DECIDUOUS TEETH AS A BIOMARKER OF EARLY LIFE LEAD EXPOSURE AND IMPACTS ON CHILD NEUROBEHAVIOURAL OUTCOMES

MILA VALCIC

A THESIS SUBMITTED TO THE FACULTY OF GRADUATE
STUDIES IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF MASTER OF ARTS

GRADUATE PROGRAM IN CLINICAL DEVELOPMENTAL PSYCHOLOGY
YORK UNIVERSITY
TORONTO, ONTARIO

July 2026

© Mila Valcic, 2026

Abstract

Background: Lead exposure during early development is associated with poorer cognitive outcomes, yet critical windows of vulnerability remain unclear. Deciduous tooth dentin offers a novel biomarker for reconstructing temporally resolved lead exposure histories.

Objective: To compare dentin lead with blood lead biomarkers and examine associations with child IQ.

Methods: Dentin lead was measured in 328 children from the MIREC cohort and compared against four blood lead biomarkers. Multivariable regression and reversed distributed lag models (rDLMs) examined associations with IQ at ages 3–4 years (n=166).

Results: Dentin lead correlated significantly with all four blood lead biomarkers. Adjusted regression models were null. rDLMs identified prenatal windows where children in the higher IQ group had significantly lower dentin lead.

Conclusion: Dentin lead showed strong concordance with blood lead biomarkers. While prenatal windows of vulnerability were identified, adjusted regression models were largely null, likely reflecting limited exposure contrast in this sociodemographically advantaged sample.

Acknowledgments

I would first like to express my sincere gratitude to my supervisor, Dr. Christine Till, for her mentorship and support throughout my graduate training. Thank you for continually encouraging my growth as both a researcher and future clinician-scientist and for challenging me to think critically. I am grateful for your confidence in me and for the countless hours you have invested in my training. Beyond your mentorship, thank you for fostering a lab environment that is welcoming, collaborative, and genuinely supportive. The sense of community you have built has made graduate school an incredibly positive experience.

I would also like to thank my thesis committee member, Dr. Rebecca Pillai Riddell, for her thoughtful feedback and suggestions. Your expertise and guidance strengthened this thesis and helped me consider new perspectives throughout the process.

I am grateful to our collaborators, particularly Dr. Vishal Midya, whose statistical expertise helped me navigate the analytical challenges of this project; Dr. Bruce Lanphear, whose expertise in lead and environmental health provided invaluable perspective throughout this work; and Dr. Manish Arora, whose laboratory conducted the dentin analyses that made this research possible. To the families who participated in this research, thank you for your time and contribution to advancing our understanding of maternal health and child development.

To my lab mates, Durdana, Meaghan, Carly, and Ana, thank you for your friendship, support, and encouragement. Whether I was troubleshooting an analysis, preparing for a presentation, or navigating coursework, you always offered thoughtful advice and reassurance. Thank you for the many lab dinners, celebrations, and laughs that made this experience so enjoyable. To my cohort, thank you for making these past two years so memorable. From our cohort socials to supporting one another through every milestone, I am grateful to be on this journey with all of you.

To my mom and dad, thank you for always supporting my goals and for being the first people I turn to with every question, accomplishment, and challenge. To my brother, thank you for always being in my corner. I am incredibly proud of all that you have accomplished and grateful to have you by my side. To my family in Serbia, especially my grandma and aunt, thank you for your support from afar. Despite the distance, you have always been among my biggest cheerleaders. To my sister-in-law, thank you for your encouragement and the many baked treats that brightened even the busiest days. To my partner, thank you for your unwavering support and encouragement throughout this journey. Thank you for listening to countless discussions about research, letting me practice every presentation with you first, celebrating every milestone alongside me, and believing in me every step of the way. To my friends, thank you for always giving me something to look forward to, whether it was a study session, a coffee break, or a much-needed night together.

And to my cat, Tuxedo, thank you for being my most loyal late-night companion. Whether curled up beside my desk or demanding a well-timed break, you made sure I never had to work alone!

Table of Contents

Abstract ... *ii*
Acknowledgments ... *iii*
Table of Contents ... *iv*
List of Tables ... *vi*
List of Figures ... *vii*
List of Abbreviations ... *viii*
Introduction ... *1*
Biology of Developmental Neurotoxicity ... **1**
Sources of Heavy Metal Exposure ... **1**
Lead Exposure and Cognitive Effects ... **2**
Prenatal Lead Exposure ... 2
Postnatal Lead Exposure ... 5
Limitations of Lead Biomarkers ... **8**
A Novel Biomarker: Deciduous Tooth Dentin ... **9**
Rationale ... *12*
Aims and Hypotheses ... *13*
AIM 1 ... **13**
AIM 2 ... **13**
Methods ... *14*
Participants ... **14**
Exposure Biomarkers ... **16**
Dentin Lead ... 16
Blood Lead Biomarkers ... 18
Neurodevelopmental Outcome Measures ... **19**
Covariates and Potential Confounders ... **19**
Ethical Considerations ... **20**
Statistical Analysis ... *20*
Descriptive Statistics ... **21**
Selection of Covariates ... **21**
Aim 1: Dentin Lead and Blood Lead Comparisons ... **22**
Aim 2: Associations Between Dentin Lead and Child IQ ... **24**
Average Lead Exposure: Multivariable Linear Regression ... 24
Identification of Critical Windows of Exposure: Reversed Distributed Lag Model ... 25
Results ... *27*

Participant Characteristics **27**

Aim 1: Dentin Lead and Blood Comparisons **36**

Trimester 3 Dentin Lead 36

Neonatal Line Dentin Lead 37

Aim 2: Associations Between Dentin Lead and Child IQ **41**

Unadjusted Linear Regression Models 41

Adjusted Linear Regression Models 42

Critical Windows of Lead Exposure: Reversed Distributed Lag Models 43

Supplementary Analyses **48**

Discussion ***49***

Dentin Lead and Blood Lead Comparisons **49**

Average Dentin Lead and Child IQ **51**

Critical Windows of Lead Exposure: rDLM Findings and the Value of Time-Varying Analysis **55**

Strengths **57**

Limitations **58**

Conclusions **59**

Appendix A: Supplemental Materials ***61***

Supplemental Table 1 ..... **61**

Supplemental Table 2 ..... **62**

Supplemental Figure 1 ..... **63**

References ***65***

List of Tables

Table 1: MIREC Cohort Participation in Neurodevelopmental Follow-Up Study.……...16
Table 2: Descriptive Characteristics of the Study Sample…….....31
Table 3: Descriptive Characteristics for Blood and Dentin Lead Levels……...33
Table 4: Dentin Lead Intensity by Child Sex…….34
Table 5: Spearman Correlations Between Dentin Lead and Blood Lead Biomarkers……...38
Table 6: Unadjusted and Adjusted Associations Between Dentin Lead Exposure and Child Cognitive Outcomes…….43
Table 7: Critical Windows of Dentin Lead Exposure Associated with Child IQ Outcomes from Unadjusted and Adjusted rDLMs……..……...48

List of Figures

Figure 1: Log-Linear Association Between Blood Lead and IQ…….7
Figure 2: Image of Deciduous Human Incisor……...18
Figure 3: Study Sample Flow Chart……...30
Figure 4: Dentin Lead Intensity Trajectories Across Early Development…….34
Figure 5: Dentin Lead Intensity Trajectories Across Early Development by Tooth Type…….35
Figure 6: Association Between Third Trimester Maternal Blood Lead and Child Dentin Lead…….39
Figure 7: Association Between Umbilical Cord Blood Lead and Neonatal Line Dentin Lead…….39
Figure 8: Time-Varying Correlation Between Third Trimester Maternal Blood Lead and Child Dentin Lead Stratified by Child Sex……...……...40
Figure 9: Time-Varying Correlation Between Umbilical Cord Blood Lead and Child Dentin Lead Stratified by Child Sex……...41
Figure 10: Unadjusted rDLMs of Dentin Lead and Full-Scale IQ, Verbal IQ, and Performance IQ……..46
Figure 11: rDLMs of Dentin Lead and Covariate-Adjusted Full-Scale IQ, Verbal IQ, and Performance IQ…….47

List of Abbreviations

ABCD	Adolescent Brain Cognitive Development
AUC	Area Under the Curve
BDNF	Brain-Derived Neurotrophic Factor
BMI	Body Mass Index
CAD	Canadian Dollars
CDC	Centers for Disease Control and Prevention
CES-D	Center for Epidemiologic Studies Depression Scale
CI	Confidence Interval
CrI	Credible Interval
DLM	Distributed Lag Model
FSIQ	Full-Scale IQ
GAMM	Generalized Additive Mixed Model
HOME	Home Observation for Measurement of the Environment
ICC	Intraclass Correlation Coefficient
INSPQ	Institut National de Santé Publique du Québec
IQ	Intelligence Quotient
IQR	Interquartile Range
LA-ICP-MS	Laser Ablation–Inductively Coupled Plasma–Mass Spectrometry
LOESS	Locally Estimated Scatterplot Smoothing
MDI	Mental Development Index
MIREC	Maternal-Infant Research on Environmental Chemicals
MIREC-CD	MIREC–Child Development
MIREC-ENDO	MIREC–Endocrine
MRI	Magnetic Resonance Imaging
NGF	Nerve Growth Factor
PIQ	Performance IQ
PROGRESS	Programming Research in Obesity, Growth, Environment, and Social Stressors
rDLM	Reversed Distributed Lag Model
SD	Standard Deviation
VIF	Variance Inflation Factor
VIQ	Verbal IQ
WHO	World Health Organization
WPPSI-III	Wechsler Preschool and Primary Scale of Intelligence, Third Edition
WSB	Weeks Since Birth

Introduction

Biology of Developmental Neurotoxicity

Fetuses and young children are particularly vulnerable to toxic chemicals due to their ongoing biological and neurological development. During this critical period, the blood-brain barrier is more permeable, allowing harmful substances to reach the brain more easily (Lanphear, 2015). These toxic exposures can interfere with critical brain development processes, such as neuronal migration and proliferation, synapse formation, and myelination, leading to long-term cognitive and functional impairments. In early development, the body's metabolic systems responsible for processing and eliminating harmful substances are still maturing (Rauh & Margolis, 2016). This reduced ability to break down and excrete toxins makes fetuses and young children more vulnerable to harmful exposures. Consequently, even low levels of toxic chemicals that may be harmless to adults can pose significant risks to the developing brain (Grandjean & Landrigan, 2006).

Sources of Heavy Metal Exposure

Heavy metals are defined as naturally occurring substances that build up over time and pose harm to the environment and living organisms, including humans (Rajkumar et al., 2023). Common methods of exposure to heavy metals include inhalation, ingestion, and skin contact. Industrial expansion has made heavy metals common pollutants in food, water, and air, leading to prenatal exposure to these toxins becoming a significant public health concern (Kou et al., 2025). Heavy metals are damaging to the human body as they create metal-specific free radicals or reactive oxygen species, which cause oxidative stress to cells. This in turn can lead to harmful consequences such as damage to DNA, cell death, and carcinogenesis (Rajkumar et al., 2023).

Lead is a particularly concerning heavy metal due to its high toxicity and long-lasting and widespread presence in the environment (Kou et al., 2025). Common sources include toys, jewelry, medications, food, indoor dust, and drinking water (Dignam et al., 2019). Residing in older homes increases the risk of lead toxicity due to exposure from old water pipes, peeling paint, and dust (Rajkumar et al., 2023). Exposure risk is also shaped by broader social and environmental conditions, with higher lead burdens observed among children living in lower-income and racially marginalized communities, partly due to older housing and neighborhood inequities (Muller et al., 2018). In fetuses, lead exposure can also occur from the release of stored lead in the mother's bones (Gulson et al., 2003). Although many countries have stopped the production of lead-containing products and the use of leaded gasoline, and blood lead levels in the Canadian general population have decreased, residual lead remains a persistent source of low-level exposure and a relevant public health concern that requires ongoing attention (Dignam et al., 2019; Nguyen et al., 2024; Obeng-Gyasi, 2019). A pooled analysis of seven international population-based longitudinal cohort studies indicated that there is no safe amount of lead exposure (Lanphear et al., 2005), a finding which prompted stricter regulatory guidelines.

Lead Exposure and Cognitive Effects

Prenatal Lead Exposure

The landmark prospective cohort study by Bellinger and colleagues, conducted in Boston, Massachusetts (USA) and published in the New England Journal of Medicine in 1987, provided some of the earliest rigorous empirical support that prenatal lead exposure negatively affects cognitive development (Bellinger et al., 1987). In this study, 249 children were categorized into low, medium, or high prenatal lead exposure groups based on umbilical cord

blood lead levels, and cognitive development was assessed semi-annually using the Mental Development Index (MDI) of the Bayley Scales of Infant Development. Children in the high cord blood lead group (≥10 μg/dL) performed significantly worse than those in the low group (<3 μg/dL) at 6, 12, 18, and 24 months of age, with the estimated deficit between highest and lowest groups exceeding 4 MDI points after covariate adjustment. Notably, postnatal blood lead levels at concurrent assessment points were less strongly correlated with MDI scores than prenatal cord blood lead, an early indication that fetal exposure may carry particular neurodevelopmental significance.

The timing of prenatal exposure appears to be critically important. In a prospective study conducted in Mexico City, Hu and colleagues measured lead in maternal plasma and whole blood across all three trimesters in 146 pregnant women and assessed offspring neurodevelopment at 12 and 24 months with the Bayley Scales MDI (Hu et al., 2006). Their findings indicated that prenatal lead exposure may exert its strongest effects during the first trimester and that maternal plasma lead was a better predictor of infant mental development than whole blood lead. Specifically, a one standard deviation increase in first-trimester maternal plasma lead was associated with a 3.5-point reduction in MDI score.

Further longitudinal evidence comes from another prospective cohort from Mexico City that followed children from pregnancy through 10 years of age (Schnaas et al., 2006). The investigators found that third-trimester maternal blood lead, representing late fetal exposure, was significantly inversely associated with child IQ measured between 6 and 10 years of age. The dose-response relationship was log-linear rather than linear, suggesting that IQ decrements per unit increase in lead were greater at lower exposure levels. The authors concluded that exposure

around 28 weeks of gestation may represent a critical window for later intellectual development and that these effects appeared to persist into childhood.

Some studies have further identified sex-specific effects, particularly among boys. For example, Dietrich et al. found that greater maternal and umbilical cord blood lead levels were associated with poorer cognitive development in infants at 3 and 6 months of age, with boys demonstrating a greater deficit than girls (Dietrich et al., 1987). Similarly, Taylor et al. reported that prenatal lead was not related to IQ scores in the full sample, but among boys, higher prenatal lead exposure predicted lower verbal, performance, and full-scale IQ at age 8 (Taylor et al., 2017). Moreover, a recent meta-analysis examining maternal lead exposure during pregnancy and child IQ suggested that boys may be particularly vulnerable to prenatal lead exposure compared to girls (Goodman et al., 2023). Specifically, the pooled effect showed that every 50% difference in prenatal lead levels was associated with a 1.1-point decrease in general intelligence in males whereas the pooled effect among females was positive, albeit non-significant. This male-specific finding was more consistent with performance (or nonverbal) IQ compared with full-scale IQ (Desrochers-Couture et al., 2018; Goodman et al., 2023).

Some studies have failed to observe significant associations between prenatal blood lead and neurodevelopmental outcomes in very young infants (Cooney et al., 1989; Inoue et al., 2022; Parajuli et al., 2015). For example, a large analysis from the Japan Environment and Children's Study of over 80,000 children found no significant association between prenatal blood lead levels and neurodevelopmental screening outcomes in the first three years of life (Inoue et al., 2022). However, as acknowledged by the authors, the use of a screening tool rather than formal cognitive testing may have limited the ability to detect subtle cognitive effects that manifest more clearly in children on formal IQ testing.

The broader consensus, grounded in multiple prospective cohort studies and meta-analytic syntheses, supports a significant adverse effect of prenatal lead exposure on child cognitive development, with no identifiable safe threshold. Effects appear to be log-linear, with greater IQ decrements at lower exposure levels, and both early and late prenatal windows have been implicated as sensitive periods across studies. The evidence also suggests that boys may be more vulnerable to prenatal lead exposure than girls, particularly for performance outcomes.

Postnatal Lead Exposure

Evidence from multiple cohort studies indicates that postnatal lead exposure is also associated with poorer cognitive outcomes in children. In the Cincinnati Lead Study, higher postnatal blood lead levels were significantly linked to lower performance IQ scores at 6.5 years of age, controlling for relevant covariates; children with lifetime average blood lead levels above 20 μg/dL scored 7-points lower on performance IQ compared to those with levels below 10 μg/dL (Dietrich et al., 1993). Interestingly, this study did not find an effect with prenatal blood lead levels on cognitive outcomes. Similarly, the Port Pirie cohort in Australia reported an inverse relationship between early childhood blood lead and IQ at age seven, with increases from 10 to 30 μg/dL associated with a 5.5 to 6.4 point decline in verbal IQ and 4.4 to 5.3 point decline in full-scale IQ (Baghurst et al., 1992). When examining prenatal lead exposure, associations with child IQ were not statistically significant after adjusting for relevant covariates. Furthermore, McMichael et al. found that higher lead levels in children's teeth were inversely associated with IQ at 7 years of age (McMichael et al., 1994). Similarly, Needleman et al. compared 1st and 2nd grade children with high versus low tooth-lead levels and found that children with high lead levels had significantly lower IQ scores (Needleman et al., 1979). Sex-

specific effects have also been observed, for example, a Japanese study reported that only postnatal childhood blood lead, not prenatal, was significantly associated with lower full-scale IQ, and this effect was evident in boys but not in girls (Tatsuta et al., 2020). Together, these findings suggest that postnatal lead exposure may adversely impact cognition. Although some studies examining postnatal lead exposure have reported stronger associations among boys, evidence for sex-specific vulnerability remains mixed, and a recent meta-analysis did not observe a significant pooled effect modification by sex for general intelligence outcomes (Goodman et al., 2023).

