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Biomarkers of maternal lead exposure during pregnancy using micro-spatial child deciduous dentine measurements

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Abstract

Background: Lead is a toxic chemical of public health concern, however limited biomarkers are able to reconstruct prior lead exposures in early-life when biospecimens are not collected and stored. Although child tooth dentine measurements accurately assess past child perinatal lead exposure, it has not been established if they reflect maternal exposure in pregnancy.

Aim: To assess the prenatal relationship between child tooth dentine and maternal blood lead measurements and to estimate maternal lead exposure during the 2nd and 3rd trimesters of pregnancy from weekly child dentine profiles.

Methods: We measured early-life lead exposure in child tooth dentine and maternal blood from 419 child-mother dyads enrolled in the Programming Research in Obesity, Growth, Environment and Social Stress (PROGRESS) cohort. We employed the Super-Learner algorithm to determine the relationship of dentine lead data with maternal blood lead concentrations and to predict maternal lead from child dentine lead data in blinded analyses. We validated and quantified the bias of our results internally.

Results: Mothers had moderate blood lead levels (trimesters: 2nd = 29.45 ug/L, 3rd = 31.78 ug/L). Trimester-averaged and weekly child dentine lead measurements were highly correlated with maternal blood levels in the corresponding trimesters. The predicted trimester-specific maternal lead levels were significantly correlated with actual measured blood values (trimesters: 2nd = 0.83; 3rd = 0.88). Biomarkers of maternal lead exposure discriminated women highly

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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 material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107529.

exposed to lead (>mean) with 85 % and 96 % specificity in the 2nd and 3rd trimesters, respectively, with 80 % sensitivity.

Discussion: Weekly child dentine lead levels can serve as biomarkers of past child and maternal lead exposures during pregnancy.

Keywords

Tooth dentine lead levels; Blood lead levels; Prenatal lead exposure; Pregnancy; Machine learning; Super-Learner algorithm

1. Introduction

Lead exposure is a significant public health concern due to its toxic nature and its multiple adverse effects on both children and adults (Bakulski et al., 2012; Claus Henn et al., 2014; Navas-Acien et al., 2007). Indeed, early-life lead exposure has an impact on child growth, obesity and neurodevelopment (Claus Henn et al., 2014); while adult lead exposure has been associated with detrimental neurological, cardiovascular and reproductive effects (Bakulski et al., 2012; Navas-Acien et al., 2007; Winder, 1993; Heindel et al., 2017). The most commonly used biomarker of lead exposure is blood lead, which has a half-life of approximately between 30 and 90 days following exposure (Navas-Acien et al., 2007; Colicino et al., 2021). In large epidemiological pre-birth studies, maternal blood samples collected during pregnancy are extensively used to assess lead exposure for both mothers and children, as maternal lead exposure directly impact fetal exposure (Téllez-Rojo et al., 2004; Ettinger et al., 2014; Gulson et al., 1997), and maternal blood lead levels are subsequently associated to both mothers and children's health outcomes (Téllez-Rojo et al., 2004; Ettinger et al., 2014; Gulson et al., 1997). However, when maternal blood samples and questionnaire data are not collected during pregnancy, limited biomarkers are able to reconstruct prior lead exposures in mothers and children.

A novel technology, developed and extended by our team, allows to accurately assess early-life environmental lead exposure through shed deciduous teeth (Arora and Austin, 2013; Arora et al., 2014; Arora et al., 2005; Arora and Hare, 2015). Teeth start forming during the 2nd trimester of gestation and follow an incremental pattern with a histological marker shaped at birth that can be used to distinguish tissue formed before or after birth (Arora et al., 2014). In prior work, we assessed a detailed weekly record of prenatal child exposure to lead from child tooth dentine in a small population study combining micro-spatial elemental analysis of teeth with detailed histological techniques (Arora et al., 2014; Arora et al., 2005; Arora and Hare, 2015). We then linked these high temporal resolution child dentine lead levels to maternal blood lead concentrations during pregnancy to show how dentine measurements can be used as a new biomarker of perinatal child chemical exposures (Arora et al., 2014; Arora et al., 2005; Arora and Hare, 2015). While previous studies have focused on developing tooth-based biomarkers of child lead exposure, no studies have tested if the same measures directly reflect maternal lead exposure during pregnancy. In addition, establishing a relationship with lead levels in blood would enhance the clinical utility of dentine lead measurements because there are clear actionable guidelines for blood lead levels but none for tooth biomarkers.

Several statistical learning approaches have been designed to develop exposure biomarkers (Colicino et al., 2021; Park et al., 2009; Marshall et al., 2020), however no studies implemented those methods to generate individual lead exposure biomarkers in critical developing life phases, such as pregnancy. In addition, all prior studies used single penalized linear regressions without evaluating the shape of outcome-predictor associations (Colicino et al., 2021; Park et al., 2009; Marshall et al., 2020), and thus limiting the accuracy of the biomarkers. The Super-Learner algorithm is a state-of-the-art ensemble learning method combining results from several statistical approaches and reporting the result combination that produces the best performance for continuous and binary exposures (Laan et al., 2007). Thus, the Super-Learner algorithm incorporates both linear and non-linear terms for the outcome-predictor associations and informs about the best outcome-predictor relationships (Laan et al., 2007).

