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Toxic and essential trace elements in human primary teeth: A baseline study within The MoBaTooth Biobank and The Norwegian Mother, Father and Child Cohort Study (MoBa)

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ABSTRACT

The Norwegian Mother, Father and Child Cohort Study (MoBa) includes a nation-wide collection of deciduous teeth located in the MoBaTooth biobank. The aim of the present study is to create a baseline for early-life metal exposure using dentine biomarkers.

Deciduous teeth were collected in the MoBaTooth biobank, a sub-study of the MoBa-study. This study uses 94 primary teeth from children with no known medical conditions at the age of 6 months, a normal birth weight (2500-4500g) and an equal number of teeth shed between 2008-2013 and 2014-2019. A total of 48 girls and 46 boys are included to create a baseline to characterise retrospective exposure to toxicants during multiple early-life developmental periods. Estimates of weekly prenatal and postnatal exposure to 18 metals by measuring dentine concentrations have been made using laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP-MS).

Temporal trends in dentine levels differed from metal to metal. Girls had higher postnatal dentine levels of Mn and Zn, compared to boys ($p = 0.020$ for postnatal Mn-levels, and $p = 0.011$ for postnatal Zn-levels).

Deciduous teeth provide retrospective information on the intensity and timing of early-life metal exposure at weekly temporal resolution. Creating a baseline, future studies can use outcomes of conditions and illness in children in case-control-studies aiming at prevention. Using deciduous teeth, a novel noninvasive biomarker, characterising early-life exposure to 18 metals in approximately weekly increments during sensitive developmental periods extending from the second trimester to 4 months postnatally has been performed.

1. Introduction

In foetal- and early life there are critical windows of susceptibility, periods when exposures to specific toxicants have a greater effect on health trajectories compared to other periods of development (Selevan et al., 2000; Meredith et al., 2012). In utero and early childhood, protective regulatory mechanisms and organs are not fully formed, making the foetus and infant particularly vulnerable to toxicant exposure (Grandjean and Landrigan, 2014; Wright, 2017; Bauer et al., 2020). Obtaining foetal samples at different stages of pregnancy without risking the health of the foetus, as well as collecting biomarkers which can characterise metal exposure during multiple developmental periods rather than at a single time point, presents a challenge in environmental epidemiology studies. Traditional biomarkers such as maternal and cord blood may represent shorter exposure windows due to the rapid clearance of many metals from blood. Furthermore, levels of metal concentrations in maternal samples do not reflect direct exposure to the foetus for all metals due to placental regulations (Weisskopf and Webster, 2017).

Shed primary teeth represents an exposure biomarker collected in childhood that can reconstruct exposure of toxic and essential trace elements, both pre-and postnatal (Tvinnereim et al., 2012; Arora et al., 2012, 2011). Trace elements from the childs environment and nutrition are captured in the mineralizing dentin matrix. Dentine (and enamel) is formed in layers according to a specific pattern and is very stable. Due to its immediate mineralization after matrix deposition, this is the

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preferred matrix for enamel, which exhibits a time lag between matrix deposition and mineralization (10). Teeth can therefore be used as storage for various exposures during the tooth formation period. Additionally, dental tissue shows morphological changes and mineralisation defects because of exposures to environmental toxins, disease, or malnutrition during tooth formation (Arora et al., 2012, 2011; Austin et al., 2013, 2016, 2023; Smith et al., 2021; Smith and Boesch, 2015).

The development of the primary teeth begins during the second month of the foetal stage. At the third and fourth months, the mineralisation of the enamel and dentine begins. By the age of one year, all the deciduous crowns are completely mineralised, and by the age of three to three and a half years, the roots are also fully developed. An important feature of tooth development is the incremental way the enamel and dentine protein matrix are deposited. This results in the formation of incremental features – short-period and long-period lines – creating growth rings in both enamel and dentine (Smith, 2008; Arora and Austin, 2013). Both the enamel and the underlying dentin have a characteristic growth line, the neonatal line, which represents altered metabolism at birth (Nanci, 2008; Blumenthal, 1990; Berkovitz et al., 2009). The neonatal line is formed because of stunting of ameloblast and odontoblasts, that deposit enamel and dentine matrix. Because of this histological landmark in the primary teeth, one can establish pre-and postnatally exposures when analysing the dental tissue (Arora and Austin, 2013).