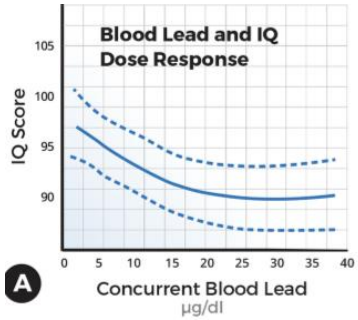
Studies show no clear threshold below which adverse effects are absent, highlighting that even low levels of exposure may be harmful. Several longitudinal studies have demonstrated these findings, which remain robust even after controlling for relevant covariates (Koller et al., 2004). For example, in a Boston cohort of children, blood lead concentrations at age 2 were inversely related to IQ at 10 years; blood lead level concentrations in this cohort were below 10 µg/dL, which was considered to be below the CDC and WHO level of concern at the time (Bellinger & Needleman, 2003). The Rochester Longitudinal Study also found higher child blood lead concentrations were associated with lower IQ scores at ages 3 and 5 years (Canfield et al., 2003). Interestingly, the estimated IQ loss for children with lifetime average blood lead concentration of up to 10 µg/dL was considerably greater (7.4 IQ points) compared with those with lifetime average blood lead concentrations that ranged from more than 10 µg/dL to 30 µg/dL (2.5 IQ points). These findings suggest that the lead-associated decrement in IQ scores may be more pronounced at lower lead levels relative to higher exposure levels. Lanphear et al. pooled data from seven prospective international cohort studies comprising 1,333 children to further characterize the exposure-response relationship (Lanphear et al., 2005). Their analysis

confirmed a significant inverse association between blood lead and IQ across the full range of exposures studied, with the association being log-linear (i.e., strongest at the lowest concentrations) as shown in Figure 1. Children whose maximal blood lead levels never exceeded 7.5 µg/dL showed significant intellectual deficits with increasing concurrent blood lead, leading the authors to conclude that environmental lead exposure in children is associated with intellectual deficits even at very low levels, and that there is no identifiable safe threshold.

Collectively, the postnatal lead literature supports an adverse association between childhood lead exposure and cognitive outcomes, with effects documented at blood lead concentrations well below 10 µg/dL and no identifiable safe threshold. The dose-response relationship appears log-linear, mirroring the pattern observed for prenatal exposure. Evidence for sex-specific vulnerability in the postnatal period is less consistent than for prenatal exposure, with some studies reporting stronger effects in boys and others finding no sex differences.

Figure 1

Log-Linear Association Between Blood Lead and IQ



Note. Restricted cubic spline showing the association between concurrent blood lead concentration and IQ scores. Dotted lines represent 95% confidence intervals. Image taken from (Lanphear, 2017).

Limitations of Lead Biomarkers

Discrepancies between studies may reflect differences in when and how lead exposure is measured. For example, blood lead can be collected at multiple developmental stages, including maternal blood during gestation, cord blood at birth, and child blood at various ages (Hu et al., 2006). Biomarkers also differ in the exposure intervals they represent. Blood biomarkers generally reflect recent exposure, while maternal bone and baby teeth reflect cumulative exposure over longer periods. These measures are only moderately correlated because they measure exposure at different time points and often serve as indirect proxies of fetal exposure (Baghurst et al., 1987). For example, maternal bone lead is a stored source, but its contribution to fetal exposure depends on bone resorption, which releases lead into maternal plasma and can be influenced by factors like calcium intake (Ettinger et al., 2009; Gulson et al., 2003). Therefore, maternal bone lead may not perfectly represent fetal exposure, particularly if bone resorption is limited. Similarly, maternal whole blood lead may not be the best proxy for fetal lead exposure because over 99% of lead in whole blood is bound to red blood cells and cannot cross the placenta, whereas the small plasma fraction (<1%) is more relevant for fetal exposure (Goyer, 1990). Individual variability in the red blood cell-to-plasma lead ratio further limits the utility of whole blood lead as a proxy for fetal exposure (Chuang et al., 2001; Goyer, 1990; Hu et al., 2006).

In contrast, cord blood lead provides a more direct measure of fetal exposure than maternal measures, as it reflects the amount of lead that has crossed the placenta into the fetal circulation (Rísová, 2019). Therefore, studies using different biomarkers may arrive at different conclusions because they capture different exposure windows or do not directly measure exposure to the fetus. Imperfect biomarkers can introduce non-differential exposure

misclassification, which would generally be expected to attenuate associations and bias results toward the null.

For example, in the Maternal-Infant Research on Environmental Chemicals (MIREC) cohort, Desrochers-Couture et al. examined multiple biomarkers of lead exposure among 601 mother-child pairs, including maternal blood during pregnancy, cord blood, and child blood lead levels, and found that only cord blood lead levels were associated with lower performance IQ scores in boys (Desrochers-Couture et al., 2018). These findings suggest that prenatal exposure to lead near time of birth may represent a critical window of vulnerability, or alternatively, that cord blood may serve as a more precise biomarker of fetal lead exposure than maternal measures. This highlights the importance of considering not only the type of biomarker used, but also the timing of the exposure window it represents and the precision with which fetal exposure is measured. Overall, there remains no consensus on the optimal biomarker for prenatal lead exposure.

A Novel Biomarker: Deciduous Tooth Dentin

Taken together, the literature supports the neurotoxicity of lead, but what remains unclear is which developmental windows are most sensitive, in part because most studies lack biomarkers spanning across pregnancy, birth, and early childhood. This makes it difficult to identify critical periods and understand how these effects may differ by sex. Most traditional biomarkers are single time-point estimates or represent cumulative exposure, rather than temporally specific data across both pregnancy and early childhood.

Deciduous (baby) teeth offer an improvement over conventional biomarkers to understand pediatric lead exposure. During fetal and early childhood development when teeth are

growing, the tooth dentin layer incorporates heavy metals in a time-sequenced manner, similar to growth rings in trees. Primary dentin begins calcifying between 14-18 weeks of gestation and continues up to 2-11 months postnatal, depending on the tooth type (Andra et al., 2015), while secondary dentin begins to form upon tooth eruption up until the tooth is shed (Arora et al., 2014; Nudel et al., 2021). At birth, an accentuated line known as the neonatal line forms in teeth, serving as a histological landmark that distinguishes pre- and post-natally formed areas within teeth (Figure 2). By analyzing lead levels in tooth dentin of shed deciduous teeth, a child's prenatal and early postnatal exposure history can be reconstructed.

Historically, studies have used lead concentrations in deciduous teeth as biomarkers for cumulative exposure during development (Gulson & Wilson, 1994; McMichael et al., 1994; Needleman et al., 1972), some of which have looked at IQ outcomes, as discussed previously. While these studies provided valuable insights, they were limited in their ability to precisely determine the timing of exposure. Advancements in analytical techniques now allow for more sensitive assessments of lead in tooth dentin, with the ability to reconstruct exposure timelines with greater temporal resolution (weekly exposure). This technique has been validated against traditional biomarkers and offers a non-invasive way to chronologically map precise and cumulative exposure across developmental periods. For example, Arora et al. conducted a validation study in which they demonstrated that dentin lead levels correlated with multiple established biomarkers, including prenatal maternal blood, cord blood, postnatal child blood, and maternal bone lead levels (Arora et al., 2014). For example, dentin-lead during the second and third trimesters significantly correlated with maternal blood lead measured concurrently (Spearman $\rho = 0.60$ and Spearman $\rho = 0.64$, respectively), dentin-lead at birth was moderately correlated with cord blood lead (Spearman $\rho = 0.69$), and lead in dentin formed at 3 months

moderately correlated with child blood lead measured at that age (Spearman $\rho = 0.64$). Similarly, Jensen et al. reported significant correlations between prenatal dentin lead levels and maternal blood collected mid-pregnancy (Jensen et al., 2025).

To date, only two studies have used dentin lead biomarkers to investigate child behavioural outcomes. Horton et al. analyzed shed baby teeth from 133 participants in a Mexico City birth cohort and assessed behavioural outcomes when children were 8-11 years old (Horton et al., 2018). They demonstrated that postnatal dentin-lead concentrations reflecting exposure at 8-11 months of age were associated with increased hyperactivity symptoms, whereas dentin-lead concentrations reflecting exposure at 9 to 10 months postnatally was associated with increased total behavioural problems. Additionally, dentin-lead concentrations reflecting exposure at 12 months of age were associated with increased anxiety symptoms. The paper also analyzed the combined effects of multiple metals (manganese, zinc, and lead) and identified a potential sensitive window between 8 and 12 months postnatal, during which exposure to the metal mixture was associated with increased anxiety symptoms in childhood, with the effect being mainly driven by lead. The researchers found no association between prenatal or cumulative dentin-lead and behavioural outcomes. More recently, Rechtman et al. extended this work by reconstructing weekly concentrations of a nine-metal mixture from dentin in 489 children from a separate Mexico City birth cohort, the Programming Research in Obesity, Growth, Environment, and Social Stressors (PROGRESS) study (Rechtman et al., 2026). Using lagged weighted quantile sum regression, they identified early and late postnatal windows during which higher metal mixture exposure was associated with increased behavioral problems, as well as prenatal and postnatal windows linked to reductions in brain volume, functional connectivity, and white matter integrity. Although lead was one of the metals measured in the mixture, it was not found

to be a major contributor to the mixture effect compared to manganese (Mn), magnesium (Mg), and tin (Sn), possibly because lead-related effects may be more pronounced for cognitive and academic outcomes.

Despite these advances, further work is needed in contemporary populations with low-level lead exposure using dentin biomarkers to capture both timing-specific and cumulative exposure, to better understand the neurodevelopmental consequences of lead, and to extend investigations to IQ outcomes.

Rationale

While evidence of lead's neurotoxicity, even at low levels, is increasingly recognized, critical knowledge gaps remain regarding its specific impacts on early neurodevelopment, which are necessary to address in order to inform effective policy changes. These gaps include: (1) precise assessment of exposure to contemporary levels of lead among children in Canada, using high-quality biomarkers (i.e., tooth dentin) that capture both timing-specific and cumulative exposure; (2) prospective evaluations of lead's effects across vulnerable developmental stages, particularly during pregnancy and infancy; and (3) assessment of a broader range of neuropsychological outcomes, including IQ scores. Further, studies need to better understand possible sex-specific effects of lead.

This prospective cohort study uses deciduous tooth dentin as a new biomarker to capture both timing-specific and cumulative lead exposure across prenatal and early postnatal development. By providing a temporally resolved measure of exposure, dentin addresses important limitations of traditional biomarkers and allows direct comparison of prenatal and postnatal exposure windows. Using this approach, the present study examines associations

between early-life lead exposure and cognitive outcomes, with consideration of sex-specific effects previously reported in the same cohort using blood lead biomarkers (Desrochers-Couture et al., 2018). Specifically, dentin lead concentrations were measured in 328 Canadian children and compared against four established blood lead biomarkers collected at multiple time points in gestation and childhood. Associations between dentin lead and neurodevelopmental outcomes were then examined in a subset of 166 children from the MIREC cohort who had data on full-scale, verbal, and performance IQ assessed at ages 3 to 4 years of age.

Aims and Hypotheses

AIM 1. To compare dentin-lead with blood lead biomarkers measured at different time points: trimesters 1 and 3, birth, and between 23 and 76 months postnatal.

Hyp 1.1. Prenatal dentin-lead levels in trimester 3 will be more strongly associated with maternal blood lead collected in trimester 3 given the temporal overlap between these two measurements, compared with maternal blood lead collected in trimester 1, umbilical cord blood lead, and childhood blood lead levels.

Hyp 1.2. Dentin-lead levels at birth (i.e., neonatal line) will be more strongly associated with umbilical cord blood lead given that both reflect fetal lead burden at the same point in time, compared with maternal blood or childhood blood lead levels.

AIM 2. To examine the association between prenatal, postnatal, and cumulative exposure to lead and child IQ outcomes at ages 3-4 years, while exploring effect modification by child sex.

Hyp 2.1. Prenatal, postnatal, and cumulative lead levels in dentin will be associated with lower intellectual ability.

Hyp 2.2. Child sex will modify the above associations between dentin lead levels and IQ outcomes. Based on the existing literature, the association is hypothesized to be stronger among boys, particularly for prenatal dentin-lead.

Methods

Participants

This study used data from the Maternal Infant Research on Environmental Chemicals (MIREC) study. MIREC is a prospective study that recruited a total of 2,001 women during their first trimester of pregnancy at ten Canadian cities (Toronto, Hamilton, Ottawa, Sudbury, Halifax, Edmonton, Winnipeg, Vancouver, Montreal, Kingston) between 2008 and 2012 (Fisher et al., 2023). Women were recruited through ultrasound, midwife, obstetrician and family doctor clinics. Inclusion criteria included: ability to consent in English or French, 18 years of age or older, less than 14 weeks of gestation at time of enrollment, willing to provide a cord blood sample, and intending to deliver at a local hospital (Arbuckle et al., 2013). Women with a history of medical complications or known fetal abnormalities were excluded. Of those recruited, 1,983 women consented to take part in the study. Participants provided blood samples in the first and third trimester of pregnancy and completed questionnaires regarding their sociodemographic information, health status, medication use, lifestyle, and diet. At birth, umbilical cord blood and meconium were also collected.

An extension study conducted from 2013 to 2015, MIREC-Child Development (MIREC-CD) Plus, followed a subset of the children between 15 months and 5 years of age. Due to resource limitations, only participants from six of the 10 cities (seven sites) with the largest number of participants meeting the age requirements for testing during the data collection period

(Vancouver, Toronto, Hamilton, Halifax, Kingston, and Montreal) were eligible for in-person follow-up visits (Fisher et al., 2023). Of the 1,459 eligible families, 1,207 were reached and 808 (67%) consented to participate in the Neurodevelopment and/or Biomonitoring visit. Of these, 610 singleton-born children aged 3 to 4 years underwent neuropsychological assessment, including administration of the WPPSI, and 601 completed IQ testing in its entirety. Inclusion criteria to participate in the neurodevelopment visit included: singleton delivery at greater than or equal to 28 weeks of gestation, no major birth defects, and no seizures or neurological disorders identified during the perinatal period.

Deciduous tooth collection occurred as part of an additional extension study, MIREC-ENDO, which aims to study the influence of early life exposures on endocrine and metabolic health (Fisher et al., 2023). Beginning in the summer of 2018, MIREC families were contacted and invited to donate naturally shed deciduous teeth. As of February 2024, at least one tooth had been donated by 360 children. Upon intake, teeth were examined by a dentist and were excluded if any of the following were identified: carious lesions, metal restoration, developmental defects, coronal dentin resorption, or significant loss of enamel or dentin. Of the 360 donated teeth, 29 failed quality control during laboratory processing and 3 teeth were excluded because duplicate teeth of the same type and position were attributed to a single participant, and the correct child's tooth could not be identified, yielding a final dentin analytical sample of 328 children with valid dentin lead data. The distribution of tooth donors across participating MIREC sites, among the subset of children with valid dentin lead and IQ data (n = 166), is presented in Table 1.

Table 1

MIREC Cohort Participation in Neurodevelopmental Follow-Up Study

Site Number	City	Participating Institutions	MIREC	MIREC-CD Plus		
				Bio-monitoring	Neuro-development	Donated tooth
01	Vancouver	BC Children's and Women's Health Centre	162	83	55	14
02	Edmonton	University of Alberta	20			0
03	Winnipeg	St. Boniface General Hospital/Health Sciences Centre	90			0
04	Toronto	Mount Sinai Hospital/Sunnybrook Health Sciences Centre	325	108	72	21
05	Hamilton	McMaster University	275	112	85	22
06	Sudbury	Sudbury Regional Hospital	130			0
07	Kingston	Kingston General Hospital	255	122	126	35
08	Ottawa	The Ottawa Hospital	119			0
09	Montreal	CHU Sainte-Justine	300	175	145	44
10	Montreal	Jewish General Hospital	25	11	9	4
11	Halifax	IWK Health Centre	300	192	118	26
		Total	2001	803	610	166

Note. Figure was adapted from table titled "MIREC Platform Sites Participation" at: https://www.mirec-canada.ca/en/about/some-facts-and-figures/.

803 of 808 respondents consented to the Biomonitoring visit and 610 of the 808 consented to Neurodevelopmental visit. MIREC: Maternal-Infant Research on Environmental Chemicals study; MIREC-CD Plus: MIREC-Child Development Plus follow-up study.

Exposure Biomarkers

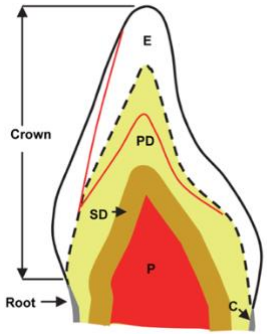
Dentin Lead

The 328 deciduous teeth with valid dentin data were analyzed at the Icahn School of Medicine at Mount Sinai in New York using laser ablation–inductively coupled plasma–mass

spectrometry (LA-ICP-MS). This technique uses a laser beam (New Wave Nd:YAG 193-nm laser) with high precision to ablate the tooth material, and this ablated material is put through an inductively-coupled plasma mass spectrometry machine (Agilent, 8800 ICP-MS) with a carrier gas for lead analysis (McRae et al., 2009). Using a lead detection limit of 0.05 μg/g, our collaborators sampled data from 50 locations, each 35 μm in diameter, within the primary dentin near the enamel-dentin junction, and from 7 locations, each 100 μm in diameter, within the secondary dentin. Weekly temporal information is assigned to each sampling point by referencing landmarks such as the neonatal line and the daily growth lines present in dentin. Temporal assignment of each ablation point is expressed in weeks since birth (WSB), where negative values denote prenatal weeks before delivery, and positive values denote postnatal weeks. Data was analyzed as ^{208}Lead:^{43}Calcium (^{208}Pb:^{43}Ca) ratios, for the purpose of controlling for calcium content in the tooth to account for natural variations in mineral content within and between samples (Arora et al., 2014; Johnston et al., 2019; Nair et al., 2020). Deciduous tooth types collected included molars/premolars (n = 200), canines (n = 54), and incisors (n = 74).