Here we leveraged the ongoing pre-birth Mexican Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS) study—which has both child tooth dentine lead measurements and maternal blood lead data collected at the 2nd and 3rd trimesters of gestation—to 1) corroborate the strong early-life exposure relationship between child tooth lead dentine and maternal blood lead measurements and 2) to develop and validate two biomarkers reflecting individual maternal lead exposure during the 2nd and 3rd trimesters of pregnancy from child dentine profiles using the Super-Learner algorithm.

2. Study participant

The PROGRESS study is a prospective cohort based in Mexico City, designed to assess child neurodevelopment in relationship to environmental exposures. Briefly, we enrolled 948 mother–child pairs followed by the Mexican Social Security System for prenatal care (Burris et al., 2014; Braun et al., 2014; Colicino et al., 2017). All eligible pregnant women enrolled in the study were ≥ 18 years of age, were free of heart or kidney disease, had access to a telephone, planned to reside in Mexico City for the following three years, made no use of steroids (including glucocorticoids) or anti-epilepsy drugs, and were not daily alcohol consumers. Demographic and socio-economic data were recorded at every visit (Burris et al., 2014; Braun et al., 2014).

3. Ethics

All mothers provided informed consent prior to 20 weeks of gestation and the study was approved by the Institutional Review Boards of Brigham and Women’s Hospital, the Icahn School of Medicine at Mount Sinai, and the National Institute of Public Health in Mexico (Burris et al., 2014; Braun et al., 2014).

4. Exposure biomarkers

We measured lead (Pb) concentrations throughout pregnancy in maternal venous blood and child deciduous tooth. Maternal blood samples were collected during the 2nd and 3rd trimesters, as previously described (Renzetti et al., 2017). Briefly, blood specimens were drawn in trace metal free tubes and stored at 2–6 °C until analysis. Lead levels were

measured by external calibration using the Agilent 8800 ICP Triple Quad (ICP-QQQ) in MS/MS mode in the trace metals laboratory at the Icahn School of Medicine at Mount Sinai. The limit of detection was < 0.2 μg/dL. Blinded quality control samples obtained from the Maternal and Child Health Bureau and the Wisconsin State Laboratory of Hygiene Cooperative Blood Lead Proficiency Testing Program showed good precision and accuracy (Renzetti et al., 2017). Due to the half-life of approximately between 30 and 90 days following exposure, we considered maternal blood lead levels as a trimester-specific biomarker of lead exposure. Child deciduous teeth were collected when shed (4–8 years of age) and were analyzed to detect the lead exposure (Arora et al., 2014). We used laser ablation-inductively coupled plasma-mass spectrometry to sample several points in dentine adjacent to the dentine-enamel junction (Arora et al., 2014). Temporal information was assigned to sampling points using the neonatal line and daily growth incremental lines visible in enamel (Arora and Austin, 2013; Arora et al., 2014). To control for variation in mineral content in a single tooth and between samples, lead was normalized to calcium (Ca) (i.e. Pb:Ca) (Arora et al., 2014). This novel technique generated precise weekly information from teeth starting from 20 weeks before birth. For this reason, we considered eight weeks in the 2nd trimester and twelve weeks in the 3rd trimester. We also considered trimester-averaged child dentine lead data as a biomarker of trimester exposure. We removed participants with missing maternal blood lead data (n = 22 for the 2nd trimester, n = 69 for the 3rd trimester) and with more than 25 % missing child weekly dentine levels in each trimester (n = 63 for the 2nd trimester, n = 0 for the 3rd trimester), thus resulting in a total of 348 and 364 for the main analyses of the 2nd and the 3rd trimesters, respectively (Fig. 1). For participants with less than 25 % of missing dentine data in each trimester, we imputed with the trimester-averaged child dentine lead levels.

5. Statistical analysis

5.1. Association between weekly child dentine lead data and maternal blood lead levels

The mother-fetus exposure exchange varies throughout pregnancy, having an accelerated rate in the last trimester, for this reason, we analyzed data of each trimester separately. We evaluated the associations between maternal blood lead concentrations with both trimester-averaged and weekly child dentine lead levels with Pearson's correlation coefficients. We also evaluated the correlations stratifying by sex and we tested the similarity of the correlation coefficients using Fisher's tests and Zou's confidence intervals. We $\log_2$-transformed blood and dentine lead levels to reduce the skewness of the distributions (Fig. 2). Using the interquartile range rule, we also identified an outlier in maternal blood lead levels and we excluded it from all analyses (Fig. 1).