The MoBaTooth biobank was established at the Department of Clinical Dentistry at the University of Bergen in 2008. The biobank registers and stores the primary teeth and as of January 2023, more than 36.000 primary teeth have been collected and registered. The MoBaTooth Biobank is the world`s largest biobank consisting of primary teeth connected to mother-, father and child data (Tvinnereim et al., 2012).

The Norwegian Mother, Father and Child Cohort Study (MoBa), conducted by the Norwegian Institute of Public Health (NIPH), is a prospective population-based cohort study in Norway (Magnus et al., 2006, 2016). Pregnant women were recruited around week 17 of pregnancy from 1999 until 2008 from all over Norway, and 41% of the invited women consented to participate. The cohort now includes approximately 114.500 children, 95.200 mothers and 75.200 fathers. MoBa data also include information from The Medical Birth Registry of Norway, which comprises information about pregnancy, delivery, and health of the mothers and the neonate of all births in Norway (Irgens, 2000). The overall goal of the MoBa-study is to determine specific etiological hypotheses by investigating the correlation between exposure and disease, with the aim of prevention. Mainly quantitative methods were used in collecting the data, with questionnaires being sourced during pregnancy as well as post-partum annual surveys. Moreover, biological material such as blood- and urine samples, cord blood and children ́s primary teeth were also collected and analysed.

The establishment of MoBa and initial data collection was based on a licence from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is currently regulated by the Norwegian Health Registry Act. The approval number of the MoBaTooth Biobank from The Regional Committees for Medical and Health Research Ethics is 2007/5697-077.07. This study is also approved by The Regional Committee for Medical Research Ethics, with reference number 140805.

Multiple toxic- and essential trace elements can be detected in primary teeth using laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP-MS). This sensitive analytical technique offers detection limits suitable for the analysis of trace elements in teeth (Arora et al., 2012, 2006, 2017; Austin et al., 2013; Arora and Austin, 2013; Hare et al., 2011; Kang et al., 2004), such as magnesium (Mg), calcium (Ca), chromium (Cr), manganese (Mn), copper (Cu), zinc (Zn), arsenic (As), strontium (Sr), tin (Sn), barium (Ba), lead (Pb), aluminum (Al), nickel (Ni), bismuth (Bi), cadmium (Cd), cobalt (Co), molybdenum (Mo) and lithium (Li). The type of elements detected, and their concentrations can vary by diet and environmental exposures (Arora and Austin, 2013; Hare et al., 2011; Kang et al., 2004; Andra et al., 2016).

This baseline study aims to 1) measure the concentrations and pattern of essential and toxic elements in coronal dentine in primary teeth from Norwegian children using LA-ICP-MS, 2) identify key patterns in pre-and postnatal distribution of elements that would provide insight into dietary or environmental exposures, and 3) establish any potential differences in metal distribution according to the child`s sex.

To the best of our knowledge, this is the first study containing nearly 100 primary teeth to create a baseline for toxic and essential trace elements in human teeth. Furthermore, this baseline can be used as a control-group for future case-control studies. Overall, this study would serve as a foundation for future studies that analyse a larger number of teeth collected in the MoBa-study.

2. Material and methods

2.1. Study population

A total of 100 naturally shed deciduous teeth collected from children living in all parts of Norway from the MoBaTooth biobank were included in the study. Due to gross attrition, 6 teeth were excluded. Furthermore, a total of 94 teeth from 94 children with the following inclusion criteria (Table 1) were then analysed.

All the children were participants in the MoBa-study, and the collected teeth were sent to the MoBaTooth biobank at the University of Bergen between 2008-2019. The parents or guardians of the children in MoBaTooth received an information-letter where they were asked to rinse the tooth in water and let it air-dry before placing it in an microtube (Axygen MCT-150-C). Written informed consent was obtained from the parents or guardians of the children, both when joining the MoBa-study and later, when they were asked to be a part of the MoBaTooth biobank. Each participant donated at least one primary tooth.

