level III (Recipe), which yielded results within 8% of certified values for all elements.

Outcome assessment

Lung function was assessed by spirometry (Micro-plus spirometer; Micro Medical Ltd., Kent, UK) (27). Measured parameters included Forced Expiratory Volume in one second (FEV₁), Forced Vital Capacity (FVC), and Forced Expiratory Flow at 25-75% of FVC (FEF₂₅₋₇₅). Participants performed three forced expiratory manoeuvres, up to a maximum of five. The highest values of FEV₁ and FVC were used in the analysis, and the proportion of individuals achieving repeatable FEV₁ and FVC (difference between highest and second highest values ≤ 0.150 L) was calculated as 87.8% and 81.7%, respectively. The FEF₂₅₋₇₅ value coming from the manoeuvre with the highest sum of FEV₁ and FVC was used in the analysis (28).

Systolic and diastolic blood pressure (SBP, DBP) were measured using an OMRON M5-I semiautomatic device after the participant had sat quietly for 5 minutes with more than 1 minute between three readings (27). The mean of the second and third readings was analysed. Aortic pulse wave velocity (PWV), central (aortic) augmentation index (Alx) and brachial BP were also measured using an Arteriograph 24-hour device (Tensiomed, Budapest, Hungary) (29, 30). The Arteriograph device has been calibrated many times against 2-point tonometry and magnetic resonance flow-wave imaging (31, 32).

Aortic PWV, in m/sec, is the 'gold standard' measure of aortic stiffening, and of great interest because of its powerful, consistent prediction of cardiovascular events and mortality over and above that of BP alone (33). Central Alx is also impressively predictive of later cardiovascular events, hence its potential utility (34). However, how much is related to reflected waves or proximal aortic 'stiffness' is uncertain. The extra 'height' of the recorded waveform above the initial peak of systolic pressure is 'augmentation', and divided by the pulse pressure (systolic minus diastolic), forms the index. Alx is therefore as much related to ambient BP as to aortic stiffness.

Covariates

A self-administered questionnaire measured smoking (active and passive), alcohol consumption and socioeconomic circumstances (own education and employment) at 21-23 years. Ethnicity was self-reported and checked against reported parental ethnicity and grandparents' country of birth. Anthropometric measurements included standing height, sitting height, weight, waist circumference and hip circumference, from which body mass index (BMI) and waist hip ratio (WHR) were calculated.

Statistical analyses

We quantified blood concentrations of lead, cadmium and arsenic (median and interquartile range) and prevalence (95% CIs) of lead concentrations ≥10µg/dL (UKHSA PHIC for adults) in the whole cohort, and then compared median concentrations of toxic metals univariately across ethnic groups (White, Black Caribbean, Black African, Indian, Bangladeshi, Pakistani, other) and socioeconomic circumstances (own education/employment, domestic crowding at age 21-23 years, index of multiple deprivation) using the Kruskal–Wallis test. To determine whether ethnicity and socioeconomic circumstances (exposure variables) were independently associated with toxic metal concentrations (continuous outcomes, log-transformed), we used multivariable linear regression with robust standard errors to estimate geometric mean ratios (GMRs) and 95% CIs in mutually adjusted models, also controlling for age, sex, and smoking.

To account for anthropometric differences, we first explored the best model predicting lung function measures by sequentially adding age², height², height³, and sitting height to a base model (age, height, and ethnicity) for each measure separately (Supplementary **Table S1**). We used linear regression to analyse associations between quintiles of blood toxic metal concentrations and lung function measures, controlling for age and height as explained above plus sex, weight, smoking status, socioeconomic circumstances, and ethnicity, informed by the literature and a directed acyclic graph (Supplementary **Figure S2**). Given this multi-ethnic population, we chose to adjust lung function for age, sex, height and ethnicity in the regression model, rather than using external (e.g. Global Lung Initiative) reference equations; whilst z-scores could be derived within this population, an advantage of presenting absolute differences in lung function is for interpretability and comparison with other exposure effect sizes. We obtained P for trend by testing median values of each quintile group as a pseudo-continuous variable in the similar multivariable regression models.

We also used linear regression to analyse associations between quintiles of blood toxic metal concentrations and systolic and diastolic blood pressure as well as PWV and central AIx, controlling for the following covariates, informed by the literature and a directed acyclic graph (Supplementary **Figure S3**): age, sex, active smoking, body mass index, waist to hip ratio, alcohol intake, socioeconomic circumstances, and ethnicity.

Using restricted cubic splines (RCS), we explored toxic metal concentrations continuously to test evidence of non-linear associations and to evaluate the dose-response relationships. We applied 3, 4, and 5 knots defined at the recommended percentiles (35) of original-scale as well as log-scale toxic metal concentrations, and at alternative points slightly shifted toward the tail (~10%) to provide extra flexibility. Of the 9 RCS models for each toxic metal, we selected the one with the lowest Akaike Information Criterion (AIC) value, representing the best goodness of fit penalised for the model's complexity, and tested nonlinearity using a likelihood ratio test (35), and visually tested the curve when evidence for a non-linear association was borderline. For presentation purposes, we dropped extreme values above the 99.5th percentile. When RCS analysis suggested a non-linear association, we estimated the changes in the outcome of interest associated with a 5µg/L reduction from the median lead concentration.

We used linear regression to analyse associations of ethnicity and socioeconomic circumstances (exposures) with health outcomes, after controlling for age and sex (and height for FVC, FEV₁, and FEF₂₅₋₇₅), and then adjusted for toxic metal concentrations to determine whether these associations (if confirmed) might partly be explained by higher toxic metal exposure. Similarly, we explored whether higher blood lead, and especially cadmium, concentrations partly explained associations of smoking with lung function.

In sensitivity analyses, we tested associations with FEV₁/FVC in those without a history of asthma and further controlled the associations with indices of arterial stiffness for brachial mean arterial pressure (MAP).

We defined a category for missing values of nominal covariates (missing-indicator method for education, employment, crowding, alcohol intake, and smoking) and imputed missing values of continuous covariates using stochastic regression imputation (24 cases for sitting height and 16 cases for waist-to-hip ratio; details in supplementary file). All statistical analyses were carried out using Stata version 18.0 (StataCorp, College Station, TX, USA).