5.2. Prediction of maternal blood lead levels from weekly child dentine lead data

To create novel biomarkers of maternal lead exposure during pregnancy from weekly child dentine lead data, we employed the Super-Learner algorithm (Laan et al., 2007), which estimates the prediction with multiple machine learning models and creates an optimal weighted average of those models. The weights are non-negative and sum to one, so they can be used as a measure of the importance for each model in the algorithm (Laan et al., 2007). Due to the different exposure exchange rate between the fetus and mother

among trimesters of gestation, we predicted (log_2-transformed) blood lead levels of the 2nd and 3rd trimester separately. For each trimester, we randomly split the initial dataset into training (60 %) and validation (40 %) sets and we evaluated the performance of three individual regressions (the outcome mean value, the Least Absolute Shrinkage and Selection Operator (LASSO) (Tibshirani, 1996), and the extreme Gradient Boosting (XGBoost) (Chen and Guestrin, 2016) regressions) and one ensemble (LASSO and XGBoost) model. We selected the LASSO and XGBoost approaches because of their complementarity. Indeed, the LASSO regression performs a shrinkage of linear coefficients mapped to the initial variables (Tibshirani, 1996), while the XGBoost approach is an efficient gradient boosting which leverages trees to evaluate non-linear associations between the initial variables and the outcome (Chen and Guestrin, 2016). We included the outcome mean value as a benchmark model. We selected the model with the best prediction performance using the Mean Square Error (MSE) and R (Claus Henn et al., 2014) in the validation sets. To quantify the agreement between the two quantitative (predicted and actual) measurements in the validation set, we used a Bland-Altman plot (Giavarina, 2015). This plot evaluates the bias between the mean differences of two quantitative measures and constructs 95 % limits of agreement within which 95 % of the differences fall (Giavarina, 2015). We finally tested the difference in mean between actual and estimated blood maternal lead levels.

5.3. Binary prediction evaluation

We also discriminated high maternal blood lead levels using as threshold the mean at each trimester (2nd trimester:4.882; 3rd trimester:4.991). At those thresholds, we performed the receiver operating characteristic (ROC) curve to visualize both specificity and sensitivity for each classifier and we provided the area under the ROC curve (AUC) to calculate accuracy. We also implemented the ROC and accuracy after characterizing high maternal blood lead levels with the reference blood lead level (50 μg/L) for adults (Very high blood lead levels among adults, 2013).

6. Results

6.1. Demographic characteristics

Women were 28.3 years old on average (SD = 5.6) at delivery and the majority of them had a high school or lower education level (76 %) (Table 1). Mothers had moderate log_2-transformed blood lead levels (2nd trimester: 4.88 (29.45 ug/L), SD = 0.87; 3rd trimester: 4.99 (31.78 ug/L), SD = 0.94, Table 1) that increased during gestation (p-value = 0.03). Similarly, trimester-averaged child dentine lead data were higher in the 3rd trimester (−3.49, SD = 1.10) than in the 2nd trimester (−3.05, SD = 1.07) (p-value < 2.2e–16). Child dentine lead data showed strong weekly correlations within trimesters (Fig. S1). T-tests and Chi-square tests showed no significant differences in demographic characteristics by sex (Maternal age at delivery: p-value = 0.31; maternal education: p-value = 0.48) and by participant exclusion in this study (Table S1).

6.2. Association between weekly child dentine lead data and maternal blood lead levels

In the overall population, trimester-averaged child dentine lead measurements were highly correlated with maternal blood levels in the corresponding trimester (2nd trimester: r = 0.76,

p-value < 0.0001, 3rd trimester: r = 0.81, p-value < 0.0001) (Fig. 3) with stronger correlation in the 3rd than in the 2nd trimester (p-value: 0.017). We did not find any statistical difference in the Pearson correlation coefficients by sex within trimesters (2nd trimester: p-value = 0.45; 3rd trimester: p-value = 0.50). Weekly child tooth dentine lead data showed high correlation with maternal blood lead levels within trimesters (2nd trimester: r > 0.7, 3rd trimester: r > 0.75; Fig. 4). Spearman's correlation coefficients showed no difference from the linear Pearson correlation coefficients (data not shown).

6.3. Prediction of maternal blood lead concentration

We included weekly dentine lead data in the Super-Learner algorithm to identify novel biomarkers of maternal lead exposure during each (2nd and 3rd) trimester of pregnancy. We trained the Super-Learner algorithm in the training sets, composed by 60 % of the initial data (2nd trimester: n = 208, 3rd trimester: n = 218) and we evaluated its performance in the validation datasets (2nd trimester: n = 140, 3rd trimester: n = 146). Both LASSO and the LASSO-XGBoost ensemble regressions had similar MSE (2nd trimester: LASSO: 0.2662; LASSO-XGBoost ensemble: 0.2664; 3rd trimester: LASSO: 0.172; LASSO-XGBoost ensemble: 0.178), showing the best fit compared to the other models (Table S3). Due to its easy interpretability and performance, we used the LASSO regression as model prediction and we reported the coefficient estimates in Table S4. The predicted maternal lead levels did not receive any contribution (Estimate = 0) from child dentine lead concentrations of the 2nd, 7th, 9th, 12th, 14th, 15th and 20th weeks before birth. The larger coefficients for the predicted maternal lead levels of the 2nd and 3rd trimesters were respectively in the 18th (Estimate: 0.34) and 10th (Estimate: 0.52) weeks before birth.