Figure 2

Image of Deciduous Human Incisor



Note. The neonatal line (indicated in red) forms in both enamel and dentin at the time of birth, serving as a histological landmark to differentiate between parts of the tooth formed before and after birth. E = enamel, PD = primary dentin, SD = secondary dentin, P = pulp chamber, C = cervical margin. Image taken from (Arora et al., 2014).

Blood Lead Biomarkers

Among the 328 children with valid dentin lead data, blood lead biomarkers were available from four time points collected as part of the main MIREC study and the MIREC-CD Plus follow-up (Arbuckle et al., 2016): maternal whole blood lead (µg/dL) at trimester 1 (n = 317), maternal whole blood lead at trimester 3 (n = 301), umbilical cord blood lead (µg/dL; n = 245), and child whole blood lead (µg/dL; n = 137) measured between 23 and 76 months postnatal age. All blood lead concentrations were measured using inductively coupled plasma mass spectrometry (PerkinElmer Elan ICP-MS DRC II) at the Centre de Toxicologie du Quebec, Institut National de Sante Publique du Quebec (INSPQ), Quebec QC, Canada (Arbuckle et al., 2016; Desrochers-Couture et al., 2018).

Neurodevelopmental Outcome Measures

Child cognitive ability was assessed using the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III), a standardized, individually administered measure of intelligence. The WPPSI-III was administered by trained assessors during the MIREC-CD Plus neurodevelopmental visit, which occurred when children were between 3 and 4 years of age. Three composite IQ scores were used as outcome measures in the present study: full-scale IQ (FSIQ; n = 166), verbal IQ (VIQ; n = 166), and performance IQ (PIQ; n = 165). FSIQ provides a measure of an individual's overall cognitive and intellectual functioning (Lange, 2011a), VIQ represents overall verbal intellectual abilities such as verbal reasoning (Lange, 2011c), and PIQ represents overall visuospatial intellectual abilities such as spatial processing (Lange, 2011b). All composite scores are standardized to a normative mean of 100 (SD = 15) based on the WPPSI-III Canadian standardization sample.

Covariates and Potential Confounders

We considered a wide range of potential covariates based on theoretical considerations and prior literature on pediatric lead exposure and neurodevelopmental outcomes including: child sex assigned at birth (male vs. female), maternal level of education (college diploma or less vs. university undergraduate or graduate degree), maternal age at delivery (continuous, years), race/ethnicity (White vs. Other), exposure to second-hand smoke during trimester 1 (yes, no), Home Observation for Measurement of the Environment (HOME) inventory score (continuous), and study site (Canfield et al., 2003; Desrochers-Couture et al., 2018; Horton et al., 2018). The HOME inventory assesses the quality and quantity of stimulation and support that children receive in their home environment (Fisher et al., 2023). This is assessed through a combination

of directly observing the child in the home and interviewing the mother. We also considered additional covariates including: pre-pregnancy body mass index (BMI), gestational age at birth, alcohol consumption during pregnancy (none/any), duration of breastfeeding (less than versus greater than 6 months), cord blood mercury concentration, and maternal depressive symptoms assessed through the Center of Epidemiologic Studies Depression Scale 10-item version (continuous) (Zhang et al., 2012).

Ethical Considerations

The proposed thesis received approval from the research ethics boards at Health Canada and York University. MIREC implements high ethical standards in all follow-up studies to ensure that the privacy and confidentiality of participants are protected. To do this, participants are identified by a unique code so that their names are not stored in the biobank. Further, every woman provided informed consent to the collection and storage of their personal information and biospecimens. Every specimen is labelled with a barcode and securely stored in a freezer room. Only select staff have access to this room, which requires fingerprint recognition and is monitored by video surveillance 24/7. Despite participants being required to provide consent at every stage of the MIREC study, there is always a risk when handling personal data and sharing findings from analyses of participants' biological information. To further protect participants against this risk, results are never shared with identification codes or barcodes still intact.

Statistical Analysis

All statistical analyses were conducted using STATA version 18.5 (STATA corporation) and R (R Core Team). A two-tailed p-value threshold of $< .05$ was used to define statistical

significance. Interaction terms were interpreted as statistically significant when *p*-values were < .10. Where distributional assumptions required it, continuous variables were $\log_e$-transformed prior to inclusion in models. Influence diagnostics using Cook's distance and leverage-versus-residual plots were conducted to rule out influential observations.

Descriptive Statistics

Univariate descriptive statistics were generated for all study variables, and histograms and boxplots were visually inspected to assess distributional characteristics. For continuous variables that were approximately normally distributed, means and standard deviations (SD) are reported; for non-normally distributed variables, medians with interquartile ranges (IQR) are presented. For categorical variables, frequencies and percentages are reported. Descriptive statistics are presented separately for the full dentin sample (N = 328), the IQ analytical sample (n = 166), and, within the IQ sample, children scoring at or below versus above the 20th percentile of FSIQ. Differences between the lower- and higher-FSIQ groups were assessed using independent-samples t-tests for continuous variables, Wilcoxon rank-sum tests for lead measures, and chi-square tests for categorical variables, with Fisher's exact test used where expected cell counts were below five.

Selection of Covariates

Covariates associated with both average cumulative dentin lead intensity and with FSIQ at $p < 0.20$ were retained, provided they were considered to lie outside the hypothetical causal pathway. These included child sex and maternal level of education. Race/ethnicity, exposure to second-hand smoke, and HOME score were included in all models as precision variables given

their established associations with child cognitive outcomes (Herrmann et al., 2008; Van Landingham et al., 2020). Study site was included in all models to account for potential variance introduced by different assessment sites and WPPSI-III examiners. Multicollinearity among covariates was assessed using variance inflation factors (VIF), and all selected variables demonstrated low collinearity. Bivariate associations between considered covariates, average cumulative dentin lead intensity, and FSIQ are presented in Supplemental Materials Table S1.

Aim 1: Dentin Lead and Blood Lead Comparisons

To examine the concordance between dentin lead intensities and maternal biomarkers, dentin lead measured across developmentally defined sampling windows were compared with traditional blood lead measures, following the framework established by Arora and colleagues (Arora et al., 2014). Because dentin mineralization in deciduous teeth begins during the second trimester and continues through approximately the second year of postnatal life (number of weeks depends on tooth type), dentin-derived lead profiles can capture exposures during the second and third trimesters and the early postnatal period. In contrast, first-trimester dentin lead are not available because tooth mineralization has not yet begun at that stage of gestation. Prenatal comparisons were therefore restricted to the third trimester, where both dentin lead and maternal blood lead data are concurrently available.

Spearman rank-order correlations were used to examine associations between dentin-lead values and its temporally corresponding blood lead measure. Two specific comparisons were conducted, each corresponding to a defined dentin-sampling window:

Trimester 3 prenatal dentin lead. Dentin lead levels were averaged within a ±2-week window centred on each participant's third-trimester maternal blood draw date (i.e., the dentin

formed at WSB corresponding to gestational week of T3 blood sampling ±2 weeks). This averaged T3 dentin lead was then correlated against: (a) concurrent third-trimester maternal whole blood lead, (b) first-trimester maternal whole blood lead, (c) umbilical cord blood lead, and (d) childhood blood lead.

Neonatal line dentin lead. Dentin lead levels in the region immediately surrounding the neonatal line (WSB = −2 to 0), representing fetal lead exposure at the time of birth, were correlated against umbilical cord blood lead and all other available blood lead measures.

Across all comparisons, correlations were computed for the full analytical sample, and then repeated separately by child sex, given that prior research has reported sex-specific differences in element levels in teeth and blood. For example, Jensen et al. found that correlations between lead in dentin and maternal blood were higher among girls (r= .58) than boys (r= .51) (Jensen et al., 2025).

In addition to the discrete sampling-window validation described above, the temporal profile of the dentin–blood lead correlation across the full developmental timeline (WSB −21 to +55) was visualized graphically. For each week in this range, Spearman correlations between $\log_e$-transformed dentin lead at that week and (a) T3 maternal blood lead and (b) cord blood lead were computed separately in boys and girls, subject to a minimum cell size of $n \geq 10$ per sex-week stratum. These week-by-week correlations were plotted as continuous functions of WSB, with the neonatal line (WSB = 0) indicated by a vertical reference line. This visualization supplements the discrete validation comparisons by characterizing how the strength of the dentin–blood lead relationship varies across the full developmental period captured in dentin, allowing assessment of whether peak correlation timing aligns with the expected biological timing of each blood biomarker. These analyses were conducted in R using the *Hmisc* package

(rcorr function) and visualized using *ggplot2*, with separate lines plotted for boys (blue) and girls (red).

Aim 2: Associations Between Dentin Lead and Child IQ

The primary neurodevelopmental outcome examined in this study was child IQ, assessed at ages 3-4 years. To ensure adequate representation of dentin data across the exposure windows of interest, IQ analyses were restricted to WSB -19 to +26, the period spanning approximately the third trimester of gestation through the first six postnatal months, where at least 50% of the IQ sample had dentin lead data available. This restriction ensured that exposure estimates were not unduly influenced by sparse data at the extremes of the developmental timeline.

Average Lead Exposure: Multivariable Linear Regression

We used multivariable linear regression to characterize the associations between averaged period-specific lead exposure as the predictor variable and IQ scores (continuous) as the dependent variable. Average dentin lead concentrations were computed separately for three exposure periods: (1) the prenatal period (WSB -19 to 0, representing second- and third-trimester in utero exposure up to the neonatal line), (2) the postnatal period (WSB 0 to +26, representing the first six postnatal months), and (3) the combined pre- and postnatal period (WSB -19 to +26, representing cumulative exposure across both the prenatal and postnatal periods). For each exposure period, multivariable linear regression models were conducted for FSIQ, VIQ, and PIQ. Models were adjusted for child sex, race, maternal level of education, second hand smoke exposure, HOME score, and study site.

Effect modification by child sex was evaluated by including a dentin lead x sex interaction term in each model, and interactions were considered statistically significant where $p < .10$. For both unadjusted and covariate-adjusted models, results are presented as unstandardized regression coefficients (B) with corresponding 95% confidence intervals (CI) and two-tailed p-values, representing the estimated difference in IQ score associated with a 50% increase in average dentin lead intensity, calculated by multiplying the log-scale coefficient by ln(1.5). Supplementary analyses were conducted examining area under the curve (AUC) as an alternative cumulative exposure metric. As AUC and period-averaged dentin lead were moderately correlated, period averages were selected as the primary exposure metric given their simpler interpretation.

Identification of Critical Windows of Exposure: Reversed Distributed Lag Model

To evaluate time-varying associations between dentin lead exposure and cognitive performance, we used a reversed distributed lag model (rDLM) framework. This method is a reparameterization of the conventional distributed lag model (DLM), in which the repeated exposure measures and the outcome exchange roles to produce a mixed-model structure appropriate for longitudinal biomarker data (Horton et al., 2018; Stokke Jensen et al., 2026). In this framework, log-transformed dentin lead at each week is modeled as the dependent variable, and cognitive group membership (binary: below vs. above the 20th percentile of IQ) is the predictor. Specifically, we are estimating the difference in lead uptake between the higher versus the lower IQ group at discrete developmental stages, while accounting for exposures at other time points. For the parameter estimates, standardized coefficients (β) and their 95% credible interval (CrI) were calculated, corresponding to the difference in log dentin lead in SD units in

the higher IQ group (relative to the lower IQ reference group) at the WSB where the effect is the strongest. Cumulative effects were additionally calculated by summing the weekly β coefficients across each significant window. A positive coefficient indicates that children with higher IQ had higher dentin lead at that time point; a negative coefficient indicates lower dentin lead in the higher-IQ group relative to the reference group of lower IQ children.

Binary cognitive group classification was based on the 20th percentile of the observed IQ distribution within the analytical sample of children with both IQ data and dentin data. This cutoff was selected to identify a relatively lower-performing group while retaining sufficient sample size for stable model estimation. Both lower and higher thresholds (i.e., the 10th and 30th percentiles) were also considered, and the 20th percentile was selected as a balance between isolating a lower-performing group and maintaining adequate group sizes for reliable estimation. FSIQ, VIQ, and PIQ were each analyzed separately, first in unadjusted and then adjusted models. For adjusted rDLM analyses, continuous IQ scores were first regressed on the full covariate set (i.e., child sex, race, maternal level of education, second hand smoke exposure in trimester 1, HOME score, study site) using linear regression; residuals from these models were then extracted and the 20th percentile of the residual distribution was used to classify cognitive group membership. This approach ensures that group assignment reflects cognitive performance after accounting for measured confounding variables.

The rDLM was estimated using a generalized additive mixed model (GAMM) framework with penalized B-splines to model the smooth temporal function over WSB (Stokke Jensen et al., 2026). A participant-level random intercept was included to account for within-subject correlation arising from repeated lead measurements. Models were fit using the *gamm4* package in R. Statistical inference for the time-varying associations was based on approximate 95%

credible intervals (CrI) estimated across the developmental period (Marra & Wood, 2012; Stokke Jensen et al., 2026). The penalized B-spline framework smooths the estimated temporal function, which guards against overfitting. Developmental windows were considered statistically significant where the credible interval excluded zero (two-sided $\alpha = 0.05$). Supplementary analyses were also conducted using continuous IQ as the outcome in the rDLM framework.

Results

Participant Characteristics

A study sample flow chart is included in Figure 3. Descriptive characteristics for the full MIREC Neurodevelopment cohort, the full dentin analytical sample (N = 328), and the subset of participants with available FSIQ data (N = 166) are presented in Table 2, along with comparisons between children scoring at or below versus above the 20th percentile of FSIQ within the IQ sample.

Among the full dentin analytical sample, mothers had a mean age of 32.8 years (SD = 4.8), and the sample was predominantly White (92.2%) (Table 1). The majority of mothers held at least a university degree (77.3%), and household incomes were roughly evenly split below and above $100,000 per year (54.0% vs. 46.0%). Approximately half of mothers were nulliparous (46.5%), and children were roughly evenly distributed by sex (46.3% male). Secondhand smoke exposure in the first trimester was rare (1.6%). With respect to breastfeeding, 57.7% of mothers breastfed exclusively for six months or longer.

Among the 328 children with valid dentin data, 166 (50.6%) had IQ data available. Within this dentin-IQ sample, 36 children (21.7%) scored at or below the 20th percentile on FSIQ (score ≤ 98) and 130 (78.3%) scored above this threshold. Mothers of children in the

lower-FSIQ group were significantly less likely to hold a university degree (55.6% vs. 80.5%; χ^2 p = .002) and more likely to report household income at or below $100,000 (65.7% vs. 43.7%; χ^2 p = .02), compared with mothers of children in the higher-FSIQ group (Table 2). Children in the lower-FSIQ group also had a lower mean HOME score (46.3 vs. 48.7; p = .002), indicating a less stimulating home environment on average. A greater proportion of mothers in the lower-FSIQ group breastfed exclusively for fewer than six months (58.8% vs. 40.0%; χ^2 p = .05). The proportion of male children was higher in the lower-FSIQ group (58.3%) than in the higher-FSIQ group (43.9%). Maternal age, race/ethnicity, parity, gestational age at blood sampling and birth, and secondhand smoke exposure were broadly similar across the two IQ groups. Children were assessed at a mean age of 3.4 years (SD = 0.3) in both IQ groups. Mean FSIQ across the full IQ sample was 109.4 (SD = 12.4), reflecting an above-average cognitive performance distribution. Children in the lower-performing group had a mean FSIQ of 91.8 (SD = 5.9), compared with 114.3 (SD = 8.7) in the higher-performing group. A similar pattern was observed for VIQ (97.3 vs. 114.8) and PIQ (89.4 vs. 110.0).

Blood lead levels were low across all measurement timepoints (Table 3). In the full dentin sample, median trimester 1 maternal blood lead was 0.62 µg/dL (IQR: 0.43–0.87; Range: 0.16 – 2.90) and trimester 3 maternal blood lead was slightly lower at 0.58 µg/dL (IQR: 0.41–0.85; Range: 0.14 – 2.90). Median cord blood lead (0.81 µg/dL, IQR: 0.60–1.08, Range: 0.15 – 2.90) exceeded maternal blood lead at both trimester timepoints. Childhood blood lead (measured between 23 and 76 months postnatal) had a median of 0.66 µg/dL (IQR: 0.46–0.99; Range: 0.14 – 2.82). Blood lead levels were broadly similar between the full dentin sample and the IQ subsample. Within the IQ subsample, trimester 1 and trimester 3 maternal blood lead levels were significantly higher in the above-20th-percentile group than in the below-20th-

percentile group (0.68 vs. 0.52 μg/dL for both; $p = .03$ and $p = .02$, respectively).

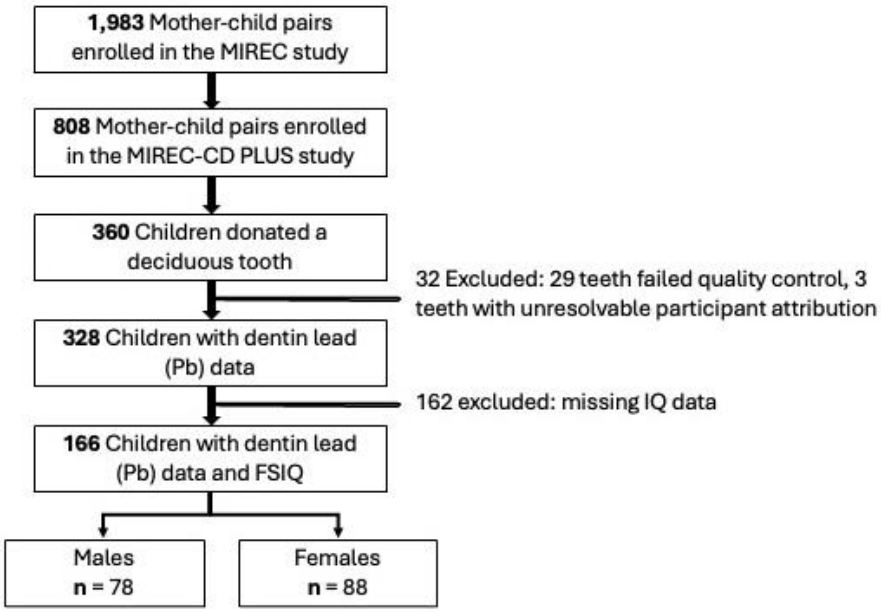
Average dentin lead intensities (^{208}Pb:^{43}Ca ratios, restricted to WSB −19 to +26) are also presented in Table 3. In the full dentin sample, median prenatal, postnatal, and cumulative dentin lead intensities were nearly identical at 0.016 (IQR: 0.012–0.023; Range: 0.003 – 0.088), 0.016 (IQR: 0.011–0.023; Range: 0.004 – 1.225), and 0.016 (IQR: 0.012–0.023; Range: 0.004 – 0.778), respectively, reflecting the overall low and homogeneous lead exposure in this cohort over time. In the IQ subsample, median dentin lead intensities were significantly higher in the above-20th-percentile FSIQ group compared with the below-20th-percentile group across the prenatal (0.019 vs. 0.014, $p = .002$), postnatal (0.017 vs. 0.014, $p = .015$), and cumulative (0.018 vs. 0.013, $p = .003$) exposure periods. Dentin lead intensity by child sex is presented in Table 4. Median dentin lead levels did not significantly differ between boys and girls across any exposure window.