Results

The mean (standard deviation) of participants' age was 22.7 (0.80), ranging from 20.9 to 24.5 years, and 228 (48.2%) were female. The geometric mean (95% CI) blood concentrations were 10.9 µg/L (10.4-11.3) for lead, 0.24 µg/L (0.22-0.25) for cadmium, and 0.79 µg/L (0.73-0.86) for arsenic. None of the participants had blood lead concentrations ≥100 µg/L, and only 3 (0.63%) had concentrations ≥50 µg/L. There was a mild correlation between blood lead and cadmium concentrations (Pearson correlation coefficient = 0.33), while the correlations with arsenic were trivial.

Risk factors for raised blood toxic metal concentrations

Table 1 shows the distribution of blood toxic metal concentrations according to sociodemographic, environmental, and behavioural factors univariately, and in mutually adjusted models using geometric mean ratios. Males had higher concentrations of lead and lower concentrations of cadmium than females, independent of all other factors. Those of Bangladeshi ethnicity had the highest concentrations of lead and cadmium, followed by Whites. These two ethnic groups still had the highest concentrations of these metals when controlled for other factors. Cadmium concentrations were higher in individuals with lower educational attainment, but this trend was almost entirely explained by other factors in the mutually adjusted model. Regular smokers had the highest concentrations of cadmium and to a lesser extent lead, followed by occasional smokers; these contrasts remained unchanged when controlled for other factors.

Lung function

Of 473 participants with toxic metal measurements, 442 individuals had lung function assessments. In our categorical analyses using quintiles, while lead concentration was positively associated with FEV₁ and FVC in crude models, these associations were substantially attenuated after controlling for potential confounders (**Table 2**). However, participants in the top quintile of lead concentration had a 5.1% lower FEV₁/FVC ratio than those in the bottom quintile; this negative association was only slightly attenuated after controlling for covariates. By comparison, FEF₂₅₋₇₅ values were nearly identical in the top and bottom quintiles of lead concentration in the crude model, but evidence of a negative association emerged after controlling for age, sex, and indicators of socioeconomic position, and did not materially change after further adjustment (**Table 2** and Supplementary **Table S2**).

In our RCS analysis, we found evidence of non-linear negative associations between lead concentrations and FEV₁/FVC and FEF₂₅₋₇₅ (P for nonlinearity 0.084 and 0.039, respectively). The shapes of the dose-response associations in **Figures 1** and **2** show similar patterns, with a rapid decline at the low end of the observed range, reaching its nadir around the 75th percentile of lead concentrations, with almost no further decline thereafter. Precision was limited (wider confidence limits) at lead concentrations higher than the median (10.7 µg/L) by relatively fewer individuals over a wide range of values. A 5µg/L decrease from the median lead concentration was associated with a 2.41% (95% CI 0.26, 4.57) higher FEV₁/FVC and a 0.29 L/s (95% CI 0.04, 0.54) higher FEF₂₅₋₇₅. To put this into clinical context, in a multivariable adjusted model, participants without asthma had 3.96% higher FEV₁/FVC (β -3.96; 95% CI -7.23, -0.68) and 0.59 L/s higher FEF₂₅₋₇₅ (β -0.59; 95% CI -0.96, -0.21) than those with asthma in the last 12 months.

We did not find convincing evidence of associations between quintiles of cadmium or arsenic concentrations and lung function measures (Supplementary **Tables S3** and **S4**), except for a negative association in the fourth quintile of cadmium with FEF₂₅₋₇₅. However, RCS analysis showed evidence of non-linear associations between cadmium and FEV₁ (P for nonlinearity 0.004) and FEF₂₅₋₇₅ (P for nonlinearity 0.009). While a higher concentration was associated with lower FEV₁ and FEF₂₅₋₇₅ (similar to lead) in most participants, an opposite trend was observed in the higher end of the distribution, starting from around the 80th percentile (Supplementary **Figures S4** and **S5**).

Blood pressure and arterial stiffness

Almost all participants with toxic metal measurements had data on blood pressure and arterial stiffness (n=472). We did not find convincing evidence of associations between blood pressure and lead, cadmium, or arsenic in categorical analyses (supplementary **Tables S2-S4**). However, participants with blood lead concentrations in the second quintile and above had a higher aortic Alx than those in the first quintile in the fully adjusted model, which persisted after further controlling for brachial BP, although slightly attenuated in the higher quintiles.

In our RCS analysis, we found evidence of non-linear associations between lead concentrations and aortic Alx and PWV (P for nonlinearity 0.006 and 0.04, respectively). The pattern of association mirrored that for lung function measures, with a steep upward trend showing greater Alx associated with higher lead concentration up to around the median level, after which it plateaued (**Figure 3** and Supplementary **Figure S6**). A 5µg/L reduction from the median lead concentration was associated with a 0.40 log% (95% CI -0.61, -0.18) lower aortic Alx and a 0.83 m/s (95% C -1.50, -0.16) lower PWV. Cadmium and arsenic were not associated with arterial stiffness. The association of arsenic concentration (log-scale) with blood pressure had a U-shaped pattern, with an extended mid-range plateau for most measures (Supplementary **Figures S7-S10**). The only exception was arteriograph aortic SBP where the association was J-shaped (Supplementary **Figures S11**). A roughly 2 µg/L decrease from the 95-percentile arsenic concentration (3.89 µg/L) was associated with -1.62 (-2.69, -0.54) mmHg DBP, -3.21 (-5.19, -1.23) mmHg arteriographic DBP, -2.29 (-4.40, -0.18) mmHg SBP, -3.18 (-5.70, -0.65) mmHg arteriographic brachial SBP, and -2.35 (-4.01, -0.69) mmHg arteriographic aortic SBP [(β (95% CI)].

Sensitivity analysis and exploration of potential mediation

In participants with no history of asthma (n=316), we found a relatively stronger association between lead concentrations and FEV₁/FVC (β comparing top to bottom quintiles: -5.23, 95% CI -9.31 to -1.15; P for trend = 0.02). The association between lead concentration and FEF₂₅₋₇₅ was slightly weaker in this subgroup (β comparing top to bottom quintiles -0.62, 95% CI -1.08 to -0.15; P for trend 0.02). The strength and shape of associations did not materially change in complete-case sensitivity analysis among ~77% of participants with no missing covariates.