We compared predicted and actual blood measured values in the validation sets (Fig. 5). For both trimesters, the Pearson correlation coefficients were >0.80 (2nd trimester R = 0.83; 3rd trimester R = 0.88), supporting the goodness of fit of the LASSO models. We finally used the Bland-Altman plots (Fig. 6) to show the agreement (bias) between predicted and actual blood measured values. The mean differences between predicted and actual measured values was close to zero in both trimesters (mean ± SD: 2nd trimester = 0.03 ± 0.52, 3rd trimester = −0.05 ± 0.41), and the mean absolute percent errors (MAPE) was small in both trimesters (2nd trimester: 8.66 %, 3rd trimester: 6.77 %). Finally, the boxplots and t-tests showed no statistical difference in mean for the predicted and actual lead levels in both 2nd and 3rd trimester of pregnancy (p > 0.05) (Fig. S2).

6.4. Binary prediction evaluation

In the validation datasets with the novel biomarkers of maternal lead exposures, we discriminated mothers with high lead levels (>mean values) with a specificity of 85 % and 96 % for the 2nd and 3rd trimester, respectively, setting the sensitivity at 80 % level. The accuracy was good for both trimesters (AUC: 2nd trimester: 91 %, 3rd trimester AUC 94 %) (Fig. 7). The LASSO regression achieved higher AUC scores and better specificity levels than all other approaches, thus supporting the goodness of this prediction model (Fig. S3; Table S3). Results characterizing high maternal blood lead levels with the reference level of 50 μg/L for adults (Very high blood lead levels among adults, 2013) were consistent with the main findings (Figs. S4-S5).

7. Discussion

In the Mexican PROGRESS cohort, we leveraged lead levels from maternal blood specimens and child tooth dentine during the prenatal period to disentangle their associations and to create trimester-specific biomarkers of maternal lead exposure. We showed significant positive associations between maternal blood lead levels and both trimester-averaged and weekly child dentine lead data, with stronger association during the last trimester of gestation. We also assessed the associations stratifying by sex and did not find significant differences in sex-stratified analyses. In addition, we utilized weekly child dentine lead levels to characterize trimester-specific maternal blood lead concentrations. We trained our results in the 60 % of the data using the Super-Learner ensemble machine learning algorithm, and then we validated them in 40 % of the data. Findings showed good accuracy and high sensitivity and specificity (>80 %) in both trimesters. In summary, our analysis confirmed that linear combinations of weekly child dentine lead levels can serve as biomarkers of past maternal lead exposures in pregnancy.

Our results were consistent with prior literature showing a positive association between maternal blood and child dentine lead levels, with stronger association in the 3rd trimester than in the 2nd trimester (Arora et al., 2014). In our data, the associations had even larger magnitude than those in the ELEMENT study (Arora et al., 2014). We extended the prior study to evaluate blood-dentine metal associations in the 2nd and 3rd trimesters, separately (Arora et al., 2014).

Previous literature has also focused on developing biomarkers of past lead exposures from several sources of data, such as epigenomics, biochemical blood parameters and socio-economic factors (Colicino et al., 2021; Park et al., 2009; Marshall et al., 2020), which are often not retrospectively available. However, no studies developed biomarkers of lead exposures during pregnancy, when lead is significantly mobilized from maternal skeletal stores into the blood circulation at an accelerated rate (Téllez-Rojo et al., 2004; Ettinger et al., 2014; Gulson et al., 1997) and then, due to ability of lead to cross the placenta, it is transferred to the fetus (Goyer, 1990; Chen et al., 2014). In contrast to all prior studies which used cross-sectional data (Colicino et al., 2021; Park et al., 2009; Marshall et al., 2020), we leveraged high-temporal resolution of tooth data. This meant that child dentine lead levels at individual weeks contributed to predicting the trimester-specific biomarkers of maternal lead exposure. Those prior biomarkers were also developed using simple or penalized linear regressions, assuming a priori a linear association between the predictors and the outcome (Colicino et al., 2021; Park et al., 2009; Marshall et al., 2020). Instead, we determined these novel maternal biomarkers of lead exposure during pregnancy, employing the Super-Learner ensemble algorithm. The contribution of this approach was twofold. First, we confirmed the strong relationship between weekly child dentine data and maternal blood lead exposure, and we showed that the relationship was linear. Second, we identified the weekly child dentine data that jointly contributed to the characterization of maternal lead exposures. In addition, we provided detailed information about the weekly coefficients to retrospectively estimate blood lead levels in pregnant mothers, whose children provided deciduous shed teeth.