The temporal distribution of dentin lead intensities across the full dentin sample (WSB −21 to +55) is illustrated in Figure 4A. The intraclass correlation coefficient (ICC) for dentin lead was 0.67, indicating that approximately 67% of the variability in dentin lead levels was attributable to between-child differences, with the remaining 33% reflecting within-child variability across time. The temporal distribution of dentin lead intensities in the IQ analytical sample, restricted to WSB −19 to +26, is illustrated in Figure 4B. In this subset, the ICC for dentin lead was 0.75, indicating that approximately 75% of the variability in dentin Pb levels was attributable to between-child differences, with the remaining 25% reflecting within-child variability across time. When stratified by tooth type (Figure 5), first and second molars provided the broadest developmental coverage extending to approximately 55 weeks after birth, followed by canines, while central and lateral incisors covered a considerably narrower

postnatal window. Across all tooth types, dentin lead trajectories showed a gradual postnatal increase.

Figure 3

Study Sample Flow Chart



Note. Flow chart illustrating the selection of the analytic sample from the Maternal-Infant Research on Environmental Chemicals (MIREC) cohort.

Table 2

Descriptive Characteristics of the Study Sample

	Dentin Sample (N = 328) Mean (SD) / n (%)	**Dentin & FSIQ Sample (N = 166) Mean (SD) / n (%)**	**Low IQ group (N = 36) Mean (SD) / n (%)**	**High IQ group (N = 130) Mean (SD) / n (%)**	**MIREC FSIQ Sample (N = 601) Mean (SD) / n (%)**
Maternal Characteristics					
Age (years)	32.8 (4.8)	32.4 (4.7)	33.3 (4.6)	32.2 (4.8)	32.5 (4.6)
White (n, %)	296 (92.2%)	155 (94.5%)	33 (91.7%)	122 (95.3%)	531 (89.2%)
University degree or higher (n, %)	248 (77.3%)	123 (75.0%)	20 (55.6%)*	103 (80.5%)	397 (66.7%)
Parity					
0	151 (46.5%)	85 (51.5)	16 (44.4%)	69 (53.5%)	259 (43.5%)
1	128 (39.4%)	59 (35.8)	15 (41.7%)	44 (34.1%)	249 (41.8%)
2+	46 (14.1%)	21 (12.7)	5 (13.9%)	16 (12.4%)	88 (14.8%)
Household income (CAD) > $100,000	145 (46.0%)	83 (51.5%)	12 (34.3%)*	71 (56.3%)	228 (39.7%)
No Secondhand Smoke Exposure in Trimester 1 (n, %)	316 (98.4%)	163 (99.4%)	36 (100.0%)	127 (99.2%)	574 (96.5%)
Gestational week at Trimester 1 blood sampling (mean; range)	11.6 (5 – 14)	11.8 (6 – 14)	11.4 (8 – 14)	11.8 (6 – 14)	11.7 (6 – 15)
Gestational week at Trimester 3 blood sampling (mean; range)	33.1 (28 – 38)	33.0 (28 – 38)	32.8 (30 – 35)	33.1 (28 – 38)	33.1 (28 – 40)
Gestational week at birth (mean; range)	39.3 (26.4 – 42.3)	39.4 (26.4 – 42.3)	39.0 (26.4 – 42.3)	39.5 (29.4 – 42.0)	39.5 (26.4 – 42.4)
Duration of exclusive breastfeeding					

0 to < 6 months	109 (42.3%)	72 (43.9%)	20 (58.8%)*	52 (40.0%)	295 (49.9%)
6 to 24 months	149 (57.7%)	92 (56.1%)	14 (41.2%)*	78 (60.0%)	296 (50.1%)
HOME Score	48.2 (4.1)	48.2 (4.2)	46.3 (5.6)*	48.7 (3.5)	47.3 (4.3)
Child characteristics					
Sex (male)	152 (46.3%)	78 (47.0%)	21 (58.3%)	57 (43.9%)	291 (48.7%)
FSIQ	-	109.4 (12.4)	91.8 (5.9)	114.3 (8.7)	106.8 (13.5)
VIQ	-	111.0 (11.8)	97.3 (9.4)	114.8 (9.3)	109.4 (13.3)
PIQ	-	105.5 (14.1)	89.4 (8.5)	110.0 (11.9)	102.9 (14.8)
Age at assessment (years)	-	3.4 (0.3)	3.4 (0.3)	3.4 (0.3)	3.4 (0.3)

Note. Descriptive statistics are presented for the analytic sample of children with dentin lead measurements and available cognitive outcomes. Continuous variables are summarized as mean (standard deviation) or median (interquartile range), as appropriate, and categorical variables are presented as frequencies (percentages). Characteristics are stratified by cognitive group: low IQ group (i.e. FSIQ ≤20th percentile) vs. high IQ group (i.e. FSIQ >20th percentile).

*/**Denotes significant differences (*: $p < .05$; **: $p < .001$) between the low IQ group compared with the high IQ group. Calculated using the Chi-square test for categorical variables and t-test for continuous variables.

Table 3

Descriptive Characteristics for Blood and Dentin Lead Levels

Lead exposure metrics	Samples with Dentin Data				MIREC FSIQ Sample (N = 601) Median (IQR)
	Full Sample (N = 328) Median (IQR)	FSIQ Sample (N = 166) Median (IQR)	Low IQ group (N = 36) Median (IQR)	High IQ group (N = 130) Median (IQR)	
Maternal Characteristics					
Trimester 1 Blood Lead, µg/dL	0.62 (0.43 – 0.87)	0.66 (0.48 – 0.89)	0.52 (0.43 – 0.77)*	0.68 (0.52 – 0.91)	0.61 (0.43 – 0.85)
Trimester 3 Blood Lead, µg/dL	0.58 (0.41 – 0.85)	0.62 (0.43 – 0.89)	0.52 (0.41 – 0.72)*	0.68 (0.47 – 0.96)	0.58 (0.41 – 0.83)
Cord Blood Lead, µg/dL	0.81 (0.60 – 1.08)	0.86 (0.64 – 1.08)	0.76 (0.66 – 0.98)	0.88 (0.63 – 1.12)	0.79 (0.58 – 1.04)
Child characteristics					
Child Blood Lead, ug/dL	0.66 (0.46 – 0.99)	0.70 (0.49 – 1.10)	0.73 (0.53 – 1.00)	0.70 (0.47 – 1.12)	0.67 (0.48 – 0.99)
Prenatal Dentin Lead Intensity[a]	0.016 (0.012 – 0.023)	0.018 (0.013 – 0.025)	0.014 (0.010 – 0.019)*	0.019 (0.013 – 0.026)	-
Postnatal Dentin Lead Intensity[a]	0.016 (0.011 – 0.023)	0.017 (0.012 – 0.024)	0.014 (0.010 – 0.020)*	0.017 (0.013 – 0.026)	-
Cumulative Dentin Lead Intensity[a]	0.016 (0.012 – 0.023)	0.017 (0.013 – 0.024)	0.013 (0.011 – 0.020)*	0.018 (0.013 – 0.024)	-

[a]Averages calculated restricted to WSB -19 to +26.

*Denotes significant differences ($p < .05$) between the low IQ group compared with the high IQ group. P-values for blood and dentin lead measures were calculated using the Wilcoxon rank-sum test.

Table 4

Dentin Lead Intensity by Child Sex

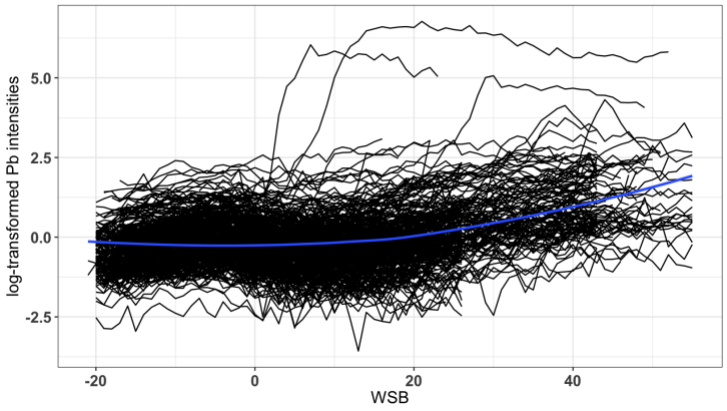
Dentin Lead Measure	Boys (N = 152) Median (IQR)	Girls (N =176) Median (IQR)
Prenatal Dentin Lead Intensity[a]	0.016 (0.012 – 0.025)	0.016 (0.012 – 0.022)
Postnatal Dentin Lead Intensity[a]	0.017 (0.013 – 0.023)	0.015 (0.010 – 0.023)
Cumulative Dentin Lead Intensity[a]	0.017 (0.013 – 0.024)	0.015 (0.011 – 0.023)

[a]Averages calculated restricted to WSB -19 to +26

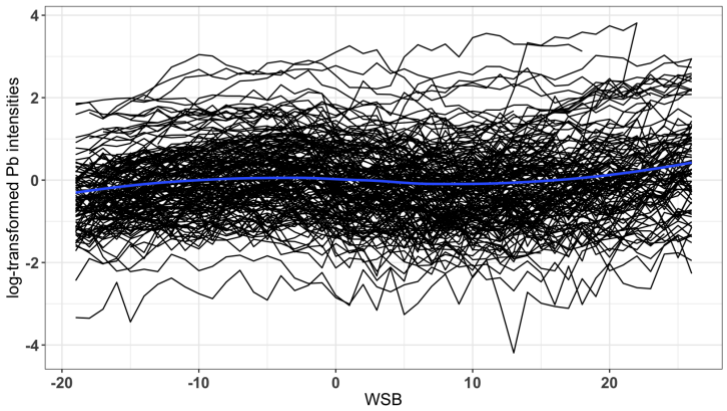
Figure 4

Dentin Lead Intensity Trajectories Across Early Development

A.



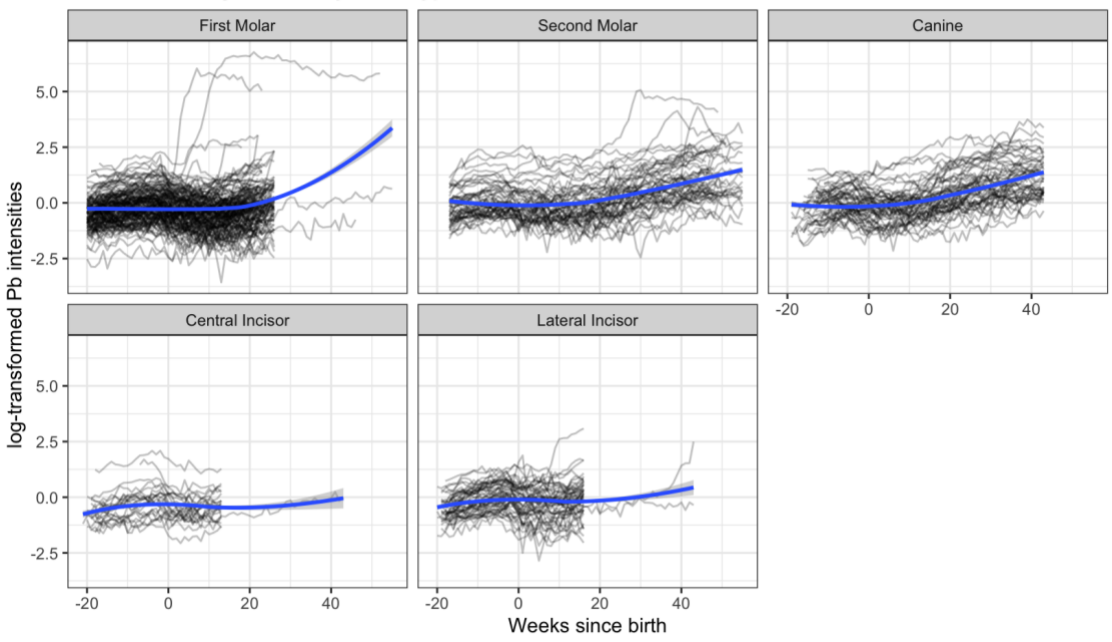
B.



Note. **A**. Individual dentin lead trajectories (log-transformed and standardized $^{208}Pb:^{43}Ca$ intensities) across weeks since birth (WSB) for all participants (N=328). **B**. Individual dentin lead trajectories across WSB −19 to +26 in the IQ sample. Each line represents repeated measurements from a single tooth sample. The solid curve represents a LOESS-smoothed average trend across all observations, with shaded areas indicating the 95% confidence interval. Negative WSB values represent prenatal periods, and positive values represent postnatal periods.

Figure 5

Dentin Lead Intensity Trajectories Across Early Development by Tooth Type



Note. Individual dentin lead trajectories (log-transformed and standardized $^{208}Pb:^{43}Ca$ intensities) across weeks since birth (WSB) by deciduous tooth type. Black lines represent individual tooth trajectories, while blue lines and shaded areas represent LOESS-smoothed mean trajectories and 95% confidence intervals, respectively.

Aim 1: Dentin Lead and Blood Comparisons

Spearman rank-order correlations between temporally defined dentin lead sampling windows and blood lead measures are reported in Table 5 for the dentin sample and stratified by child sex.

Trimester 3 Dentin Lead

Dentin lead averaged within ±2 weeks of the third-trimester maternal blood draw was more strongly correlated with concurrently measured trimester 3 maternal blood lead ($\rho = 0.82$, $p < 0.001$) than with trimester 1 maternal blood lead ($\rho = 0.71$, $p < 0.001$; Table 5). Associations between trimester 3 dentin lead and cord blood lead were moderate ($\rho = 0.64$, $p < 0.001$). In contrast, the weakest correlation was observed with childhood blood lead measured postnatally ($\rho = 0.40$, $p < 0.001$; Table 5), which is consistent with the temporal gap between the prenatal dentin measurement window and later postnatal blood measurement.

In sex-stratified analyses, correlations between trimester 3 dentin lead and trimester 3 maternal blood lead were consistently strong for both boys and girls and tended to be slightly higher in females across most blood lead comparisons (e.g., trimester 3 maternal blood: females: $\rho = 0.85$; males: $\rho = 0.78$; Table 5 and Figure 6). However, none of these sex differences reached statistical significance. The week-by-week WSB correlation plot for trimester 3 maternal blood lead (Figure 8) shows that the dentin–blood lead correlation peaks during the late prenatal period, declines after birth, and is broadly parallel for boys and girls, with girls showing higher correlations across most prenatal weeks.

Neonatal Line Dentin Lead

Dentin lead measured at the neonatal line (WSB = −2 to 0), representing fetal lead burden near birth, showed its strongest correlation with trimester 3 maternal blood lead (ρ = 0.80, $p < 0.001$; Table 5 and Figure 7). Notably, this correlation with trimester 3 maternal blood lead was stronger than the correlation with cord blood lead (ρ = 0.60, $p < 0.001$), suggesting that late-pregnancy maternal blood lead is a stronger predictor of dentin lead at the neonatal line than cord blood collected at delivery. Correlations with trimester 1 maternal blood lead were moderate (ρ = 0.68), while associations with childhood blood lead were weakest (ρ = 0.40, $p < 0.001$).

As with trimester 3 dentin, sex-stratified analyses of neonatal line dentin revealed modestly higher correlations in females than in males across most blood lead comparisons. Of all sex-stratified comparisons, only the correlation between neonatal line dentin lead and trimester 3 maternal blood lead differed significantly by sex (Fisher r-to-z: Z = 3.13, $p < 0.05$), with a stronger correlation among females. Correlations with cord blood were nearly identical between sexes at the neonatal line (males ρ = 0.59, females ρ = 0.61). The week-by-week WSB correlation plot for cord blood lead (Figure 9) shows that the dentin–cord blood correlation peaks in the late prenatal period and attenuates following birth.

Table 5

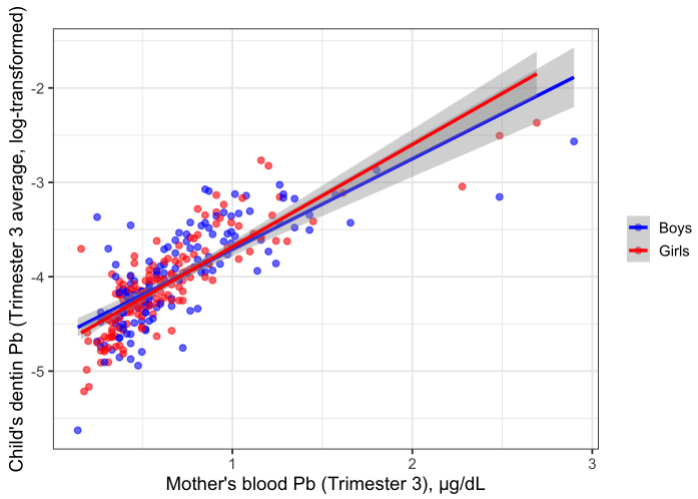
Spearman Correlations Between Dentin Lead and Blood Lead Biomarkers

Lead exposure variables	Overall sample (N=328)	Males (N=152)	Females (N=176)
T3 Dentin (+/-2 weeks from blood sampling)			
T3 maternal blood lead	0.82	0.78	0.85
T1 maternal blood lead	0.71	0.66	0.75
Cord blood lead	0.64	0.62	0.63
Child blood lead	0.40	0.32	0.47
Neonatal Line Dentin (WSB = -2 to 0)			
T3 maternal blood lead	0.80	0.73	0.86
T1 maternal blood lead	0.68	0.66	0.69
Cord blood lead	0.60	0.59	0.61
Child blood lead	0.40	0.30	0.48

Note. Spearman correlation coefficients (ρ) are presented for associations between dentin lead and corresponding blood lead biomarkers in the full dentin sample. Third trimester (T3) dentin Pb was calculated as the average log-transformed $^{208}Pb{:}43^{Ca}$ intensity within ±2 weeks of the maternal T3 blood sampling time point. Neonatal line dentin lead was calculated as the average log-transformed $^{208}Pb{:}^{43}Ca$ intensity from weeks since birth (WSB) −2 to 0. Correlations are shown overall and stratified by sex. All p-values < .001 with the exception of child blood lead for males where $p < .02$.