We explored associations between ethnicity, index of multiple deprivation, education, and smoking and measures of lung function, blood pressure, and arterial stiffness (Supplementary **Tables S5** and **S6**). Non-white ethnicities had lower FEV₁, FVC, FEF₂₅₋₇₅, SBP and Aortic PWV, compared to Whites, independent of age, sex, and height. However, ethnic differences did not materially change when controlled for lead or cadmium concentrations. We did not find convincing evidence of associations between IMD and health outcomes. Education was negatively associated with FEV₁/FVC and positively with PWV, but the associations were not materially changed when controlled for lead or cadmium.

Regular smokers had a 3.6% lower FEV₁/FVC than never smokers (β -3.59, 95% CI -6.35 to -0.84), and this was slightly attenuated to around 2.9% when controlled for lead (β -2.89, 95% CI -5.68 to -0.11) or cadmium (β -2.91, 95% CI -6.25 to 0.43). The negative association between lead and FEV₁/FVC and FEF₂₅₋₇₅ remained of similar magnitude in a subgroup of 295 non-smokers (β comparing top to bottom quintiles -4.40%, 95% CI -8.07 to -0.73; P for trend 0.03 and -0.46 L/Sec, 95% CI -0.90 to -0.01; P for trend 0.06). Similarly, evidence for associations between lead and other lung function measures, as well as for associations between cadmium and arsenic and lung function, was limited among non-smokers.

Discussion

In this population-based cross-sectional study of young London adults, higher blood concentrations of lead were non-linearly associated with a lower FEV₁/FVC ratio and FEF₂₅₋₇₅, indicating an obstructive lung function deficit, including small airway involvement. The % increase in FEV₁/FVC associated with a 5µg/L reduction in blood lead concentration below the median was equivalent to 61% of the difference in this parameter, comparing non-asthmatic with asthmatic individuals in this cohort. For cadmium, there was some evidence for negative associations with FEV₁ and FEF₂₅₋₇₅ at low concentrations.

These findings add to growing evidence from previous cross-sectional studies of adolescents and adults suggesting that higher exposure to lead and/or cadmium is associated with impaired lung function, especially airflow obstruction (3–6, 8–12, 36). To our knowledge, we are the first to confirm this in the UK. In contrast to previous studies (13), we did not confirm restrictive lung function impairment associated with higher arsenic exposure, although those studies were predominantly in LMICs, where higher levels of arsenic exposure are likely.

Importantly, our findings show that detrimental, non-linear associations with lung function are seen at very low blood concentrations of lead; no individual had concentrations $\geq 100\mu\text{g/L}$ ($10\mu\text{g/dL}$), the UKHSA PHIC for adults, and only three individuals had concentrations $\geq 50\mu\text{g/L}$. We cannot comment on the comparability of lead exposure levels in previous studies of lead and lung function, as the majority did not measure lead concentrations in whole blood. Of note, the restricted cubic spline curves clearly demonstrated that these associations were characterised by steeper reductions at lower lead concentrations, with a flattening of the associations at higher concentrations, in other words a ‘decelerating dose-response curve’. While monotonic (linear) dose-response associations are uncommon, and most biological relationships are indeed non-linear (37), they remain fundamental to causal assessment in fields such as toxicology (38). However, the absence of a dose-response relationship does not exclude causality, given possible threshold or non-monotonic responses (39). A decelerating dose-response curve has been reported in studies of childhood lead exposure and cognitive function (40). Whilst it has been mooted that this phenomenon might have arisen through failure to adjust for a strong, non-linear confounder, it has been argued that this is unlikely (41). To our knowledge, we are the first to describe a decelerating dose-response curve for lead and lung function. Use of restricted cubic spline curves enabled us to fully understand this non-linear relationship; this approach is particularly useful when the distribution of the exposure is very low and/or within a narrow range, and conventional quantile analysis has limitations (42), as was the case with blood lead concentrations in our dataset.

The higher blood concentrations of lead and especially cadmium in smokers were expected (25), and thus helped to validate our data. There are two potential explanations for the modest attenuation of the association between smoking and lower FEV_1/FVC on adjustment for blood lead and cadmium concentrations. Either these metals are on the causal pathway, or there was misclassification of reported smoking habits, which was reduced by adjustment for these objective biomarkers of smoking. Interestingly, a reduction in FEV_1/FVC with higher blood lead concentrations was also seen in non-smokers, suggesting that sources of lead exposure other than tobacco smoke may be important. These may include leaded paint or lead water pipes in older housing (23), spices from Asia (21), and (perhaps most relevant to lung function) air pollution. Toxic metals do not degrade, and a study of London air particles, contemporary with blood samples collected in our study, reported that much of the lead still in London air was derived from petrol, even though leaded petrol was banned in 2000 (43). Whilst non-White ethnicities had lower lung function than Whites, as expected, these differences were not explained by higher toxic metal exposure.

We found no association between blood lead concentrations and blood pressure, in contrast to a systematic review (15) and studies of low-level lead exposure (44, 45), which reported positive associations with adult blood pressure and hypertension. Nor did we confirm an association between higher blood cadmium concentrations and raised blood pressure (16, 44–47). A potential explanation is that we lacked statistical power to detect small differences in blood pressure in a sample of young adults in whom high blood pressure is uncommon.

We detected a positive association between blood arsenic concentrations and blood pressure, although urine, and not blood, is the optimal sample type for measuring arsenic exposure. In keeping with a systematic review (14), the association was non-linear; unlike that review, which reported associations predominantly with systolic blood pressure, we found similar associations with systolic and diastolic blood pressure.

Evidence is limited on lead and Alx (which mainly indicates greater height of reflected waves from across the body) and PWV (as the measure of arterial stiffness) in population-based studies, but our findings are in keeping with two cross-sectional studies of adults in the US (17, 18).

Regarding potential mechanisms, we speculate that the association between lead and airflow obstruction reflects airway damage mediated by oxidative stress (48). Epigenetic mechanisms involving altered DNA methylation may also operate (49). Both mechanisms may mediate the association between lead and arterial stiffness.