Our results showed good performance for both biomarkers with stronger association between predicted and actual lead levels in the 3rd than in the 2nd trimester. This can be explained by there being a larger sample size in the 3rd than in the 2nd trimester and the stronger exposure exchange between the fetus and mother during the 3rd than in the 2nd trimester (Riess and Halm, 2007). Furthermore, the last trimester of pregnancy is when most of the lead is mobilized and redistributed from mineralized tissues into the maternal bloodstream (Ettinger et al., 2014; Gulson et al., 1997). Indeed in early pregnancy, only maternal trabecular bones with lower lead content are resorbed; while in late pregnancy, resorption of maternal cortical bones with higher lead content leads to an increase in maternal blood lead levels (Riess and Halm, 2007). In addition, as lead freely crosses the placental membranes by passive diffusion (Goyer, 1990; Chen et al., 2014), the lead burden for the fetus increases and lead accumulates in fetal tissues, including teeth (Arora and Austin, 2013; Goyer, 1990; Chen et al., 2014). For this reason, child dentine lead data may be more representative of maternal lead concentrations in the 3rd than in the 2nd trimester.

Dentine data has been validated as a biological marker of child perinatal chemical exposures (Arora and Austin, 2013), however, due to the interplay between mothers and children's exposures in early-life (Goyer, 1990; Chen et al., 2014; Krachler et al., 1999), such data may also capture important information on maternal environmental exposures. Although in birth studies, maternal lead exposure is commonly measured in whole blood, cohorts without that tissue would not able to identify maternal lead burden. The ability to reconstruct past exposure to lead during pregnancy, even retrospectively using child dentine data, may help to assess lead burden for pregnant women and its long-term health effects on mothers. Furthermore, due to limited public health guidelines on dentine lead biomarkers, these methods may clinically help with environmental monitoring and misdiagnosis of past lead exposures for both mothers and children using the established recommendations for blood lead levels.

Our results leveraged a homogeneous Hispanic cohort with moderate levels of lead exposure, and those population characteristics may limit the generalizability of our findings to other more heterogeneous populations with different exposure ranges. Further studies should also consider to externally validate our results. In addition, we did not control for potential confounders for which we lacked appropriate measures, such as maternal calcium supplement during pregnancy. Another limitation may be selection bias if loss to follow up was associated with lead exposure. However, we did not find any statistically significant differences in lead exposure between the participants included and those excluded in this analysis.

In conclusion, our analysis confirmed the strong association between maternal blood levels during pregnancy and child tooth dentine lead levels *in utero*. In addition, child dentine measurements accurately predicted maternal blood lead levels in the 2nd and 3rd trimester of pregnancy. These novel biomarkers may help to identify consequences for maternal exposure during pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Data will be made available on request.

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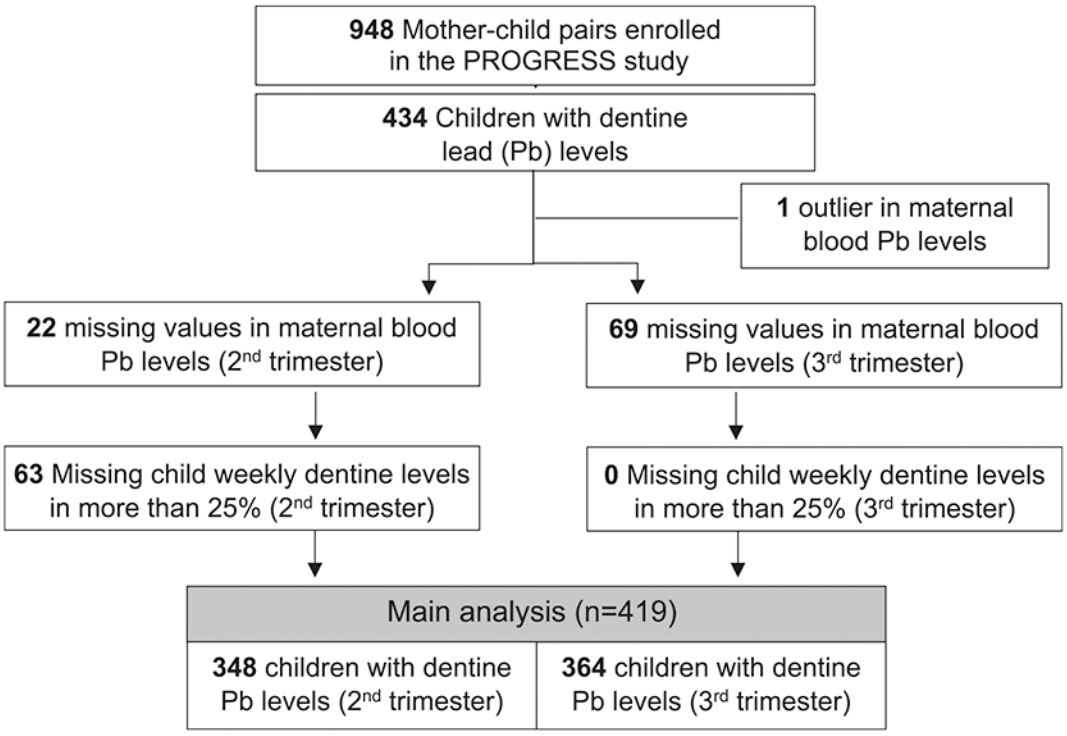

Fig. 1.
Overview of participants' exclusion in the present study.