Figure 6

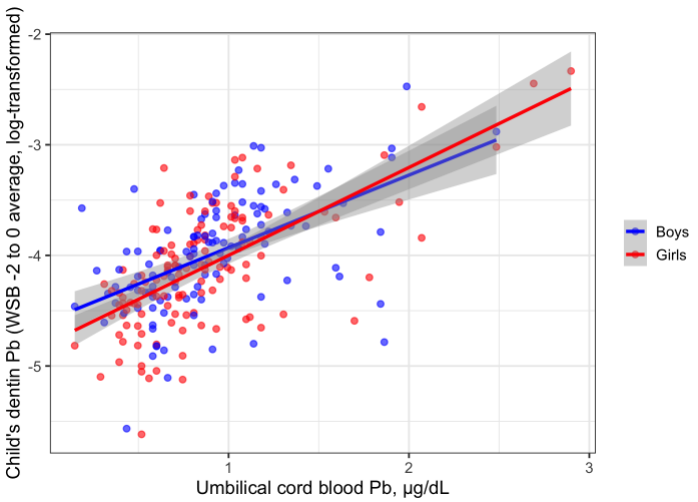
Association Between Third Trimester Maternal Blood Lead and Child Dentin Lead



Note. Child dentin lead was averaged within a ±2-week window around each participant's third trimester maternal blood draw. Dentin lead values are log-transformed ^{208}Pb:^{43}Ca intensities. Lines represent fitted linear trends shown separately for boys and girls.

Figure 7

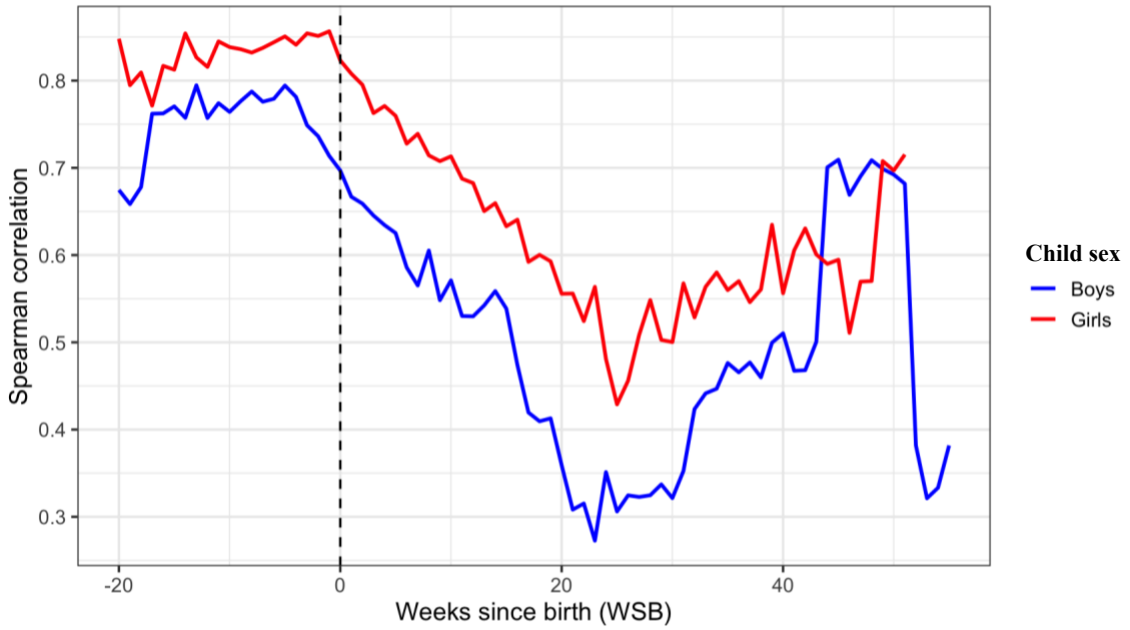
Association Between Umbilical Cord Blood Lead and Neonatal Line Dentin Lead



Note. Neonatal line dentin lead was averaged from WSB −2 to 0, representing dentin formed immediately before birth. Dentin lead values are log-transformed ^{208}Pb:^{43}Ca intensities. Lines represent fitted linear trends shown separately for boys and girls.

Figure 8

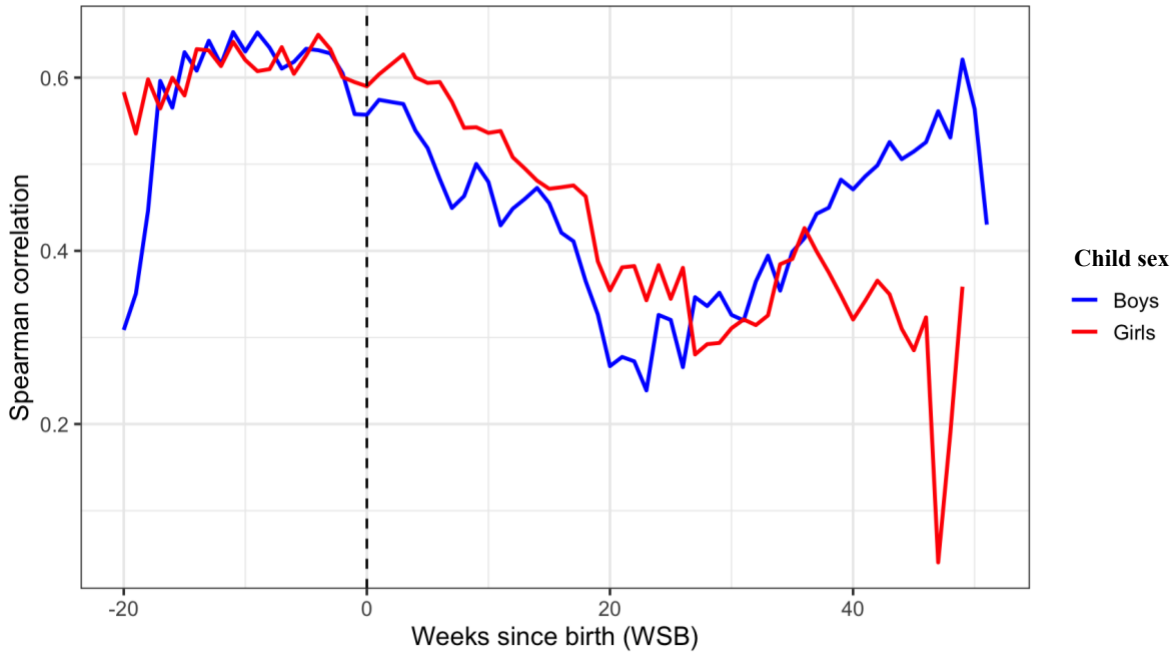
Time-Varying Correlation Between Third Trimester Maternal Blood Lead and Child Dentin Lead Stratified by Child Sex



Note. Spearman correlations between third trimester maternal blood lead and child dentin lead (log-transformed ^{208}Pb:^{43}Ca ratios) are plotted across weeks since birth (WSB). Correlations were calculated separately at each weekly time point for boys and girls, with a minimum of ten observations required per estimate. The dashed vertical line at WSB = 0 indicates birth, with negative values representing prenatal periods and positive values representing postnatal periods.

Figure 9

Time-Varying Correlation Between Umbilical Cord Blood Lead and Child Dentin Lead Stratified by Child Sex



Note. Spearman correlations between umbilical cord blood lead and child dentin lead (log-transformed ^{208}Pb:^{43}Ca ratios) are plotted across weeks since birth (WSB). Correlations were calculated separately at each weekly time point for boys and girls, with a minimum of ten observations required per estimate. The dashed vertical line at WSB = 0 indicates birth, with negative values representing prenatal periods and positive values representing postnatal periods.

Aim 2: Associations Between Dentin Lead and Child IQ

Unadjusted Linear Regression Models

Unadjusted associations between average log-transformed dentin lead and child IQ are presented in Table 6. Across all three exposure periods (prenatal, postnatal, and cumulative),

higher average dentin lead was positively and statistically significantly associated with FSIQ. Specifically, a 50% increase in average prenatal dentin lead was associated with a 1.57-point higher FSIQ score (95% CI: 0.12, 3.03; $p = .03$); the corresponding estimate for postnatal average dentin lead was B = 1.55 (95% CI: 0.19, 2.91; $p = .03$), and for cumulative average dentin lead B = 1.77 (95% CI: 0.29, 3.24; $p = .02$).

The direction of association was positive for VIQ and PIQ as well, though these did not reach statistical significance. For VIQ, the unadjusted B for prenatal lead was 1.16 (95% CI: −0.25, 2.55; $p = .11$), postnatal B = 1.02 (95% CI: −0.29, 2.34; $p = .13$), and cumulative B = 1.22 (95% CI: −0.20, 2.64; $p = .09$). For PIQ, the estimates were similarly positive: prenatal B = 1.40 (95% CI: −0.27, 3.07; $p = .10$), postnatal B = 1.53 (95% CI: −0.03, 3.09; $p = .05$), and cumulative B = 1.68 (95% CI: −0.02, 3.37; $p = .052$).

Adjusted Linear Regression Models

Results for covariate-adjusted models were attenuated and no longer statistically significant for FSIQ across the prenatal period (B = 1.41; 95% CI: −0.13, 2.95; $p = .07$), postnatal period (B = 1.09; 95% CI: −0.34, 2.51; $p = .14$), and for the cumulative period (B = 1.39; 95% CI: −0.18, 2.96; $p = .08$) (Table 6). Covariate-adjusted models for VIQ and PIQ were also not significant across all three exposure periods. Finally, no evidence of effect modification by child sex was found in any of the adjusted models (p-interaction terms all > .40).

Table 6

Unadjusted and Adjusted Associations Between Dentin Lead Exposure and Child Cognitive Outcomes

		Prenatal		**Postnatal**		**Cumulative**
Models	**n**	**B (95% CI), *p***	**n**	**B (95% CI), *p***	**n**	**B (95% CI), *p***
Full Scale IQ						
Unadjusted	166	**1.57 (0.12, 3.03), .03**	166	**1.55 (0.19, 2.92), .03**	166	**1.77 (0.29, 3.24), .02**
+ covariates	161	1.41 (-0.13, 2.95), .07	161	1.09 (-0.34, 2.51), .14	161	1.39 (-0.18, 2.96), .08
Verbal IQ						
Unadjusted	166	1.16 (-0.25, 2.55), .11	166	1.02 (-0.29, 2.34), .13	166	1.22 (-0.20, 2.64), .09
+ covariates	161	1.37 (-0.02, 2.76), .05	161	0.94 (-0.34, 2.24), .15	161	1.27 (-0.15, 2.70), .08
Performance IQ						
Unadjusted	165	1.40 (-0.27, 3.07), .10	165	1.53 (-0.03, 3.10), .05	165	1.68 (-0.02, 3.37), .05
+ covariates	160	0.93 (-0.89, 2.76), .32	160	0.82 (-0.87, 2.51), .34	160	1.00 (-0.86, 2.86), .29

Note. Dentin lead exposure was summarized as the average log-transformed ^{208}Pb:^{43}Ca intensity across prenatal (WSB −19 to 0), postnatal (WSB >0 to +26), and cumulative (WSB −19 to +26) periods. Covariates included child sex, maternal education, race/ethnicity, second-hand smoke exposure, HOME score, and study site. B coefficients and 95% confidence intervals are expressed per 50% increase in average dentin lead intensity.

Critical Windows of Lead Exposure: Reversed Distributed Lag Models

rDLMs were used to identify specific developmental windows during which dentin lead levels differed significantly between children in the lower (≤20th percentile) and higher (>20th percentile) IQ groups. Meaningful sensitive windows were identified when the estimated point wise 95% credible interval (CrI) excluded zero. Results are displayed in two-panel figures for each IQ outcome: the upper panel shows estimated dentin lead trajectories for the lower- and higher-IQ groups across the developmental windows, and the lower panel shows the between-group difference with adjusted 95% CrIs. Unadjusted models used observed IQ group

classification; adjusted models used IQ group classification derived from residuals after regressing each IQ score on the full covariate set. As the two classification methods are based on different criteria, group membership was not identical across models; overlap in low IQ group classification between unadjusted and adjusted methods was 77.1% for FSIQ, 65.0% for VIQ, and 64.3% for PIQ. Results are presented in Table 7 as the maximum estimated difference in log-transformed dentin lead between the higher- and lower-IQ groups at each developmental interval, expressed in standard-deviation (SD) units. Cumulative effects (i.e., summing significant coefficients across weeks within an interval) are also reported in Table 7.

Full-Scale IQ (FSIQ)

In the unadjusted model, children in the higher FSIQ group had dentin lead levels that were 0.07 SD *lower* than those in the lower FSIQ group during the prenatal period between 19 and 15 weeks before birth (maximum β = -0.07 SD [95% CrI: -0.12, -0.03]) (Figure 10; Table 7). A similar prenatal window was observed in the adjusted model, with *lower* dentin lead levels in the higher FSIQ group between 19 and 17 weeks before birth (maximum β = -0.06 [95% CrI: -0.10, -0.01]) (Figure 11; Table 7). The adjusted model additionally identified a second prenatal window between 12 and 4 weeks before birth that showed *higher* lead levels among children in the higher FSIQ group (maximum β = 0.02 [95% CrI: 0.01, 0.04]).

Postnatally, between 13 and 21 weeks after birth, lead levels were significantly *higher* in the higher FSIQ group in the unadjusted (maximum β = 0.03 [95% CrI: 0.01, 0.04]), but this window did not retain significance in the adjusted model. In the adjusted model, a brief postnatal window at approximately 7 weeks after birth showed *lower* dentin lead levels in the higher FSIQ group (maximum β = -0.01 [95% CrI: -0.03, -0.00]).

Verbal IQ (VIQ)

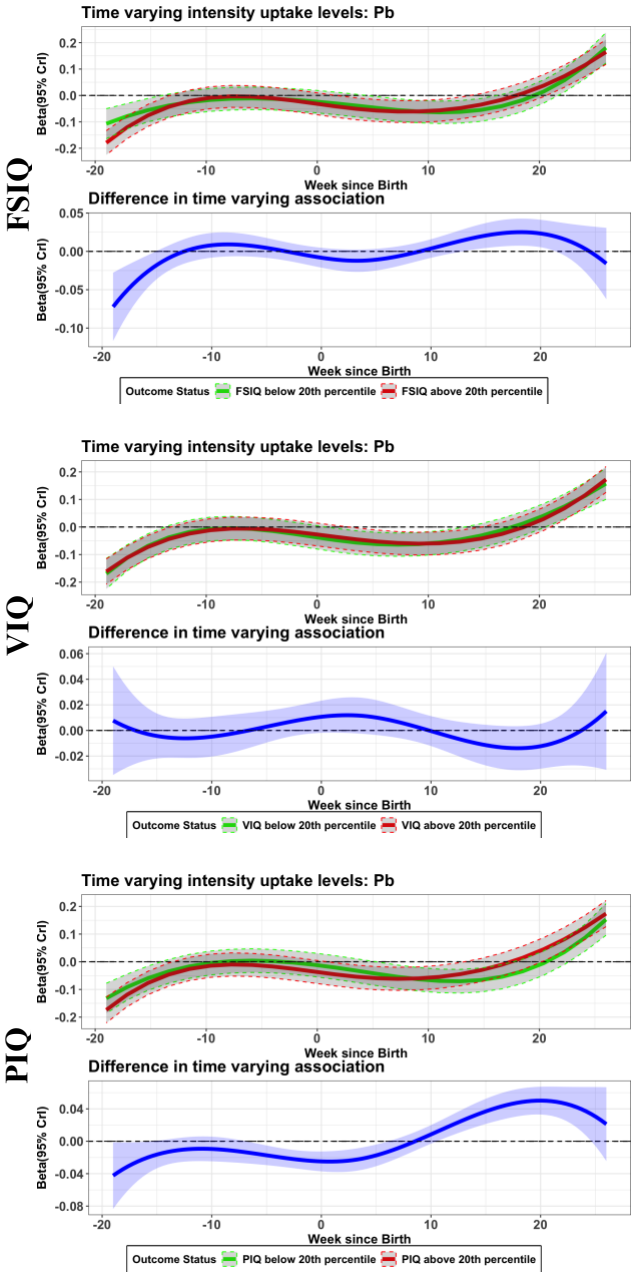
No significant windows of difference in dentin lead levels were identified between VIQ groups in the unadjusted nor adjusted model (Figures 10 and 11; Table 7).

Performance IQ (PIQ)

In the unadjusted model, children in the higher PIQ group had dentin lead levels that were 0.04 SD *lower* than those in the lower PIQ group between 19 and 16 weeks before birth (maximum $\beta = -0.04$ [95% CrI: -0.08, -0.00]) (Figure 10; Table 7). A similar prenatal pattern was observed in the adjusted model, though only a single time point at 19 weeks before birth retained significance, with *lower* dentin lead levels in the higher PIQ group (maximum $\beta = -0.05$ [95% CrI: -0.09, -0.00]) (Figure 11; Table 7). In the unadjusted model, a second window extending through the perinatal period, between 7 weeks before and 6 weeks after birth, similarly showed *lower* dentin lead levels in the higher PIQ group (maximum $\beta = -0.03$ [95% CrI: -0.04, -0.01]). Postnatally, between 11 and 25 weeks after birth, dentin lead levels were *higher* in the higher PIQ group in the unadjusted model (maximum $\beta = 0.05$ [95% CrI: 0.03, 0.07]), but this window did not retain significance after adjustment.