Given the ages of the participants, minimal lung function decline will have occurred by the ages under study. Therefore, it seems likely that lead exposure will have caused damage to airway growth. Blood lead concentrations are correlated with bone lead levels (50), which are a biomarker for chronic, cumulative exposure (half-life in bone 20–30 years) (51).

Our novel finding, that associations between lead and both lung function and arterial stiffness are characterised by a decelerating dose response curve, suggests a potential saturable process as lead exposure increases, although this is speculative. As the precise mechanism underlying this phenomenon is unknown, a causal interpretation should be cautious.

Our population-based study has a number of strengths. First, it fills a gap in knowledge regarding contemporary exposure to toxic metals and associations with multiple health outcomes in the UK; data on lead exposure have been lacking since the early 1990s. Second, the sensitivity of our laboratory assay enabled us to measure very low blood concentrations of the three metals, and hence to determine whether, even low levels of exposure, were associated with poorer health outcomes. Third, in contrast to previous studies of lead/cadmium and lung function, which mainly used urine samples to measure exposure, we measured these two metals in whole blood; lead concentration in whole blood is the preferred biomarker to monitor lead exposure (2). Our study also had a number of limitations. As our analyses were cross-sectional, causal inference is limited, although we would argue that reverse causation (by which lower lung function or higher arterial stiffness would cause higher blood lead concentrations) is unlikely. The importance of controlling rigorously for potential confounding of lead-cognitive function associations at low levels of lead exposure has been

highlighted (52, 53); whilst we controlled for a large number of potential confounders, as with any observational study, the possibility of unmeasured or residual confounding cannot be ruled out. Other limitations included measurement of total arsenic in blood (urine samples are preferred, but were not available); a lack of post-bronchodilator spirometry to confirm whether airflow obstruction was fixed, although the relation between lead and FEV₁/FVC was stronger in those without asthma, suggesting fixed obstruction; and the modest sample size and statistical power, which may have limited our ability to detect small associations between the toxic metals and blood pressure.

Public health implications

Although the drastic reduction in lead exposure resulting from the removal of lead from petrol and paint (54) should be regarded as a public health success, our study suggests that low levels of lead exposure (well below the current UK PHIC for adults) may contribute to airflow obstruction and arterial stiffness. Whilst our findings should be further investigated in longitudinal studies, they are in keeping with other evidence suggesting that chronic, low-level lead poisoning is a risk factor for adult health, including cardiovascular disease, and that there may be no safe level of lead exposure (54). If true, we would call into question the usefulness of an arbitrary PHIC if we wish to protect the general population, for two reasons. First, given the lack of a blood lead screening programme, the UKHSA has no population-based data to act on, only passive surveillance of suspected cases of lead poisoning. Second, our data suggest that the greatest risks of adverse consequences for lung and cardiovascular health are seen at blood lead concentrations which are ten-fold lower than the current PHIC for adults.

Declarations

Ethics approval and consent to participate: The study was approved by the National Health Service South East Scotland Research Ethics Committee (reference 11/SS/0051). Written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication: Not applicable

Availability of data and materials: The DASH data are available to researchers via a data request to Professor Seeromanie Harding (seeromanie.harding@kcl.ac.uk). The data sharing policy for DASH reflects the MRC guidance on data sharing with the aim of making the data as widely and freely available as possible while safeguarding the privacy of participants, protecting confidential data, and maintaining the reputation of the study. All potential collaborators work with a link person, an experienced DASH researcher, to support their access to and analysis of the data. The variable-level metadata is available from the study team and via the MRC Data Gateway.

Competing 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.

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Authors' contributions (CRediT):

MT: Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review and editing. **AG:** Funding acquisition, Supervision of laboratory analyses, Writing - review and editing. **PG:** laboratory analyses, Writing - review and editing. **AK:** Writing - review and editing. **JKC:** Writing - review and editing. **SH:** Funding acquisition, Resources, Writing - review and editing. **SS:** Funding acquisition, Conceptualization, Methodology, Project administration, Writing - original draft, Writing - review and editing. All authors read and approved the final manuscript.

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Tables

Table 1. Blood concentrations of lead, cadmium, and arsenic according to ethnic and sociodemographic characteristics and lifestyle factors in univariate and mutually adjusted models.