2.2. Sample preparation

The method for tooth analyses has been validated (Arora et al., 2012, 2014; Austin et al., 2017, 2013; Kang et al., 2004). The preparations and analysis of the primary teeth were performed at the Senator Frank R. Lautenberg Environmental Health Sciences Laboratory, at the Icahn School of Medicine, Mount Sinai, New York, USA. Teeth were examined under a stereo microscope and gross features recorded, including tooth type, degree of attrition, presence or absence of fillings, cracks in enamel, or any unusual anatomical features.

Teeth were then washed in trace-element free Milli-Q water and sectioned in a vertical (labio-lingual/bucco-lingual) plane. One cut fragment was embedded in resin (EpoxiCure, Buehler) overnight, then ground and polished to a 1 μm finish. Temporal developmental zones were assigned after identifying the neonatal line under a microscope, following published methods (Arora et al., 2006, 2012; Arora and Austin, 2013).

Table 1
Inclusion criteria of 94 children and their deciduous teeth included in this study.

Children	Deciduous teeth
No known medical conditions at 6 months	Teeth from the MoBaTooth biobank
Child sex assigned at birth: 48 females and 46 males	No dental caries
Normal birth weight between 2500-4500g (World Health Organization)	No dental restorations
Equal number of teeth shed between 2008-2013 and 2014-2019	No gross attrition, abrasion or erosion
Participant in both the MoBa-study and the MoBaTooth Biobank	No developmental defects

2.3. Laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP-MS)

Teeth were analysed for trace elements at 30 µm resolution using a New Wave 193-nm excimer laser ablation system coupled to an ICP-MS (Agilent, 8800 ICP-MS) (Arora et al., 2012, 2011, 2006). This resolution relates to approximately 32 time points/tooth representing weekly exposure from 20 weeks gestation through 16 weeks postnatal age. Tooth metals were normalised to tooth Ca levels (e.g., as ^{55}Mn:^{43}Ca or ^{208}Pb:^{43}Ca) to account for mineral density variation within teeth and between tooth type and individuals.

Toxic and essential trace elements were measured by scanning the laser beam along the dentine-enamel junction for all 94 teeth included in this study. A spot diameter of 30 µm was used in these analyses. Operating conditions for the optimised LA–ICP–MS have been previously described (Sanders et al., 2022).

2.4. Statistical analysis

Graphical presentation of the mean relationship between mineral concentrations and weeks were calculated using generalised additive mixed models (gamm). For testing of difference in the level of minerals between boys and girls and the average slope in change of the minerals, before and after birth (week 0), general linear models were applied. The statistical models were performed using the mgcv library in the statistical package R. The p-values less than 0.05 were considered statistically significant.

3. Results

A total of 94 children with tooth metals data were included in the final analysis. The results of this study provide a detailed high-resolution (30 µm) elemental profile of toxic and essential trace elements in human primary teeth. For all primary teeth, 18 metals were measured in dentine and the levels and ranges of the measured metals are shown in Fig. 1.

In Fig. 2, the focus of the results is on Pb, Mn, Zn, Mg and Ba given the known neurotoxicity of Pb and Mn, prior findings of tooth Ba as a dietary marker and Zn and Mg as important essential elements for development in children (Austin et al., 2013; Horton et al., 2018; Boyes, 2010; Kopp et al., 2012; Michalke and Fernsebner, 2014; Arbuckle et al., 2016). In some of these trace elements there are also statistically significant differences in gender distribution.

The total number of measurements of dentine metals values per participant varied, with a mean (range) of 32.4 (24–37) measurements. The levels of dentine Pb increases in the prenatal period ($p < 0.001$), decreases around week 5 prenatally and then flattens in the postnatal period ($p = 0.516$) (Fig. 2). There were no statistically significant differences between the Pb-levels for boys and girls in either the pre-or postnatal period ($p = 0.500$ and $p = 0.412$). Levels of dentine Mn were highest in the early prenatal period (second trimester) and decreased steadily until birth, with a slower decrease and flattening of the curve in the postnatal period, $p < 0.001$ for both periods. In the prenatal period there were no statistically significant differences between the genders ($p = 0.051$), but in the postnatal period there were higher levels of Mn found in girls ($p = 0.020$).