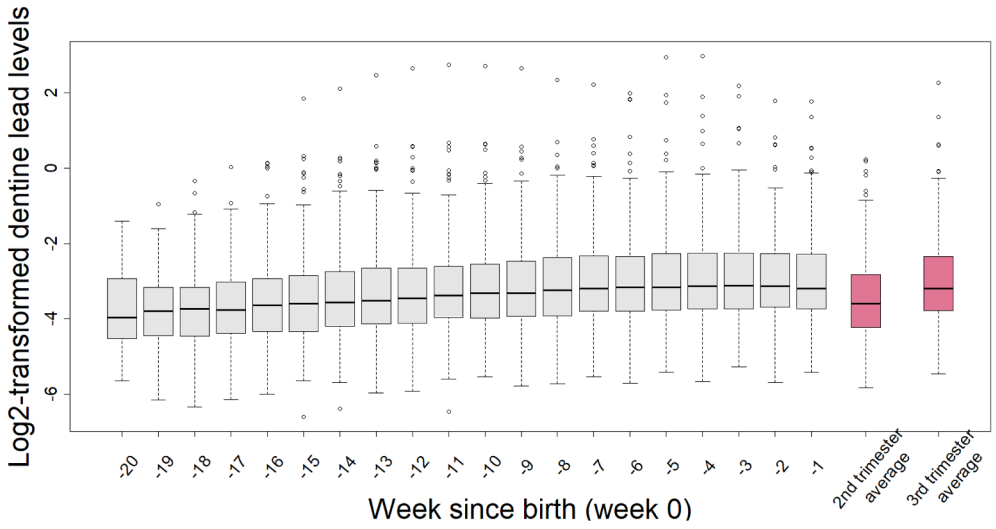

Fig. 2. Boxplot of log2-transformed dentine lead levels by week of gestation (in grey) and by trimester average (2nd and 3rd trimesters) (in red).

Weekly negative values indicate week since birth (week 0).

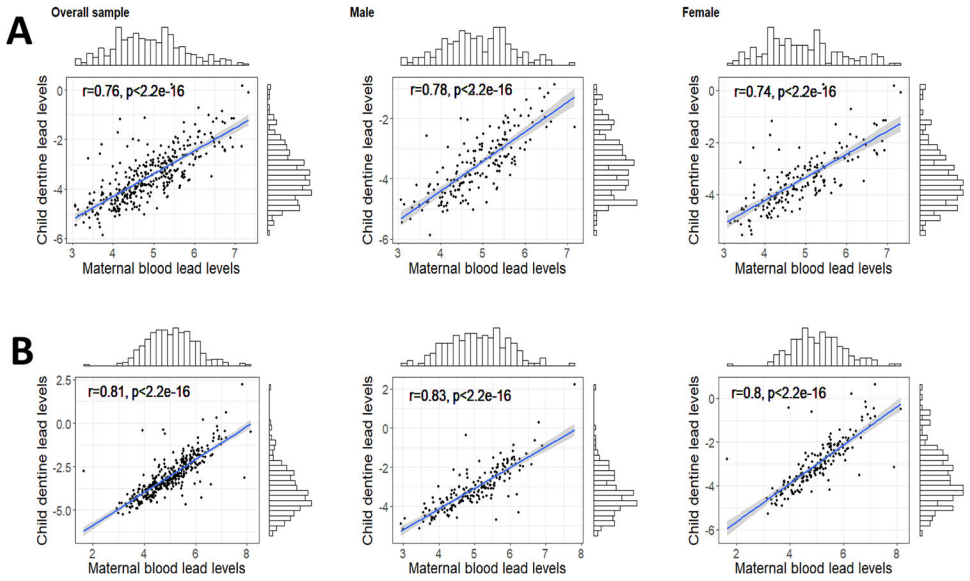

Fig. 3. Scatter plots and Pearson correlation coefficients (r) between log_2-transformed maternal blood lead (Pb) levels (x-axis) and log_2-transformed trimester-averaged child dentine Pb levels (y-axis) in the overall sample, and by child sex (male and female).

Panel A) indicates exposures at the 2nd trimester of gestation, while panel B) indicates exposures at the 3rd trimester of gestation. We identified no difference in r between male and female (p-value > 0.05 in both 2nd and 3rd trimesters).