		Lead (µg/L)		Cadmium (µg/L)		Arsenic (µg/L)	
	N (%)	Median (IQR)	GMR [†] (95% CI)	Median (IQR)	GMR [†] (95% CI)	Median (IQR)	GMR [†] (95% CI)
Age at interview, y	473 (100%)		0.99 (0.95-1.05)		1.04 (0.96-1.13)		0.96 (0.86-1.07)
Sex							
Female	228 (48.2%)	9.79 (5.06)	1.00	0.24 (0.22)	1.00	0.77 (1.04)	1.00
Male	245 (51.8%)	11.70 (7.68)	1.18 (1.10-1.28)	0.18 (0.26)	0.74 (0.65-0.83)	0.80 (0.90)	1.12 (0.93-1.34)
<i>P</i> -value*		<0.001		0.008		0.67	
Ethnicity							
White	98 (20.7%)	12.03 (8.78)	1.24 (1.06-1.45)	0.28 (0.66)	1.47 (1.19-1.81)	0.75 (1.32)	1.21 (0.87-1.68)
Black Caribbean	67 (14.2%)	8.26 (4.80)	1.00	0.17 (0.16)	1.00	0.72 (0.84)	1.00
Black African	96 (20.3%)	10.97 (4.83)	1.27 (1.11-1.45)	0.21 (0.20)	1.23 (1.02-1.47)	0.82 (0.83)	1.17 (0.88-1.55)
Indian	62 (13.1%)	10.55 (4.76)	1.18 (1.00-1.40)	0.24 (0.29)	1.25 (1.00-1.56)	0.52 (0.78)	0.74 (0.51-1.07)
Pakistani	41 (8.7%)	11.67 (6.86)	1.17 (0.97-1.41)	0.22 (0.25)	1.10 (0.83-1.48)	0.71 (1.00)	1.06 (0.73-1.53)
Bangladeshi	32 (6.8%)	12.73 (7.40)	1.37 (1.12-1.66)	0.29 (0.36)	1.33 (1.03-1.72)	0.71 (0.76)	1.02 (0.72-1.43)
Mixed/Other	77 (16.3%)	10.65 (5.50)	1.13 (0.97-1.30)	0.17 (0.22)	1.08 (0.88-1.32)	0.97 (1.00)	1.44 (1.06-1.95)
<i>P</i> -value*		<0.001		<0.001		0.005	
Education							
Degree	222 (46.9%)	10.33 (5.88)	1.00	0.19 (0.21)	1.00	0.81 (1.14)	1.00
A level/Prof	187 (39.5%)	11.16 (5.94)	1.04 (0.95-1.13)	0.24 (0.24)	0.97 (0.85-1.10)	0.76 (0.83)	0.84 (0.68-1.03)
GCSE/None	23 (4.9%)	13.11 (9.51)	1.19 (0.98-1.45)	0.43 (0.49)	1.02 (0.70-1.47)	0.93 (1.34)	1.20 (0.78-1.83)
Missing	41 (8.7%)	11.15 (7.43)	0.94 (0.72-1.24)	0.33 (0.40)	1.18 (0.87-1.59)	0.75 (0.84)	0.79 (0.37-1.66)
<i>P</i> -value*		0.07		0.021		0.37	
Employment							
Working Ft/Pt	219 (46.3%)	11.40 (6.22)	1.00	0.23 (0.27)	1.00	0.77 (0.88)	1.00
Student	147 (31.1%)	10.06 (5.71)	0.93 (0.85-1.02)	0.20 (0.18)	0.92 (0.80-1.06)	0.81 (0.97)	0.94 (0.75-1.18)
Others	44 (9.3%)	10.02 (7.08)	0.89 (0.76-1.04)	0.19 (0.20)	0.80 (0.67-0.97)	0.92 (1.26)	1.18 (0.88-1.60)
Missing	63 (13.3%)	11.15 (7.05)	1.11 (0.94-1.32)	0.26 (0.32)	0.97 (0.74-1.27)	0.80 (0.96)	1.19 (0.85-1.68)
<i>P</i> -value*		0.095		0.20		0.27	
No. per bedroom							
≤1	177 (37.4%)	10.79 (6.94)	1.00	0.21 (0.23)	1.00	0.77 (1.03)	1.00
>1<1.5	103 (21.8%)	9.92 (5.14)	0.95 (0.85-1.06)	0.23 (0.26)	1.08 (0.92-1.27)	0.74 (0.97)	0.95 (0.76-1.20)
≥1.5<2	88 (18.6%)	11.35 (5.94)	1.05 (0.93-1.18)	0.22 (0.20)	1.05 (0.90-1.22)	0.85 (1.07)	1.05 (0.82-1.35)
≥2	57 (12.1%)	11.67 (6.72)	1.03 (0.90-1.18)	0.20 (0.22)	1.08 (0.90-1.31)	0.82 (0.72)	0.90 (0.68-1.18)
Missing	48 (10.1%)	10.11 (7.83)	0.89 (0.73-1.08)	0.25 (0.30)	0.91 (0.66-1.25)	0.79 (0.94)	1.00 (0.60-1.68)
<i>P</i> -value*		0.64		0.90		0.72	
National Deciles of IMD							
D1: Most deprived	61 (12.9%)	10.54 (6.51)	0.92 (0.81-1.05)	0.24 (0.16)	0.89 (0.73-1.10)	0.75 (0.88)	0.99 (0.72-1.35)
D2	111 (23.5%)	11.30 (6.98)	1.04 (0.92-1.18)	0.22 (0.23)	0.94 (0.78-1.14)	0.80 (1.00)	0.95 (0.74-1.22)
D3-4	79 (16.7%)	10.55 (5.21)	0.98 (0.86-1.11)	0.20 (0.26)	0.95 (0.77-1.17)	0.72 (0.97)	0.91 (0.68-1.21)
D5-6	89 (18.8%)	10.38 (6.03)	0.97 (0.86-1.09)	0.18 (0.20)	0.81 (0.67-0.97)	0.77 (0.87)	0.92 (0.70-1.20)
D7-10: Least deprived	102 (21.6%)	11.15 (7.03)	1.00	0.24 (0.27)	1.00	0.84 (1.06)	1.00

Missing	31 (6.6%)	11.49 (5.63)	1.01 (0.87-1.19)	0.19 (0.27)	0.85 (0.68-1.07)	0.71 (0.79)	0.74 (0.53-1.03)
<i>P</i> -value*		0.82		0.26		0.98	
Smoking frequency							
Never	187 (39.5%)	9.93 (5.29)	1.00	0.17 (0.15)	1.00	0.78 (0.98)	1.00
Past	115 (24.3%)	10.41 (6.79)	1.09 (0.97-1.21)	0.17 (0.15)	0.96 (0.83-1.11)	0.77 (0.85)	1.07 (0.84-1.35)
Occasional	56 (11.8%)	11.55 (5.80)	1.13 (0.99-1.30)	0.26 (0.31)	1.55 (1.24-1.94)	0.92 (1.44)	1.26 (0.87-1.82)
Regular	79 (16.7%)	12.52 (7.78)	1.22 (1.08-1.38)	0.64 (0.84)	3.79 (3.13-4.60)	0.69 (1.06)	0.97 (0.74-1.28)
Missing	36 (7.6%)	11.04 (7.90)	1.62 (1.10-2.38)	0.33 (0.38)	1.96 (0.86-4.48)	0.77 (0.87)	0.35 (0.05-2.35)
<i>P</i> -value*		<0.001		<0.001		0.80	
Alcohol consumption							
Never	157 (33.2%)	10.70 (6.08)	1.00	0.22 (0.20)	1.00	0.76 (0.85)	1.00
Occasional	151 (31.9%)	9.48 (5.10)	0.87 (0.78-0.97)	0.19 (0.19)	0.92 (0.78-1.08)	0.78 (0.99)	0.96 (0.76-1.22)
Weekly	128 (27.1%)	12.45 (8.29)	1.11 (0.97-1.28)	0.25 (0.37)	0.94 (0.77-1.16)	0.81 (1.13)	0.91 (0.69-1.20)
Missing	37 (7.8%)	10.92 (7.38)	0.70 (0.48-1.02)	0.33 (0.37)	0.90 (0.36-2.27)	0.79 (0.89)	2.41 (0.40-14.65)
<i>P</i> -value*		<0.001		0.14		0.92	
BMI, kg/m²							
<18.5	19 (4.0%)	11.28 (6.72)	0.95 (0.79-1.15)	0.27 (0.21)	0.96 (0.67-1.36)	0.64 (0.90)	0.97 (0.58-1.62)
18.5-24.9	272 (57.5%)	11.16 (5.93)	1.00	0.23 (0.25)	1.00	0.79 (0.86)	1.00
25-29.9	121 (25.6%)	10.52 (7.47)	0.95 (0.87-1.04)	0.18 (0.23)	0.87 (0.74-1.01)	0.94 (1.24)	1.15 (0.93-1.40)
>30	61 (12.9%)	9.48 (5.61)	0.93 (0.82-1.06)	0.17 (0.24)	0.89 (0.74-1.07)	0.67 (0.90)	0.94 (0.71-1.24)
<i>P</i> -value*		0.21		0.03		0.27	