Figure 10

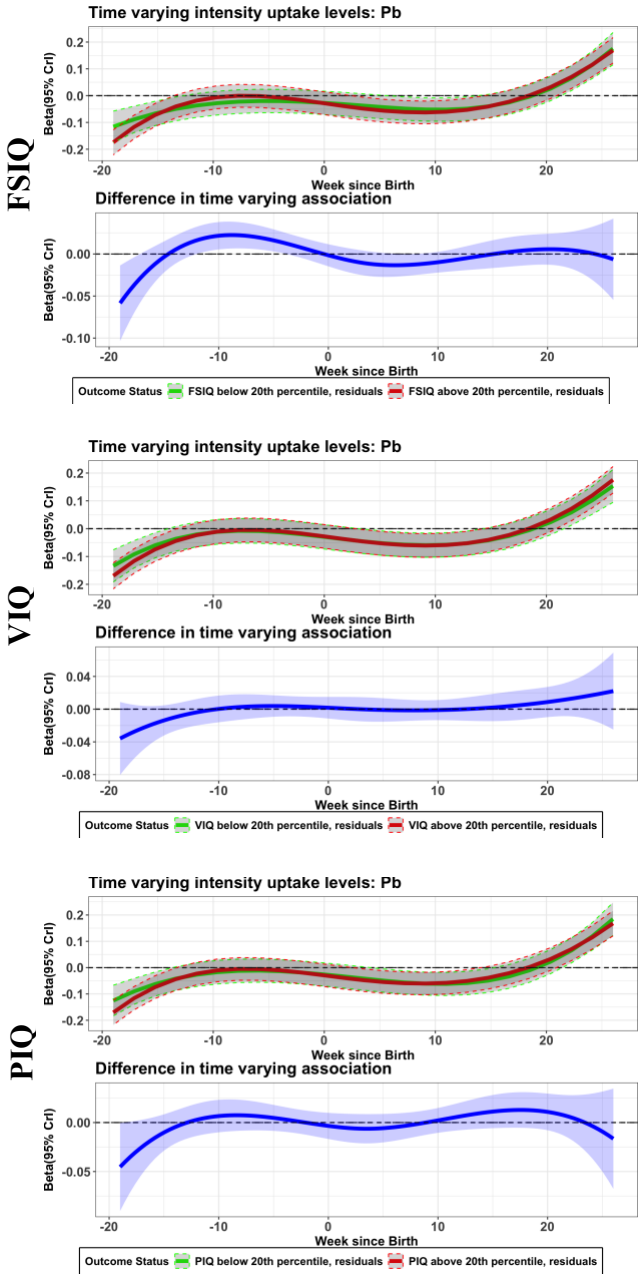
Unadjusted rDLMs of Dentin Lead and Full-Scale IQ, Verbal IQ, and Performance IQ



Note. For each outcome, the upper plot shows estimated dentin lead trajectories by IQ group, and the lower plot shows the difference between groups with 95% credible intervals, where values below and above the zero dotted line indicate lower and higher dentin lead in the higher-IQ group, respectively.

Figure 11

rDLMs of Dentin Lead and Covariate-Adjusted Full-Scale IQ, Verbal IQ, and Performance IQ



Note. For each outcome, the upper plot shows estimated dentin lead trajectories by IQ group, and the lower plot shows the difference between groups with 95% credible intervals, where values below and above the zero dotted line indicate lower and higher dentin lead in the higher-IQ group, respectively.

Table 7

Critical Windows of Dentin Lead Exposure Associated with Child IQ Outcomes from Unadjusted and Adjusted rDLMs

Outcome/Model		Critical Window (WSB)	Maximum β [95% CrI]	Cumulative β across the critical window
FSIQ				
	Unadjusted	-19 to -15 prenatally	-0.07 (-0.12, -0.03)	-0.40
	Unadjusted	13 to 21 postnatally	0.03 (0.01, 0.04)	0.40
	Adjusted	-19 to -17 prenatally	-0.06 (-0.10, -0.01)	-0.22
	Adjusted	-12 to -4 prenatally	0.02 (0.01, 0.04)	0.35
	Adjusted	7 postnatal	-0.01 (-0.03, -0.00)	-0.03
VIQ				
	Unadjusted	No significant windows	-	-
	Adjusted	No significant windows	-	-
PIQ				
	Unadjusted	-19 to -16 prenatally	-0.04 (-0.08, -0.00)	-0.24
	Unadjusted	-7 to 6 perinatally	-0.03 (-0.04, -0.01)	-0.60
	Unadjusted	11 to 25 postnatally	0.05 (0.03, 0.07)	1.22
	Adjusted	-19 prenatal	-0.05 (-0.09, -0.00)	-0.05

Note. Maximum β represents the peak difference in scaled log dentin lead between the higher and lower IQ groups within each window. Cumulative β represents the sum of weekly β estimates across the critical window.

Supplementary Analyses

Associations between prenatal, postnatal, and cumulative AUC dentin lead and child IQ outcomes are presented in Table S2; results were null across all exposure periods and IQ outcomes.

Supplementary rDLM analyses using continuous IQ as the outcome similarly revealed no significant time-varying associations across the developmental window for any IQ outcome (Figure S1).

Discussion

This study used deciduous tooth dentin analyzed by LA-ICP-MS to reconstruct temporally resolved prenatal and early postnatal lead exposure in children from the MIREC cohort. The study addressed two primary objectives: (1) validating dentin lead as a biomarker against concurrent traditional blood lead measures in this contemporary low-exposure Canadian cohort, and (2) examining associations between period-specific dentin lead and child IQ, with attention to critical developmental windows of susceptibility. To our knowledge, this is the first study to use temporally resolved dentin lead to examine IQ outcomes in a Canadian cohort, and among the first to apply the rDLM framework to IQ rather than to behavioural outcomes.

Dentin Lead and Blood Lead Comparisons

The first contribution of this study is the strong concordance between dentin lead intensities and established blood lead biomarkers. As hypothesized, third-trimester dentin lead correlated most strongly with concurrently measured trimester 3 maternal blood lead ($\rho = 0.82$), followed by trimester 1 maternal blood lead ($\rho = 0.71$), cord blood ($\rho = 0.64$), and postnatal childhood blood lead ($\rho = 0.40$). These findings indicate that dentin lead reflects circulating lead at the time of mineralization and that correlations attenuate with increasing temporal distance between biomarkers. These findings replicate and extend the work of Arora et al., who reported significant correlations between trimester 3 dentin lead and concurrently measured maternal blood lead in a Mexico City pregnancy cohort (Spearman $\rho = 0.64$), and between dentin lead at birth and cord blood lead (Spearman $\rho = 0.69$) (Arora et al., 2014). The stronger correlations observed in the current study compared with those reported by Arora et al (0.82 vs. 0.64) may reflect both methodological improvements in LA-ICP-MS since that earlier work

and the tighter temporal matching between dentin sampling windows and blood collection timepoints in our study, as well as the substantially larger sample size available for trimester 3 analyses in the present study. The validation framework is also broadly consistent with the recent work of Punshon et al. and Bauer et al. in the New Hampshire Birth Cohort Study, who similarly demonstrated that dentin element concentrations correlate meaningfully with environmental measures of exposure across diverse cohorts (Bauer et al., 2024; Punshon et al., 2024). Collectively, these findings provide strong evidence that deciduous teeth can serve as reliable retrospective archives of prenatal and early-life lead exposure, enabling researchers to reconstruct temporally resolved exposure histories years after the exposure period has occurred. This unique capability offers substantial opportunities for future epidemiologic studies to investigate critical windows of susceptibility when prospective biospecimen collection is unavailable or incomplete.

The sex-stratified validation analyses revealed a pattern of descriptively stronger dentin–blood lead correlations in girls than in boys across most sampling windows. When formally tested, only the correlation between neonatal line dentin and trimester 3 maternal blood lead differed significantly by sex. Median dentin lead levels did not significantly differ by sex across prenatal, postnatal, or cumulative exposure windows, suggesting that the observed differences in correlation strength were unlikely to reflect systematic differences in exposure levels. The direction of these findings, together with the one statistically significant comparison, is broadly consistent with the recent findings of Jensen et al. who reported sex-specific correlations between elements in deciduous tooth dentin and maternal blood in the Norwegian Mother, Father and Child Cohort Study (Jensen et al., 2025). Potential mechanisms may reflect known sex differences in metal toxicokinetics, including differences in bone lead

storage and mobilization, as well as hormonal and physiological factors that influence metal metabolism (Vahter et al., 2007). Given that most sex differences were not statistically significant, these findings should be considered preliminary; nonetheless, they suggest that sex-stratified validation analyses should be considered when applying the dentin biomarker to neurodevelopmental outcomes, as pooled estimates may mask sex-differential biomarker performance.

Another contribution of this study was the ability to characterize changes in lead exposure over time within the same biomarker. Results revealed an increasing trend in dentin lead intensities from the prenatal period into the postnatal weeks, highlighting the importance of measuring lead at multiple developmental time points rather than relying on a single summary measure. This is particularly important because susceptibility to lead toxicity varies across developmental stages, and exposures occurring during specific windows may have disproportionate effects on later health and neurodevelopment. By preserving a temporally resolved record of exposure, deciduous teeth can identify critical periods of elevated lead exposure that would be obscured by conventional biomarkers that provide only a snapshot of exposure at a single point in time. Such information may improve our ability to identify sensitive windows of vulnerability and strengthen investigations of how the timing of exposure influences developmental outcomes.

Average Dentin Lead and Child IQ

Although unadjusted regression models showed a positive and significant association between average dentin lead and IQ, these findings attenuated and were no longer statistically significant following adjustment for key covariates. Thus, the adjusted findings provide limited

evidence of an association between dentin lead and IQ in this sample. Past studies have reported null or inverse associations between prenatal or early-life lead exposure and cognitive outcomes (Canfield et al., 2003; Lanphear et al., 2005; Needleman et al., 1979).

Notably, Desrochers-Couture et al. had previously identified a significant negative association specifically between cord blood lead and PIQ in boys (B = -3.28), but not girls (B = 0.16) from the MIREC cohort, albeit their sample size was much larger relative to the current study (601 vs. 160 participants) due to an imputed dataset (Desrochers-Couture et al., 2018). To examine whether this finding replicated in the present analytical sample, sex-stratified regressions of cord blood lead on PIQ were performed and findings showed the expected inverse association among boys, B = −2.30 (p = .59), but not girls, B = 4.45 (p = .23), though the sex interaction term did not reach significance (p = .18). However, when the same regression was repeated using dentin lead averaged across the neonatal line window (WSB −2 to 0), the results were consistently *positive* for both boys (per 50% increase in dentin lead: B = 1.18; 95% CI: −1.53, 3.90; p = .39) and girls (per 50% increase in dentin lead: B = 1.01; 95% CI: −1.45, 3.47; p = .42), diverging from the cord blood direction. These findings suggest that dentin lead measured around the neonatal line may capture a somewhat different period or pattern of exposure than cord blood lead, which could help explain observed differences in associations with PIQ. Supporting this possibility, in Aim 1 we observed a stronger correlation between neonatal dentin lead and third-trimester maternal blood lead (ρ = 0.80) than between neonatal dentin lead and cord blood lead (ρ = 0.60).

The largely null findings of the present study may reflect both selection bias and limited exposure contrast within the analytical sample, reducing our ability to detect an adverse dose-response relationship between dentin lead and child IQ. The MIREC cohort represents a

sociodemographically advantaged subset of Canadian pregnant women, and the dentin-IQ sample (N=166) appears to be further selected relative to the full MIREC IQ sample (N=601). Compared to the full MIREC IQ sample, the dentin-IQ sample included a higher proportion of university-educated mothers (77.3% vs. 66.7%), higher household incomes (51.5% vs. 39.7% earning >$100K), a greater proportion of White mothers (94.5% vs. 89.2%), less secondhand smoke exposure (0.6% vs. 3.5%), slightly higher HOME scores (48.2 vs. 47.3), and higher mean child IQ scores across all three outcomes (FSIQ: 109.4 vs. 106.8; VIQ: 111.0 vs. 109.4; PIQ: 105.5 vs. 102.9).

Loss to follow-up across the parent MIREC, MIREC-CD Plus, and MIREC-ENDO extension studies, combined with voluntary participation in deciduous tooth donation, likely further restricted socioeconomic variability and resulted in an analytic sample that under-represents populations with greater risk of environmental lead exposure in Canada, including those with lower educational attainment and lower-income housing conditions (Nguyen et al., 2024; Fisher et al., 2023). This selection may have contributed to the relatively low and narrow distribution of lead exposure in our sample. Indeed, the dentin-IQ sample has lower blood lead concentrations (i.e. median blood lead values < 0.90 ug/dL) than many of the international cohorts in which inverse lead–IQ associations have been documented (Lanphear et al., 2005), which may further reflect the relatively advantaged socioeconomic profile of this sample. Although previous studies have reported inverse associations between blood lead concentrations below 5 µg/dL and IQ, including in cohorts with median blood lead levels as low as 1.5 µg/dL (Jusko et al., 2008; Lucchini et al., 2012), the narrow range of exposure within our sample may have limited the statistical power to detect a dose-response relationship.

Additionally, while median blood and dentin lead was paradoxically higher in the

higher-FSIQ group than the lower-FSIQ group across prenatal biomarkers (e.g., trimester 3 blood lead: 0.68 vs. 0.52 μg/dL), the higher-FSIQ group had a greater proportion of nulliparous mothers compared to the lower-FSIQ group (53.5% vs. 44.4%). Prior research has shown that nulliparous women tend to have higher blood lead levels than multiparous women, likely reflecting differences in bone resorption and placental detoxification across pregnancies (Manton et al., 2003; Palir et al., 2024). This imbalance in parity between IQ groups may help explain the observed exposure pattern.

Beyond low overall exposure levels, the sociodemographic characteristics of our sample may have also buffered children against potential neurotoxic effects of lead. High maternal education, household income, and home stimulation may mask associations that would otherwise be detectable in more socioeconomically diverse populations. This interpretation is given additional weight by experimental and human evidence that environmental enrichment buffers the neurotoxic effects of lead exposure on the developing brain. Schneider et al. demonstrated that rats exposed to lead from weaning onward and raised in an enriched environment with group housing and toys performed comparably to non-exposed controls on the Morris water maze and showed substantially preserved hippocampal expression of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), whereas lead-exposed rats raised in isolation showed both behavioural deficits and the lowest neurotrophin expression (Schneider et al., 2001). Lead-exposed rats in the enriched condition showed intermediate but significantly higher neurotrophin expression than their isolation-reared counterparts, indicating that environmental enrichment ameliorated the lead-induced reduction of factors critical for hippocampal neuron survival and synaptogenesis. Marshall et al. extended this finding to humans using the Adolescent Brain Cognitive Development (ABCD) Study, showing that the

structural and cognitive consequences of geocoded lead-risk neighborhoods, including smaller cortical volumes, reduced surface areas, and lower cognitive scores, were considerably stronger in low-income families than in high-income families (Marshall et al., 2020). At the highest lead-risk level, low-income children showed 8.2% smaller cortical surface areas, 9.6% smaller cortical volumes, and 12.2% lower cognitive performance than their high-income peers in the same high-risk areas, with these effects attenuating at lower exposure levels. In other words, families with higher socioeconomic resources may be better able to buffer their children against the neurotoxic effects of lead. Within this context, the MIREC analytical sample reflects a population with characteristics that may be associated with greater environmental and developmental support, including higher maternal education, higher socioeconomic status, and enriched home environments. These features of the sample may contribute to the absence of expected inverse lead–IQ associations in the present analyses, even if underlying neurotoxic mechanisms remain.

Critical Windows of Lead Exposure: rDLM Findings and the Value of Time-Varying Analysis

The reversed distributed lag model (rDLM) analyses offer a more temporally resolved view than the period-averaged regression analyses or the traditional blood biomarker approach. Although adjusted rDLM findings were largely null, the unadjusted models identified several significant windows of association for FSIQ and PIQ that are nonetheless worth considering in the context of known neurodevelopmental vulnerability to lead. Keeping in mind that the children identified in the lower-IQ group differ between the unadjusted and adjusted models (e.g., 77.1% overlap in the lower-FSIQ group), it is worthwhile to discuss the results of both models.

For FSIQ, both the unadjusted and adjusted models identified a prenatal window of *lower* dentin lead in the higher FSIQ group (unadjusted: weeks -19 to -15; adjusted: weeks -19 to -17), coinciding with a particularly dynamic phase of cortical and subcortical brain development. White matter is the dominant tissue undergoing rapid expansion during mid-gestation, while gray matter dominates late-gestational and early postnatal growth, with subcortical gray matter structures showing earlier peak growth rates than cortical structures (Khan et al., 2026). Lead produces lasting structural consequences when delivered during this gestational period: in rat models, gestational lead exposure produces reductions in pyramidal neurons in CA1, CA3, and the dentate hilus of the hippocampus, in granule neurons of the dentate gyrus, in Purkinje cells of the cerebellar cortex, and in amygdalar neurons, whereas pre-gestational exposure alone yields no detectable neuronal loss (Barkur & Bairy, 2016). In humans, Wylie et al. demonstrated that higher maternal urinary lead at mid-pregnancy was associated with smaller bilateral amygdala volumes detectable by magnetic resonance imaging (MRI) in neonates as early as approximately two weeks of age, indicating that the structural consequences of lead exposure during this gestational period are detectable from birth (Wylie et al., 2024).