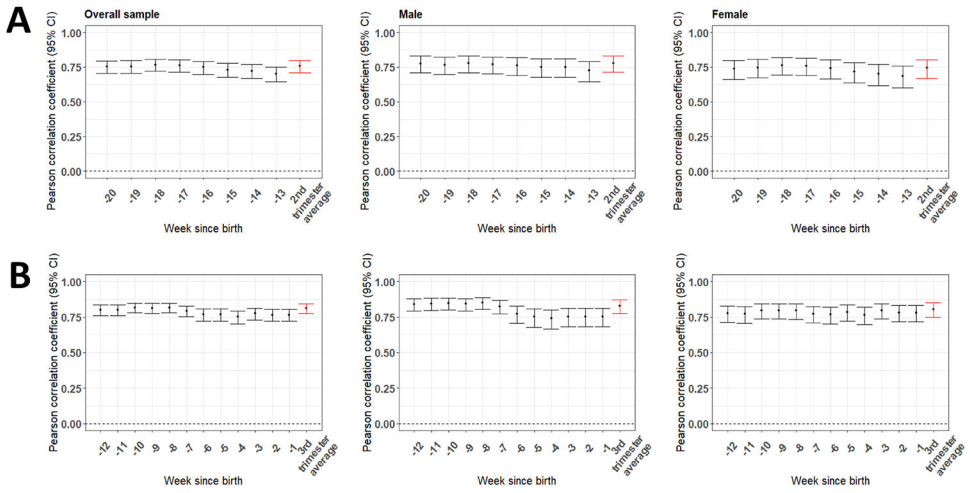

Fig. 4. Pearson correlation coefficients (r) and 95 % Confidence Intervals (95 %CI) between (weekly and trimester-averaged) log_2-transformed child dentine lead (Pb) data and log_2-transformed maternal blood Pb levels during the 2nd and the 3rd trimesters of gestation, in the overall sample, and by child sex (male and female).

Panel A) indicates exposures at the 2nd trimester of gestation, Panel B) indicates exposures at the 3rd trimester of gestation.

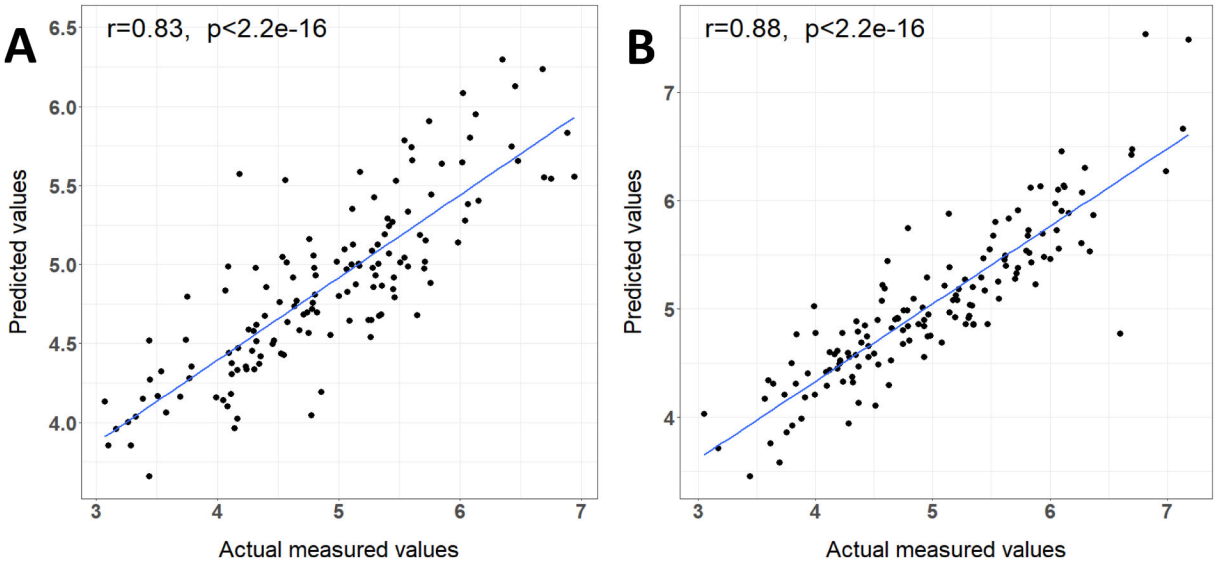

Fig. 5. Scatter plots and Pearson correlation coefficients of observed (x-axis) vs predicted (y-axis) values of log2-transformed maternal blood lead (Pb) levels in 40% (validation) of the original datasets. (Panel A: 2nd trimester, Panel B: 3rd trimester).

To predict maternal blood Pb levels we used the Least Absolute Shrinkage and Selection Operator (LASSO) regression after evaluating four models through the Super-Learner algorithm.