GMR: Geometric mean ratio; IQR: Interquartile range; IMD: Index of multiple deprivation; BMI: Body mass index

* *P*-values were calculated by the Kruskal–Wallis test; the missing categories were excluded from the test

† Mutually adjusted for all factors shown in the table.

Table 2. Lung function measures according to quintiles of blood lead concentrations

	Quintiles of Lead					P-trend
	Q1	Q2	Q3	Q4	Q5	
Median (Range), µg/L	6.06 (3.39-7.56)	8.48 (7.59-9.59)	10.7 (9.60-11.9)	13.1 (11.9-15.7)	19.2 (15.8-65.4)	
FEV₁, L						
mean ± SD	3.17 ± 0.75	3.34 ± 0.81	3.25 ± 0.75	3.33 ± 0.78	3.67 ± 0.84	
Crude model	0.00	0.17 (-0.07, 0.40)	0.08 (-0.16, 0.31)	0.16 (-0.08, 0.39)	0.50 (0.27, 0.74)	<0.001
Adjusted model	0.00	-0.04 (-0.19, 0.11)	-0.07 (-0.22, 0.09)	-0.06 (-0.22, 0.10)	-0.04 (-0.21, 0.12)	0.71
FVC, L						
mean ± SD	3.76 ± 0.96	4.10 ± 1.01	3.98 ± 0.99	4.17 ± 1.14	4.62 ± 1.00	
Crude model	0.00	0.33 (0.03, 0.64)	0.22 (-0.09, 0.52)	0.40 (0.10, 0.71)	0.86 (0.55, 1.17)	<0.001
Adjusted model	0.00	0.05 (-0.16, 0.26)	0.03 (-0.19, 0.24)	0.10 (-0.12, 0.31)	0.16 (-0.07, 0.39)	0.13
FEV₁/FVC, %						
mean ± SD	84.95 ± 8.10	81.88 ± 8.11	82.50 ± 9.79	81.39 ± 11.43	79.87 ± 9.86	
Crude model	0.00	-3.07 (-5.91, -0.23)	-2.46 (-5.31, 0.39)	-3.56 (-6.40, -0.72)	-5.09 (-7.97, -2.21)	0.001
Adjusted model	0.00	-2.62 (-5.55, 0.32)	-2.22 (-5.20, 0.77)	-2.83 (-5.87, 0.21)	-4.78 (-7.97, -1.59)	0.008
FEF₂₅₋₇₅, L/s						
mean ± SD	3.41 ± 1.09	3.22 ± 1.30	3.24 ± 1.22	3.15 ± 1.28	3.42 ± 1.31	
Crude model	0.00	-0.19 (-0.56, 0.18)	-0.17 (-0.54, 0.20)	-0.26 (-0.63, 0.11)	0.01 (-0.36, 0.39)	0.76
Adjusted model	0.00	-0.31 (-0.66, 0.03)	-0.30 (-0.64, 0.05)	-0.40 (-0.76, -0.05)	-0.45 (-0.82, -0.07)	0.04

FEV₁: Forced Expiratory Volume in one second, FVC: Forced Vital Capacity, FEF₂₅₋₇₅: Forced Expiratory Flow at 25-75% of FVC

Associations are reported as regression β coefficient (95% Confidence Interval) for crude and adjusted models.

The adjusted model included age, sex, ethnicity, education, employment, number of people per bedroom, index of multiple deprivation, active smoking, weight, and height (except FEV₁/FVC), plus age², height² and sitting height for FEV₁ and FVC.

N=442 for FEV₁, FVC, and FEV₁/FVC and n=440 for FEF₂₅₋₇₅.