The unadjusted perinatal window for PIQ (weeks -7 to +6), during which children in the higher PIQ group had lower dentin lead, spans the period immediately surrounding birth and into the first postnatal weeks, a developmental period that animal and human studies suggest is sensitive to lead's neurotoxic effects on brain regions involved in cognition. Evidence for postnatal vulnerability is seen in the work of Barkur and Bairy, who exposed rat pups to lead during one of four developmental windows, including pregestational, gestational, lactational, and combined exposure, and then assessed neuronal counts in the hippocampus, cerebellum,

and amygdala at postnatal day 30 (Barkur & Bairy, 2016). Pups exposed only during the lactational period showed neuronal loss that was comparable to those exposed across both gestation and lactation combined, despite experiencing a shorter overall exposure duration. This pattern was consistent across all three brain regions, suggesting that the early postnatal period represents a particularly sensitive phase during which lead exposure may result in disproportionately greater structural damage relative to exposure during gestation. Earlier work by Gietzen and Woolley similarly identified the cerebellum as particularly vulnerable to lead during the first 20 postnatal days, a period coinciding with rapid postnatal cerebellar growth and Purkinje cell maturation (Gietzen & Woolley, 1984). Purkinje cells serve as the primary output neurons of the cerebellar cortex, and their loss has widespread implications for cerebellar-cortical communication, memory, and higher-order cognitive outcomes (Cooper et al., 2024).

Taken together, the timing of the unadjusted windows that were directionally consistent with the lead neurotoxicity literature coincides with phases of rapid brain development identified in both animal and human studies. These findings highlight the potential value of dentin as a time-resolved exposure biomarker and underscore the importance of examining lead exposure across discrete developmental windows rather than relying on a single summary measure.

Strengths

This study has several notable strengths. The MIREC cohort is a well-characterized, prospective, multi-site Canadian pregnancy and birth cohort with rich covariate data and multiple biospecimen timepoints, providing information on both prenatal and postnatal lead

exposure alongside neurodevelopmental outcomes. The use of LA-ICP-MS dentin lead with odontochronological assignment of weekly temporal resolution constitutes a substantial methodological advancement over prior bulk-tooth or single-timepoint blood lead studies, enabling the identification of developmentally specific exposure windows that are not possible with conventional biomarkers (Andra et al., 2015; Arora et al., 2014). With respect to measurement precision, repeat LA-ICP-MS analyses conducted on a subset of teeth demonstrated generally high concordance in measured lead intensities, though the odontochronological assignment of weekly timepoints may vary by approximately one week between runs. The comparison of the dentin biomarker against four blood lead measures, trimester 1 and trimester 3 maternal blood, cord blood, and childhood blood, represents the first characterization of this methodology in a Canadian cohort and provides a foundation for interpreting the dentin-IQ associations. The application of the rDLM framework to IQ outcomes represents a rigorous and novel methodological contribution to the dentin biomarker literature.

Limitations

Although the study has several strengths, certain limitations should be considered. As discussed, there is potential selection bias, as dentin lead and IQ data were only available for about one-quarter of the original MIREC sample (Fisher et al., 2023). As mentioned above, our dentin-IQ sample was more educated, White, and had a higher income relative to the full MIREC child IQ sample. Generalizability may also be limited, as the sample is predominantly Caucasian and of higher socioeconomic status. Statistical power was also limited given the modest overall sample size and restricted exposure range. The relatively wide confidence

intervals observed across regression models indicate imprecision in the effect estimates, which may have limited our ability to detect small associations between dentin lead and IQ. Notably, sex-stratified rDLM analyses could not be reliably conducted, as dividing the sample by sex resulted in very small subgroups (e.g., 21 boys and 15 girls in the ≤ 20th percentile FSIQ group) which would have been insufficient for stable window detection. As a result, potential sex-differential effects in the timing of lead exposure and cognitive outcomes could not be examined in the rDLM analysis. A further limitation relates to how dentin lead was measured. Because lead intensities are expressed as a ratio of lead to calcium rather than as absolute concentrations, it is not possible to directly compare dentin lead levels to those reported in other studies using absolute units such as parts per million (ppm), as reported by other studies using LA-ICP-MS (Bauer et al., 2024). Finally, although a second tooth was collected from 190 participants, this data was not available at the time of analysis. Future analyses incorporating multiple teeth per participant would allow for an extension of the postnatal period to roughly 10-12 months postnatal.

Conclusions

The results of this study provide strong support for the use of dentin lead as a biomarker of exposure, demonstrating high correlations with established blood lead measures when exposure windows align. By capturing exposure across both prenatal and early postnatal development, dentin offers a level of temporal specificity that is not possible with traditional biomarkers. Although associations between lead exposure and IQ were largely null and did not follow the expected inverse pattern in this cohort, this may reflect characteristics of the analytical sample, including low exposure levels and a relatively advantaged socioeconomic profile with

above-average cognitive performance. Importantly, the use of dentin enabled the examination of time-varying exposure patterns across development, illustrating its potential to identify sensitive windows that are otherwise obscured by conventional approaches. This represents a meaningful methodological advancement in developmental toxicology. Given the well-established neurotoxicity of lead and the substantial public health impact of even small shifts in population cognitive ability (Taylor et al., 2025), the ability to accurately reconstruct early-life exposure is critical. Deciduous tooth dentin provides a powerful tool to address this need. Future work applying this biomarker in more diverse populations with broader exposure ranges will be essential for clarifying critical periods of vulnerability and informing prevention efforts.

Appendix A: Supplemental Materials

Supplemental Table 1

Bivariate associations between dentin lead intensities, full scale IQ, and potential covariates.

Potential covariates	***Dentin Lead Intensities***	***Full-Scale IQ***
[rb]Child sex[a]	*-0.07#*	*0.17**
[rb]Maternal education	0.15**	*0.16**
Maternal age at visit 1	*0.24***	-0.04
Gestational Age at delivery	0.008	*0.11#*
[rb]Race[b]	-0.07	*0.11#*
[rb]Second Hand Smoke 1st trimester	-0.001	*0.19**
HOME total score	-0.04	*0.17**
Pre-pregnancy BMI	-0.05	-0.01
[rb]Alcohol use during pregnancy	0.18**	-0.03
[rb]Duration exclusively breastfed	-0.02	0.11#
CES-D	-0.02	0.01
Age at testing	0.07	*0.12#*
Mercury Cord	0.26**	0.08

[a]0 = Male, 1 = Female

[b]0 = Other, 1 = White

[rb]biserial correlation. [#]$p < 0.2$; *$p < 0.05$; **$p < 0.01$

Supplemental Table 2

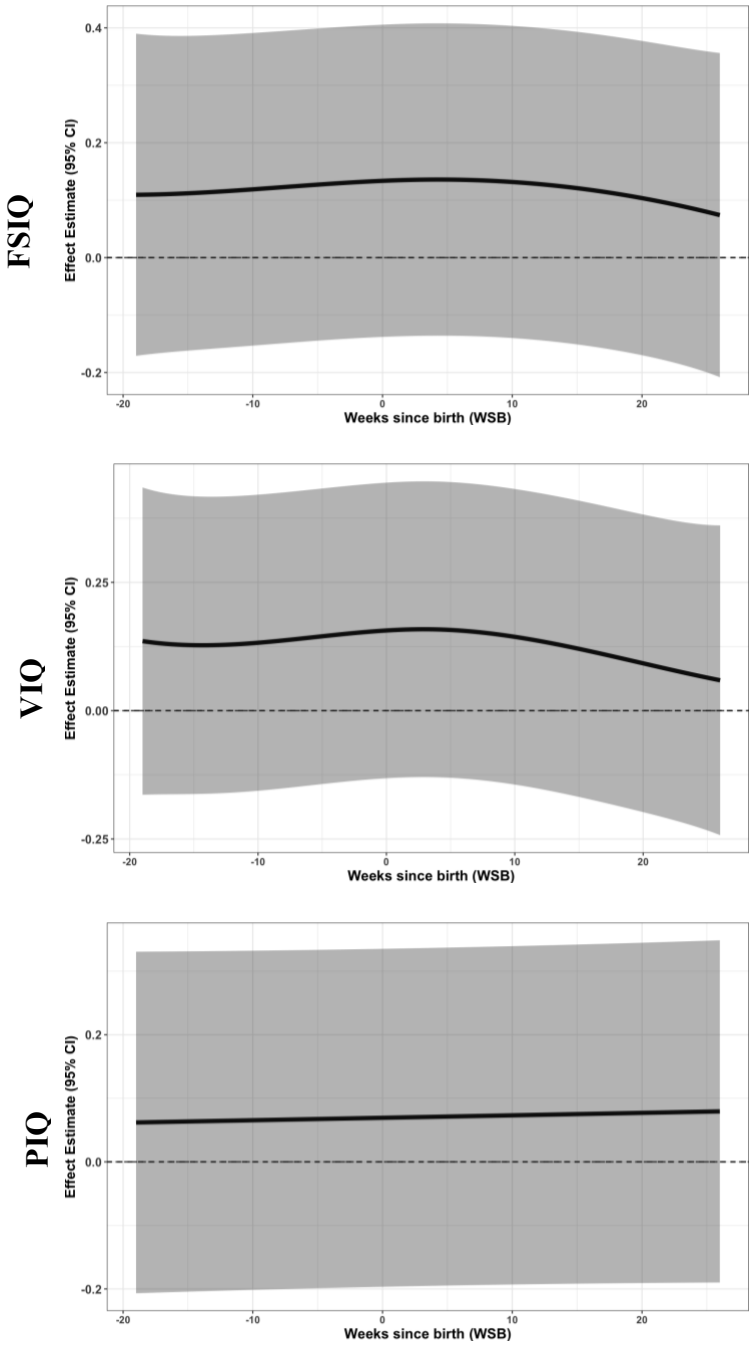
Adjusted Associations Between Dentin Lead Exposure Deciles and Child IQ Outcomes

	Prenatal		Postnatal		Cumulative	
	n	**B (95% CI), *p***	**n**	**B (95% CI), *p***	**n**	**B (95% CI), *p***
Full Scale IQ	161	0.85 (-0.05, 1.76), .06	161	0.35 (-0.74, 1.44), .53	161	0.79 (-0.23, 1.82), .13
Verbal IQ	161	0.81 (-0.01, 1.62), .053	161	0.53 (-0.44, 1.51), .28	161	0.79 (-0.14, 1.71), .10
Performance IQ	160	0.57 (-0.50, 1.64), .29	160	-0.02 (-1.31, 1.26), .97	160	0.49 (-0.73, 1.71), .43

Note. Dentin lead exposure was summarized as the area under the curve (AUC) of log-transformed Pb208 intensities across prenatal (WSB -19 to 0), postnatal (WSB 0 to 26), and cumulative (WSB -19 to 26) windows and ranked into deciles. Models were adjusted for child sex, maternal education, race/ethnicity, secondhand smoke exposure, HOME score, study site, and number of WSB measurements per exposure window.

Supplemental Figure 1

Time-Varying Association Between Dentin Lead and IQ Outcomes in Adjusted Continuous rDLMs



Note. The figure displays the time-varying association between dentin lead and IQ scores across WSB (-19 to +26) for FSIQ (top), VIQ (middle), and PIQ (bottom), derived from

adjusted rDLMs. Shaded regions indicate 95% confidence intervals. The dotted horizontal line represents the null effect.

References

Andra, S. S., Austin, C., Wright, R. O., & Arora, M. (2015). Reconstructing pre-natal and early childhood exposure to multi-class organic chemicals using teeth: Towards a retrospective temporal exposome. *Environment International*, *83*, 137–145. https://doi.org/10.1016/j.envint.2015.05.010

Arbuckle, T. E., Fraser, W. D., Fisher, M., Davis, K., Liang, C. L., Lupien, N., Bastien, S., Velez, M. P., von Dadelszen, P., Hemmings, D. G., Wang, J., Helewa, M., Taback, S., Sermer, M., Foster, W., Ross, G., Fredette, P., Smith, G., Walker, M., … Ouellet, E. (2013). Cohort Profile: The Maternal-Infant Research on Environmental Chemicals Research Platform. *Paediatric and Perinatal Epidemiology*, *27*(4), 415–425. https://doi.org/10.1111/ppe.12061

Arbuckle, T. E., Liang, C. L., Morisset, A.-S., Fisher, M., Weiler, H., Cirtiu, C. M., Legrand, M., Davis, K., Ettinger, A. S., & Fraser, W. D. (2016). Maternal and fetal exposure to cadmium, lead, manganese and mercury: The MIREC study. *Chemosphere*, *163*, 270–282. https://doi.org/10.1016/j.chemosphere.2016.08.023

Arora, M., Austin, C., Sarrafpour, B., Hernández-Ávila, M., Hu, H., Wright, R. O., & Tellez-Rojo, M. M. (2014). Determining Prenatal, Early Childhood and Cumulative Long-Term Lead Exposure Using Micro-Spatial Deciduous Dentine Levels. *PLoS ONE*, *9*(5), e97805. https://doi.org/10.1371/journal.pone.0097805

Baghurst, P. A., McMichael, A. J., Vimpani, G. V., Robertson, E. F., Clark, P. D., & Wigg, N. R. (1987). Determinants of blood lead concentrations of pregnant women living in Port Pirie and surrounding areas. *The Medical Journal of Australia*, *146*(2), 69–73. https://doi.org/10.5694/j.1326-5377.1987.tb136265.x

Baghurst, P. A., McMichael, A. J., Wigg, N. R., Vimpani, G. V., Robertson, E. F., Roberts, R. J., & Tong, S.-L. (1992). Environmental Exposure to Lead and Children's Intelligence at the Age of Seven Years. *New England Journal of Medicine*, *327*(18), 1279–1284. https://doi.org/10.1056/NEJM199210293271805

Barkur, R. R., & Bairy, L. K. (2016). Histological study on hippocampus, amygdala and cerebellum following low lead exposure during prenatal and postnatal brain development in rats. *Toxicology and Industrial Health*, *32*(6), 1052–1063. https://doi.org/10.1177/0748233714545624

Bauer, J. A., Punshon, T., Barr, M. N., Jackson, B. P., Weisskopf, M. G., Bidlack, F. B., Coker, M. O., Peacock, J. L., & Karagas, M. R. (2024). Deciduous teeth from the New Hampshire birth cohort study: Early life environmental and dietary predictors of dentin elements. *Environmental Research*, *256*, 119170. https://doi.org/10.1016/j.envres.2024.119170

Bellinger, D. C., & Needleman, H. L. (2003). Intellectual Impairment and Blood Lead Levels. *New England Journal of Medicine*, *349*(5), 500–502. https://doi.org/10.1056/NEJM200307313490515

Bellinger, D., Leviton, A., Waternaux, C., Needleman, H., & Rabinowitz, M. (1987). Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development. *The New England Journal of Medicine*, *316*(17), 1037–1043. https://doi.org/10.1056/NEJM198704233161701

Canfield, R. L., Henderson, C. R., Cory-Slechta, D. A., Cox, C., Jusko, T. A., & Lanphear, B. P. (2003). Intellectual Impairment in Children with Blood Lead Concentrations below 10 μg

per Deciliter. *New England Journal of Medicine*, *348*(16), 1517–1526. https://doi.org/10.1056/NEJMoa022848

Chuang, H. Y., Schwartz, J., Gonzales-Cossio, T., Lugo, M. C., Palazuelos, E., Aro, A., Hu, H., & Hernandez-Avila, M. (2001). Interrelations of lead levels in bone, venous blood, and umbilical cord blood with exogenous lead exposure through maternal plasma lead in peripartum women. *Environmental Health Perspectives*, *109*(5), 527–532. https://doi.org/10.1289/ehp.01109527

Cooney, G. H., Bell, A., Mcbride, W., & Carter, C. (1989). Neurobehavioural consequences of prenatal low level exposures to lead. *Neurotoxicology and Teratology*, *11*(2), 95–104. https://doi.org/10.1016/0892-0362(89)90047-0

Cooper, C. P., Cheng, L., Bhatti, J., Melendez, E. R., Huell, D., Banuelos, C., Perez, E., Long, J. M., & Rapp, P. R. (2024). Cerebellum Purkinje Cell Vulnerability in Aged Rats with Memory Impairment. *The Journal of Comparative Neurology*, *532*(4), e25610. https://doi.org/10.1002/cne.25610

Desrochers-Couture, M., Oulhote, Y., Arbuckle, T. E., Fraser, W. D., Séguin, J. R., Ouellet, E., Forget-Dubois, N., Ayotte, P., Boivin, M., Lanphear, B. P., & Muckle, G. (2018). Prenatal, concurrent, and sex-specific associations between blood lead concentrations and IQ in preschool Canadian children. *Environment International*, *121*, 1235–1242. https://doi.org/10.1016/j.envint.2018.10.043

Dietrich, K. N., Berger, O. G., Succop, P. A., Hammond, P. B., & Bornschein, R. L. (1993). The developmental consequences of low to moderate prenatal and postnatal lead exposure: Intellectual attainment in the cincinnati lead study cohort following school entry.

Neurotoxicology and Teratology, *15*(1), 37–44. https://doi.org/10.1016/0892-0362(93)90043-N

Dietrich, K. N., Krafft, K. M., Bornschein, R. L., Hammond, P. B., Berger, O., Succop, P. A., & Bier, M. (1987). Low-Level Fetal Lead Exposure Effect on Neurobehavioral Development in Early Infancy. *Pediatrics*, *80*(5), 721–730. https://doi.org/10.1542/peds.80.5.721

Dignam, T., Kaufmann, R. B., LeStourgeon, L., & Brown, M. J. (2019). Control of Lead Sources in the United States, 1970-2017: Public Health Progress and Current Challenges to Eliminating Lead Exposure. *Journal of Public Health Management and Practice : JPHMP*, *25*(Suppl 1 LEAD POISONING PREVENTION), S13–S22. https://doi.org/10.1097/PHH.0000000000000889

Ettinger, A. S., Lamadrid-Figueroa, H., Téllez-Rojo, M. M., Mercado-García, A., Peterson, K. E., Schwartz, J., Hu, H., & Hernández-Avila, M. (2009). Effect of Calcium Supplementation on Blood Lead Levels in Pregnancy: A Randomized Placebo-Controlled Trial. *Environmental Health Perspectives*, *117*(1), 26–31. https://doi.org/10.1289/ehp.11868

Fisher, M., Muckle, G., Lanphear, B., Arbuckle, T. E., Braun, J. M., Zidek, A., Vélez, M. P., Lupien, N., Bastien, S., Ashley-Martin, J., Oulhote, Y., Borghese, M. M., Walker, M., Asztalos, E., Bouchard, M. F., Booij, L., Palmert, M. R., Morrison, K. M., Cummings, E. A., … Fraser, W. D. (2023). Cohort profile update: The Canadian Maternal–Infant Research on Environmental Chemicals Child Development study (MIREC-CD PLUS). *Paediatric and Perinatal Epidemiology*, *37*(8), 719–732. https://doi.org/10.1111/ppe.13013

Gietzen, D. W., & Woolley, D. E. (1984). Acetylcholinesterase activity in the brain of rat pups and dams after exposure to lead via the maternal water supply. *Neurotoxicology*, *5*(3), 235–246.