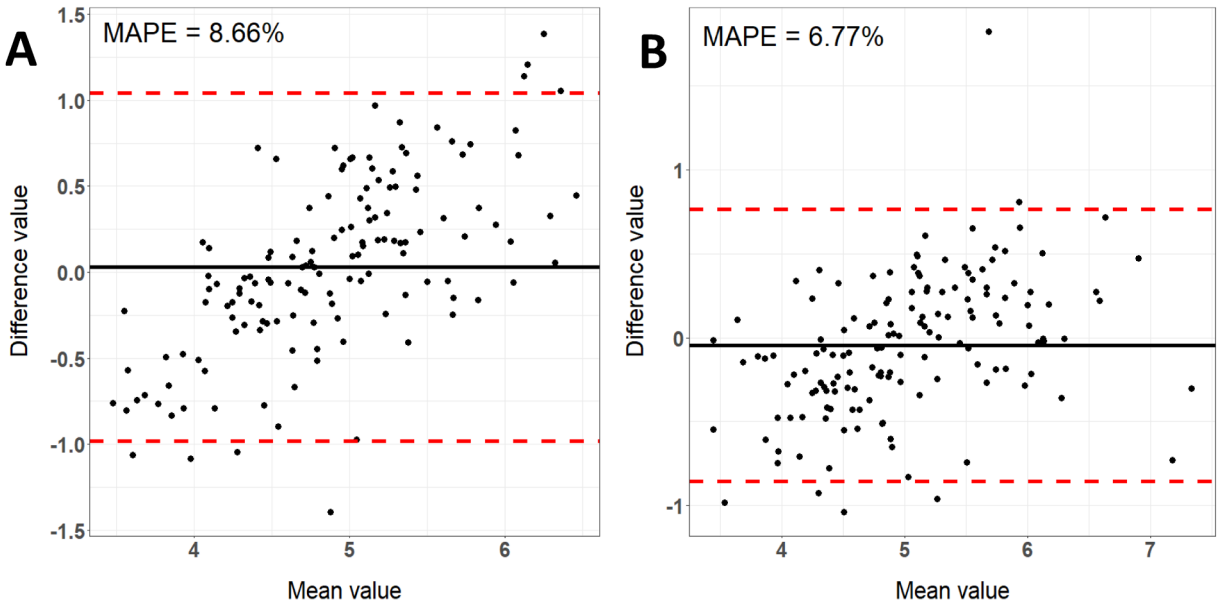

Fig. 6. Bland-Altman plots of lead (Pb) levels showing the difference (y-axis) and mean (x-axis) between the predicted and actual measured values in 40% (validation) of the original datasets by trimester (Panel A: 2nd trimester, Panel B: 3rd trimester).

The Mean Absolute Percentage Error (MAPE) indicates the average absolute difference between observed and predicted values.

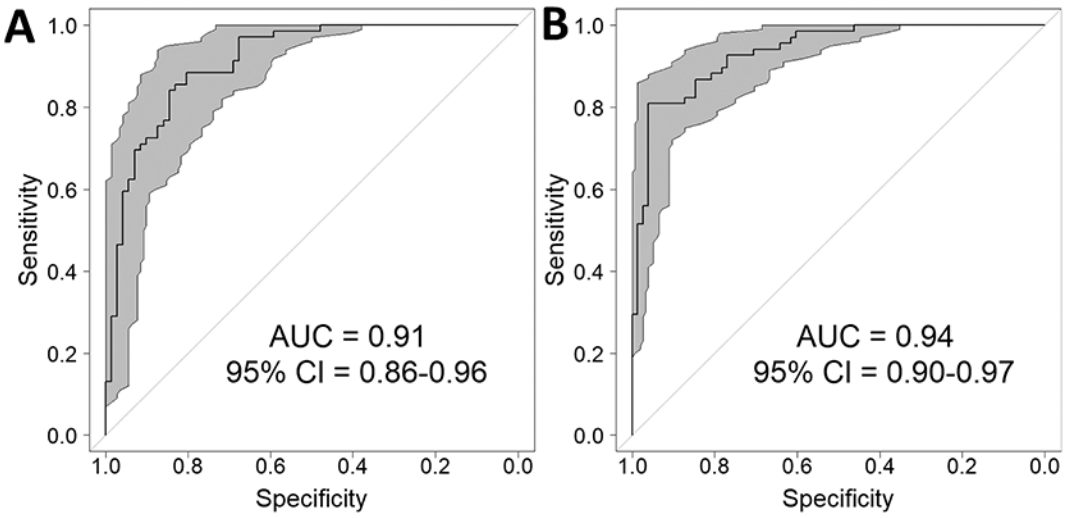

Fig. 7. Receiver Operating Characteristic (ROC) Curves, Area Under the Curve (AUC) and 95 % Confidence Interval (95 %CI) for the maternal blood level predictions during the 2nd (panel A) and 3rd (panel B) trimesters of pregnancy.

Log2-transformed maternal blood lead levels in each trimester were dichotomized using the mean values. The binary outcomes were predicted using LASSO (Least Absolute Shrinkage and Selection Operator). 95 %CI for the ROC curves were estimated using a bootstrap approach.

Table 1

Main characteristics of the PROGRESS participants.

Characteristics	Full sample (*n = 419*)		Male (*n = 208*)		Female (*n = 211*)	
	Mean or n	SD or %	Mean or n	SD or %	Mean or n	SD or %
Maternal age at delivery (years)	28.27	5.55	28.54	5.3	27.99	5.78
Maternal education:						
<= High School	317	75.66	161	77.40	156	73.93
> High School	102	24.34	47	22.60	55	26.07
Log_2-transformed blood lead (Pb) levels						
2nd trimester[a]	4.88	0.87	4.89	0.81	4.87	0.93
3rd trimester[b]	4.99	0.94	4.99	0.86	4.99	1.00

SD: Standard Deviation; %: Percentage.

[a] 2 T Blood levels: male (*n = 172*), female (*n = 176*), full sample (*n = 348*).

[b] 3 T Blood levels: male (*n = 178*), female (*n = 186*), full sample (*n = 364*).