Figures

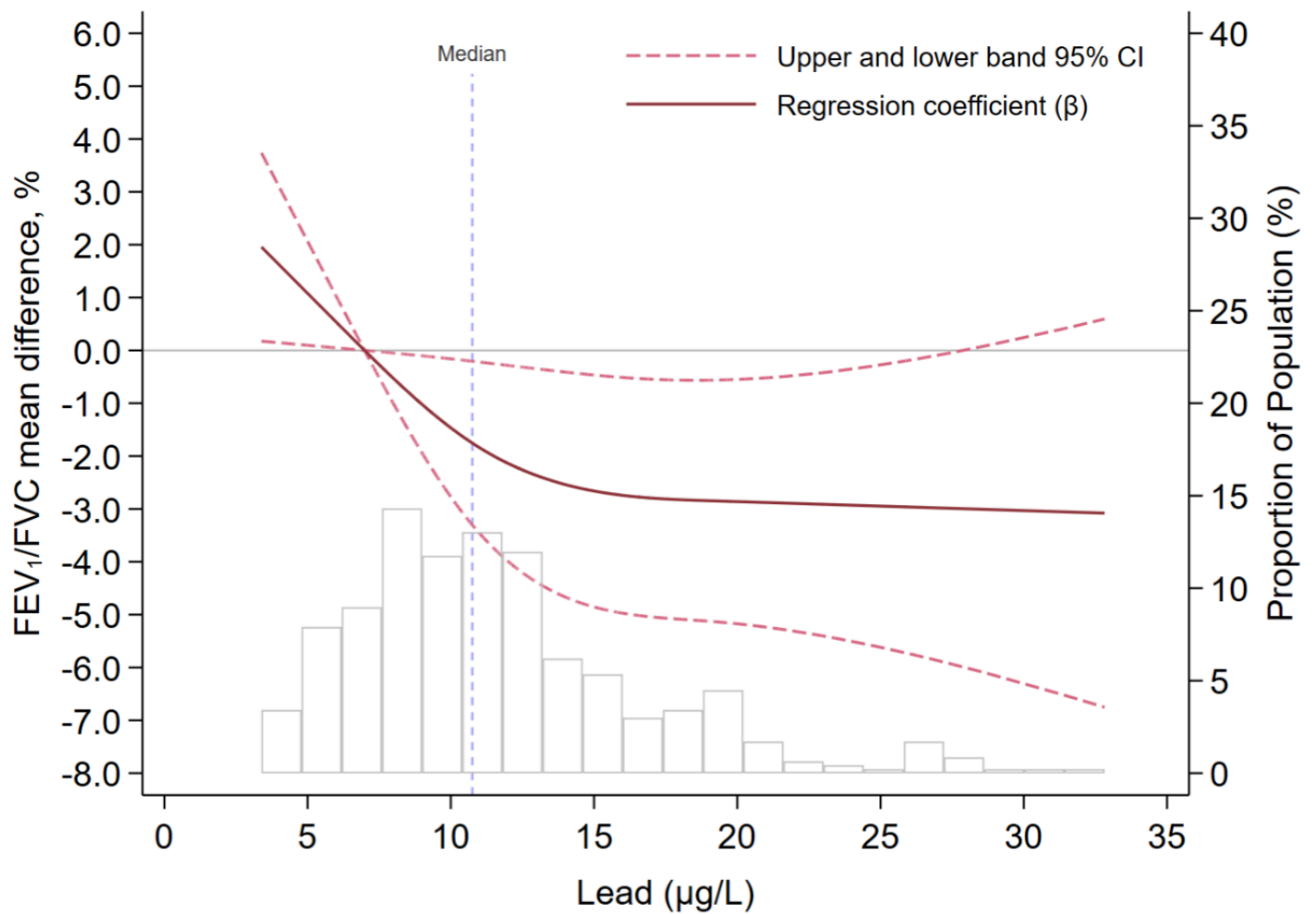


Figure 1

Restricted cubic spline graph for the association between blood lead concentrations and forced expiratory volume in one second to forced vital capacity ratio in a multivariable adjusted model (n=442; P for non-linearity= 0.08).

Restricted cubic spline models achieved the best model fit using three knots at 10 (6.07 $\mu\text{g/L}$), 50 (10.8 $\mu\text{g/L}$), and 90 (19.2 $\mu\text{g/L}$) percentiles. We produced the graph using a reference point at the 15th percentile. We omitted four participants with lead concentrations over the 99th percentile (>34.3 $\mu\text{g/L}$) for presentation purposes.