Goodman, C. V., Green, R., DaCosta, A., Flora, D., Lanphear, B., & Till, C. (2023). Sex difference of pre- and post-natal exposure to six developmental neurotoxicants on intellectual abilities: A systematic review and meta-analysis of human studies. *Environmental Health*, *22*(1), 80. https://doi.org/10.1186/s12940-023-01029-z

Goyer, R. A. (1990). Transplacental transport of lead. *Environmental Health Perspectives*, *89*, 101–105. https://doi.org/10.1289/ehp.9089101

Grandjean, P., & Landrigan, P. (2006). Developmental neurotoxicity of industrial chemicals. *The Lancet*, *368*(9553), 2167–2178. https://doi.org/10.1016/S0140-6736(06)69665-7

Gulson, B. L., Mizon, K. J., Korsch, M. J., Palmer, J. M., & Donnelly, J. B. (2003). Mobilization of lead from human bone tissue during pregnancy and lactation—A summary of long-term research. *The Science of the Total Environment*, *303*(1–2), 79–104. https://doi.org/10.1016/s0048-9697(02)00355-8

Gulson, B., & Wilson, D. (1994). History of lead exposure in children revealed from isotopic analyses of teeth. *Archives of Environmental Health*, *49*(4), 279–283. https://doi.org/10.1080/00039896.1994.9937480

Herrmann, M., King, K., & Weitzman, M. (2008). Prenatal tobacco smoke and postnatal secondhand smoke exposure and child neurodevelopment. *Current Opinion in Pediatrics*, *20*(2), 184. https://doi.org/10.1097/MOP.0b013e3282f56165

Horton, M. K., Hsu, L., Claus Henn, B., Margolis, A., Austin, C., Svensson, K., Schnaas, L., Gennings, C., Hu, H., Wright, R., Rojo, M. M. T., & Arora, M. (2018). Dentine

biomarkers of prenatal and early childhood exposure to manganese, zinc and lead and childhood behavior. *Environment International*, *121*(Pt 1), 148–158. https://doi.org/10.1016/j.envint.2018.08.045

Hu, H., Téllez-Rojo, M. M., Bellinger, D., Smith, D., Ettinger, A. S., Lamadrid-Figueroa, H., Schwartz, J., Schnaas, L., Mercado-García, A., & Hernández-Avila, M. (2006). Fetal Lead Exposure at Each Stage of Pregnancy as a Predictor of Infant Mental Development. *Environmental Health Perspectives*, *114*(11), 1730–1735. https://doi.org/10.1289/ehp.9067

Inoue, H., Sanefuji, M., Sonoda, Y., Ogawa, M., Hamada, N., Shimono, M., Suga, R., Nakayama, S. F., Taniguchi, Y., Kusuhara, K., Ohga, S., Kamijima, M., The Japan Environment and Children's Study Group, Kamijima, M., Yamazaki, S., Ohya, Y., Kishi, R., Yaegashi, N., Hashimoto, K., … Katoh, T. (2022). No association between prenatal lead exposure and neurodevelopment during early childhood in the Japan Environment and Children's Study. *Scientific Reports*, *12*(1), 15305. https://doi.org/10.1038/s41598-022-19509-6

Jensen, S. S., Arora, M., Austin, C., Brantsæter, A. L., Haug, L. S., Knutsen, H. K., Lie, S. A., & Klock, K. S. (2025). Toxic and essential elements in primary teeth and maternal blood during pregnancy: The Norwegian Mother, Father and Child Cohort Study (MoBa) and the MoBaTooth Biobank. *Environmental Research*, *274*, 121316. https://doi.org/10.1016/j.envres.2025.121316

Johnston, J., Franklin, M., Roh, H., Austin, C., & Arora, M. (2019). Lead and Arsenic in Shed Deciduous Teeth of Children Living Near a Lead-Acid Battery Smelter. *Environmental Science & Technology*, *53*(10), 6000–6006. https://doi.org/10.1021/acs.est.9b00429

Jusko, T. A., Henderson, C. R., Lanphear, B. P., Cory-Slechta, D. A., Parsons, P. J., & Canfield, R. L. (2008). Blood Lead Concentrations < 10 μg/dL and Child Intelligence at 6 Years of Age. *Environmental Health Perspectives*, *116*(2), 243–248. https://doi.org/10.1289/ehp.10424

Khan, Y. T., Tsompanidis, A., Radecki, M. A., Allison, C., Lai, M.-C., Bethlehem, R. A. I., & Baron-Cohen, S. (2026). Mapping brain growth and sex differences across prenatal to postnatal development. *Scientific Reports*, *16*(1), 3843. https://doi.org/10.1038/s41598-025-33981-w

Koller, K., Brown, T., Spurgeon, A., & Levy, L. (2004). Recent Developments in Low-Level Lead Exposure and Intellectual Impairment in Children. *Environmental Health Perspectives*, *112*(9), 987–994. https://doi.org/10.1289/ehp.6941

Kou, X., Millán, M. P., Canals, J., Moreno, V. R., Renzetti, S., & Arija, V. (2025). Effects of prenatal exposure to multiple heavy metals on infant neurodevelopment: A multi-statistical approach. *Environmental Pollution*, *367*, 125647. https://doi.org/10.1016/j.envpol.2025.125647

Lange, R. T. (2011a). Full Scale IQ. In J. S. Kreutzer, J. DeLuca, & B. Caplan (Eds.), *Encyclopedia of Clinical Neuropsychology* (pp. 1103–1105). Springer New York. https://doi.org/10.1007/978-0-387-79948-3_1549

Lange, R. T. (2011b). Performance IQ. In J. S. Kreutzer, J. DeLuca, & B. Caplan (Eds.), *Encyclopedia of Clinical Neuropsychology* (pp. 1907–1908). Springer New York. https://doi.org/10.1007/978-0-387-79948-3_1066

Lange, R. T. (2011c). Verbal IQ. In J. S. Kreutzer, J. DeLuca, & B. Caplan (Eds.), *Encyclopedia of Clinical Neuropsychology* (pp. 2606–2607). Springer New York. https://doi.org/10.1007/978-0-387-79948-3_1072

Lanphear, B. P. (2015). The Impact of Toxins on the Developing Brain. *Annual Review of Public Health*, *36*(1), 211–230. https://doi.org/10.1146/annurev-publhealth-031912-114413

Lanphear, B. P. (2017). Low-level toxicity of chemicals: No acceptable levels? *PLOS Biology*, *15*(12), e2003066. https://doi.org/10.1371/journal.pbio.2003066

Lanphear, B. P., Hornung, R., Khoury, J., Yolton, K., Baghurst, P., Bellinger, D. C., Canfield, R. L., Dietrich, K. N., Bornschein, R., Greene, T., Rothenberg, S. J., Needleman, H. L., Schnaas, L., Wasserman, G., Graziano, J., & Roberts, R. (2005). Low-Level Environmental Lead Exposure and Children's Intellectual Function: An International Pooled Analysis. *Environmental Health Perspectives*, *113*(7), 894–899. https://doi.org/10.1289/ehp.7688

Lucchini, R. G., Zoni, S., Guazzetti, S., Bontempi, E., Micheletti, S., Broberg, K., Parrinello, G., & Smith, D. R. (2012). Inverse association of intellectual function with very low blood lead but not with manganese exposure in Italian adolescents. *Environmental Research*, *118*, 65–71. https://doi.org/10.1016/j.envres.2012.08.003

Manton, W. I., Angle, C. R., Stanek, K. L., Kuntzelman, D., Reese, Y. R., & Kuehnemann, T. J. (2003). Release of lead from bone in pregnancy and lactation. *Environmental Research*, *92*(2), 139–151. https://doi.org/10.1016/S0013-9351(03)00020-3

Marra, G., & Wood, S. N. (2012). Coverage Properties of Confidence Intervals for Generalized Additive Model Components. *Scandinavian Journal of Statistics*, *39*(1), 53–74. https://doi.org/10.1111/j.1467-9469.2011.00760.x

Marshall, A. T., Betts, S., Kan, E. C., McConnell, R., Lanphear, B. P., & Sowell, E. R. (2020). Association of lead-exposure risk and family income with childhood brain outcomes. *Nature Medicine*, *26*(1), 91–97. https://doi.org/10.1038/s41591-019-0713-y

McMichael, A. J., Baghurst, P. A., Vimpani, G. V., Wigg, N. R., Robertson, E. F., & Tonq, S. (1994). *Tooth Lead Levels and IQ in School-Age Children: The Port Pirie Cohort Study*. *140*(6).

McRae, R., Bagchi, P., Sumalekshmy, S., & Fahrni, C. J. (2009). In Situ Imaging of Metals in Cells and Tissues. *Chemical Reviews*, *109*(10), 4780–4827. https://doi.org/10.1021/cr900223a

Muller, C., Sampson, R. J., & Winter, A. S. (2018). Environmental Inequality: The Social Causes and Consequences of Lead Exposure. *Annual Review of Sociology*, *44*(Volume 44, 2018), 263–282. https://doi.org/10.1146/annurev-soc-073117-041222

Nair, N., Austin, C., Curtin, P., Gouveia, C., Arora, M., Torres, J., Dubinsky, M., Colombel, J.-F., & Peter, I. (2020). Association Between Early-life Exposures and Inflammatory Bowel Diseases, Based on Analyses of Deciduous Teeth. *Gastroenterology*, *159*(1), 383–385. https://doi.org/10.1053/j.gastro.2020.03.040

Needleman, H. L., Gunnoe, C., Leviton, A., Reed, R., Peresie, H., Maher, C., & Barrett, P. (1979). Deficits in Psychologic and Classroom Performance of Children with Elevated Dentine Lead Levels. *New England Journal of Medicine*, *300*(13), 689–695. https://doi.org/10.1056/NEJM197903293001301

Needleman, H. L., Tuncay, O. C., & Shapiro, I. M. (1972). Lead Levels in Deciduous Teeth of Urban and Suburban American Children. *Nature*, *235*(5333), 111–112. https://doi.org/10.1038/235111a0

Nguyen, K. C., Karthikeyan, S., Lye, E. J. D., Masoud, H., Clarke, J., Yome, J. L., Vladisavljevic, D., Chan, L. H. M., & St-Amand, A. (2024). Blood lead levels in the general population and vulnerable sub-populations and related risk factors for lead exposure in Canada. *Hygiene and Environmental Health Advances*, *9*, 100088. https://doi.org/10.1016/j.heha.2024.100088

Nudel, I., Pokhojaev, A., Bitterman, Y., Shpack, N., Fiorenza, L., Benazzi, S., & Sarig, R. (2021). Secondary Dentin Formation Mechanism: The Effect of Attrition. *International Journal of Environmental Research and Public Health*, *18*(19), 9961. https://doi.org/10.3390/ijerph18199961

Obeng-Gyasi, E. (2019). Sources of lead exposure in various countries. *Reviews on Environmental Health*, *34*(1), 25–34. https://doi.org/10.1515/reveh-2018-0037

Palir, N., Stajnko, A., Mazej, D., France Štiglic, A., Rosolen, V., Mariuz, M., Ronfani, L., Snoj Tratnik, J., Runkel, A. A., Tursunova, V., Marc, J., Prpić, I., Špirić, Z., Barbone, F., Horvat, M., & Falnoga, I. (2024). Maternal *APOE* ε2 as a possible risk factor for elevated prenatal Pb levels. *Environmental Research*, *260*, 119583. https://doi.org/10.1016/j.envres.2024.119583

Parajuli, R. P., Umezaki, M., Fujiwara, T., & Watanabe, C. (2015). Association of Cord Blood Levels of Lead, Arsenic, and Zinc and Home Environment with Children Neurodevelopment at 36 Months Living in Chitwan Valley, Nepal. *PLOS ONE*, *10*(3), e0120992. https://doi.org/10.1371/journal.pone.0120992

Punshon, T., Bauer, J. A., Karagas, M. R., Coker, M. O., Weisskopf, M. G., Mangano, J. J., Bidlack, F. B., Barr, M. N., & Jackson, B. P. (2024). Quantified retrospective biomonitoring of fetal and infant elemental exposure using LA-ICP-MS analysis of

deciduous dentin in three contrasting human cohorts. *Journal of Exposure Science & Environmental Epidemiology*, *34*(6), 1000–1011. https://doi.org/10.1038/s41370-024-00652-3

Rajkumar, V., Lee, V. R., & Gupta, V. (2023). Heavy Metal Toxicity. In *StatPearls [Internet]*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK560920/

Rauh, V. A., & Margolis, A. E. (2016). Research Review: Environmental exposures, neurodevelopment, and child mental health – new paradigms for the study of brain and behavioral effects. *Journal of Child Psychology and Psychiatry*, *57*(7), 775–793. https://doi.org/10.1111/jcpp.12537

Rechtman, E., Reichenberg, A., Invernizzi, A., Fleysher, L., Rebello, V., Oluyemi, K., Rodriguez, M. A., Sather, A., Torres-Olascoaga, L. A., Bautista-Arredondo, L. F., Martínez-Medina, S., Lara-Estrada, R., Gennings, C., Téllez-Rojo, M. M., Wright, R. O., Arora, M., & Horton, M. K. (2026). Fetal and postnatal metal metabolism-related changes in brain function are associated with childhood behavioral deficits. *Science Advances*, *12*(17), eadz1340. https://doi.org/10.1126/sciadv.adz1340

Rísová, V. (2019). The pathway of lead through the mother's body to the child. *Interdisciplinary Toxicology*, *12*(1), 1–6. https://doi.org/10.2478/intox-2019-0001

Schnaas, L., Rothenberg, S. J., Flores, M.-F., Martinez, S., Hernandez, C., Osorio, E., Velasco, S. R., & Perroni, E. (2006). Reduced Intellectual Development in Children with Prenatal Lead Exposure. *Environmental Health Perspectives*, *114*(5), 791–797. https://doi.org/10.1289/ehp.8552

Schneider, J. S., Lee, M. H., Anderson, D. W., Zuck, L., & Lidsky, T. I. (2001). Enriched environment during development is protective against lead-induced neurotoxicity. *Brain Research*, *896*(1), 48–55. https://doi.org/10.1016/S0006-8993(00)03249-2

Stokke Jensen, S., Midya, V., Arora, M., Eek Brandlistuen, R., Havdahl, A., Dehli Andersen, G., & Klock, K. S. (2026). Pre- and postnatal trace element levels in primary teeth of children with and without an autism spectrum diagnosis. *Environmental Research*, *295*, 124001. https://doi.org/10.1016/j.envres.2026.124001

Tatsuta, N., Nakai, K., Kasanuma, Y., Iwai-Shimada, M., Sakamoto, M., Murata, K., & Satoh, H. (2020). Prenatal and postnatal lead exposures and intellectual development among 12-year-old Japanese children. *Environmental Research*, *189*, 109844. https://doi.org/10.1016/j.envres.2020.109844

Taylor, C. M., Kordas, K., Golding, J., & Emond, A. M. (2017). Effects of low-level prenatal lead exposure on child IQ at 4 and 8 years in a UK birth cohort study. *NeuroToxicology*, *62*, 162–169. https://doi.org/10.1016/j.neuro.2017.07.003

Taylor, K. W., Eftim, S. E., Sibrizzi, C. A., Blain, R. B., Magnuson, K., Hartman, P. A., Rooney, A. A., & Bucher, J. R. (2025). Fluoride Exposure and Children's IQ Scores. *JAMA Pediatrics*, *179*(3), 282–292. https://doi.org/10.1001/jamapediatrics.2024.5542

Vahter, M., Åkesson, A., Lidén, C., Ceccatelli, S., & Berglund, M. (2007). Gender differences in the disposition and toxicity of metals. *Environmental Research, Scientific Group on Methodologies for the Safety Evaluation of Chemicals: Workshop 16---Gender Differences and Human and Ecological Risk*, *104*(1), 85–95. https://doi.org/10.1016/j.envres.2006.08.003

Van Landingham, C., Fuller, W. G., & Schoof, R. A. (2020). The effect of confounding variables in studies of lead exposure and IQ. *Critical Reviews in Toxicology*, *50*(9), 815–825. https://doi.org/10.1080/10408444.2020.1842851

Wasserman, G. A., Factor-Litvak, P., Liu, X., Todd, A. C., Kline, J. K., Slavkovich, V., Popovac, D., & Graziano, J. H. (2003). The Relationship Between Blood Lead, Bone Lead and Child Intelligence. *Child Neuropsychology*, *9*(1), 22–34. https://doi.org/10.1076/chin.9.1.22.14497

Wylie, A. C., Short, S. J., Fry, R. C., Mills-Koonce, W. R., & Propper, C. (2024). Maternal prenatal lead levels and neonatal brain volumes: Testing moderations by maternal depressive symptoms and family income. *Neurotoxicology and Teratology*, *102*, 107322. https://doi.org/10.1016/j.ntt.2024.107322

Zhang, W., O'Brien, N., Forrest, J. I., Salters, K. A., Patterson, T. L., Montaner, J. S. G., Hogg, R. S., & Lima, V. D. (2012). Validating a Shortened Depression Scale (10 Item CES-D) among HIV-Positive People in British Columbia, Canada. *PLoS ONE*, *7*(7), e40793. https://doi.org/10.1371/journal.pone.0040793