FEV₁: Forced Expiratory Volume in one second, FVC: Forced Vital Capacity

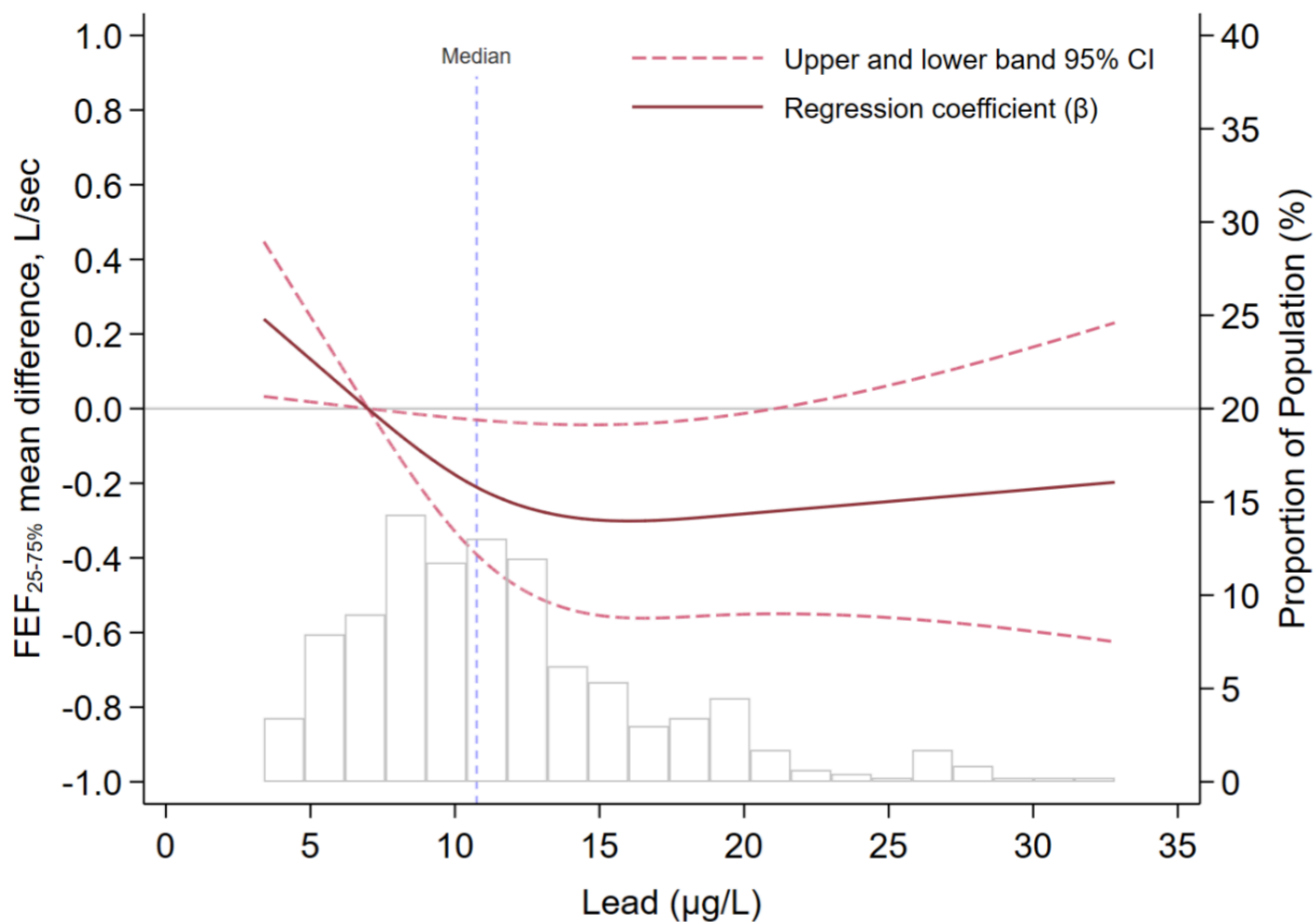


Figure 2

Restricted cubic spline graph for the association between blood lead concentrations and forced expiratory flow at 25-75% of forced vital capacity in a multivariable adjusted model ($n=440$; P for non-linearity= 0.04).

Restricted cubic spline models achieved the best model fit using three knots at 10 (6.07 $\mu\text{g/L}$), 50 (10.8 $\mu\text{g/L}$), and 90 (19.2 $\mu\text{g/L}$) percentiles. We produced the graph using a reference point at the 15th percentile. We omitted four participants with lead concentrations over the 99th percentile (>34.3 $\mu\text{g/L}$) for presentation purposes.

FEF₂₅₋₇₅: Forced Expiratory Flow at 25-75% of Forced Vital Capacity

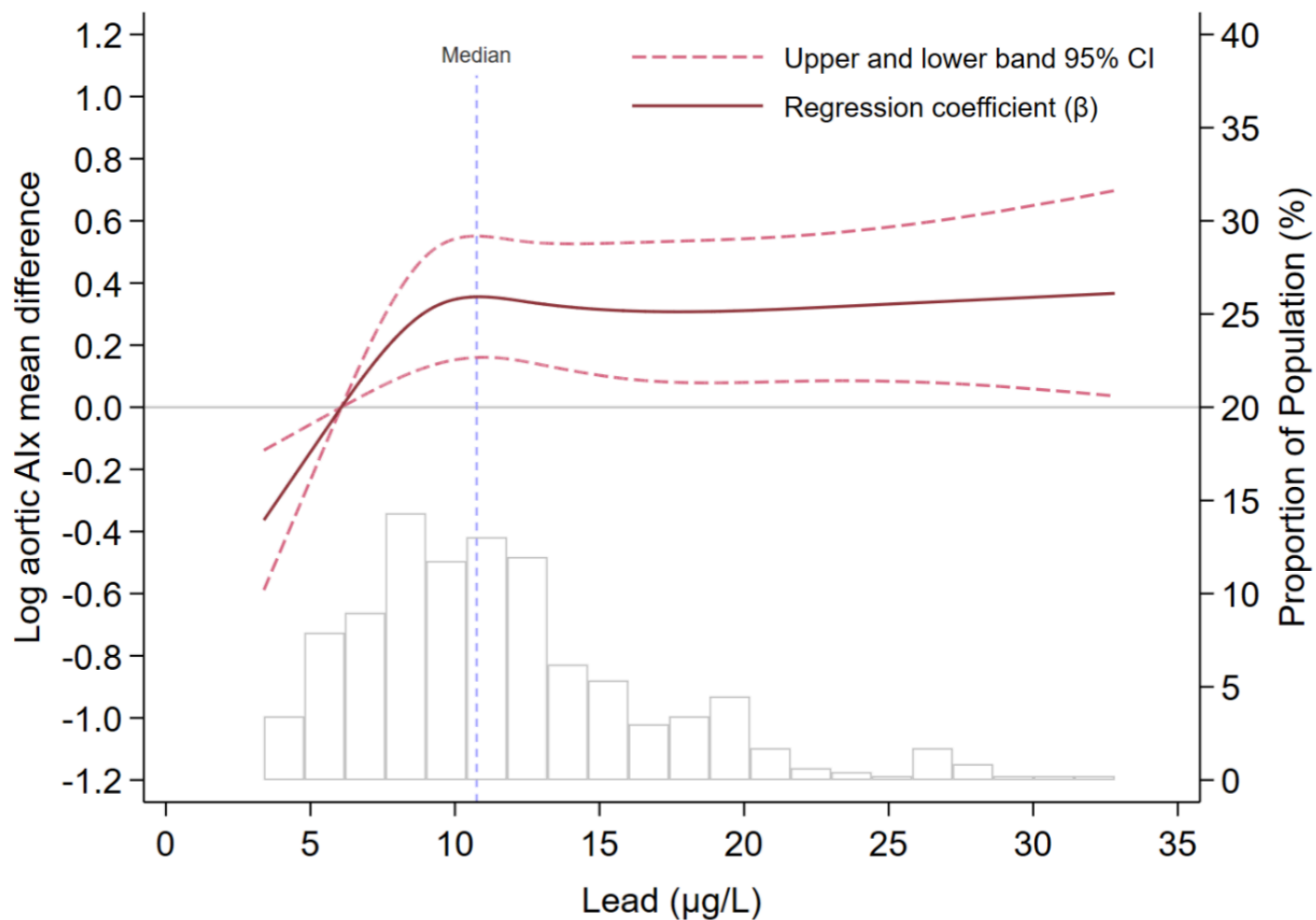


Figure 3

Restricted cubic spline graph for the association between blood lead concentrations and aortic central augmentation index in a multivariable-adjusted model (n=473; P for non-linearity= 0.006).

Restricted cubic spline models achieved the best model fit using four knots at 5 (5.42 µg/L), 35 (9.12 µg/L), 65 (12.5 µg/L), 95 (22.9 µg/L) percentiles. We produced the graph using a reference point at the 15th percentile. We omitted four participants with lead concentrations over the 99th percentile (>34.3 µg/L) for presentation purposes.

AIx: Augmentation Index

Supplementary Files

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