The Zn-levels in dentine were highest in the early prenatal period (second trimester) and decreased until birth ($p < 0.001$). At week 8 postnatally a new increase in Zn was found. In the prenatal period, there were no statistically significant differences in Zn-dentine levels between the genders, but in the postnatal period girls have a higher level of Zn compared to boys ($p = 0.011$). Levels of dentine Mg were lowest in the early prenatal period (second trimester) and increased steadily until birth, and then continued to increase in the postnatal period ($p < 0.001$). There was no statistically significant difference between genders for dentine Mg-levels in either the pre-or postnatally period ($p = 0.951$ and $p = 0.166$). For Ba-dentine levels, there was an increase in the prenatal period until week 4 ($p < 0.001$), and then the curve flattens postnatally for both genders ($p = 0.205$). There were no statistically significant differences between boys and girls for the Ba-dentine levels in either the pre-or postnatally period ($p = 0.358$ and $p = 0.539$).

4. Discussion

In this baseline study, characterising retrospective exposure to multiple metals during critical developmental periods using deciduous teeth as a biomarker of prenatal and postnatal exposure has been performed. Temporal trends of dentine metal values differed from metal to metal. Dentine Mn levels decreased from the second trimester until birth, whereas dentine Pb remained more constant throughout the prenatal period and early life. Pb levels increased in the latter part of the third trimester. This increase is consistent with transfer of Pb from maternal stores, likely following calcium as the foetal growth accelerated in the third trimester. Maternal skeletal stores provide much of the mineral demands of the foetus (Berkovitz et al., 2017; Gulson et al., 2003; Daniel and Chiego, 2018; Francis-West PRB et al., 2021). Pb levels dropped immediately after birth indicating lower exposure from breastmilk and infant environmental sources. This provides an example of how spatio-temporal mapping of lead in teeth can reveal periods of high exposure that cannot be captured by blood measurements.

The observed decrease in dentine Mn from the second trimester to the first 4 months of life has been reported in other studies, and is likely related in part to the physiologic need for Mn as an essential nutrient to support healthy growth in early development (Horton et al., 2018; Bauer et al., 2017; Claus Henn et al., 2018). The prenatal period is a time of rapid growth and development of the foetus, during which the demand for Mn may be greatest (Claus Henn et al., 2018). This is compatible with the increase in maternal blood Mn during pregnancy, reported in previous studies (Kopp et al., 2012; Arbuckle et al., 2016; Zota et al., 2009), which supports the notion of a biological role of Mn during gestation. In foetal life, the placenta may protect the foetus from direct effects of Mn overexposure (Claus Henn et al., 2017), whereas after birth, the placenta no longer regulates Mn levels that are transported to the foetus. While development continues, the relative demand for Mn may be lower than in the prenatal period. The observed flattening in Mn exposure postnatally may be related to both differential exposures in the postnatal versus prenatal environments, as well as direct exposure to Mn in the environment and biological changes such as varied absorption of Mn in the gut in the postnatal period compared to the prenatal period (Krachler et al., 1999).

The dentine levels of both Mn and Zn differ by the sex of the child, with girls having higher levels than boys in the postnatal period. Previous studies have found that there is both epidemiological and toxicological evidence indicating that females, compared to males, may have increased Mn absorption (Williams et al., 2012; Balachandran et al., 2020; Oulhote et al., 2014; Zheng et al., 2000). Iron (Fe) status has been suggested as a possible hypothesis for the difference between females and males because females on average are more iron deficient than males (Williams et al., 2012; Mirza et al., 2018; Fitsanakis et al., 2010). Mn and Fe share common absorption and transport pathways, and increased Mn absorption may be due to lower Fe levels among females (Tholin et al., 1995; Yoon et al., 2011; Aschner and Aschner, 2005; Wolff et al., 2018).

Deciduous teeth are particularly useful as a biomarker when past exposure occurring in early life is of interest and shed teeth are readily available. In scenarios that require immediate exposure information and/or where children are too young to shed teeth, this biomarker is less advantageous. However, teeth allow for the direct examination of foetal and infant metal levels, rather than using biomarkers of current or recent childhood exposure such as blood, hair and nail, or maternal blood to estimate prenatal exposure. Previous epidemiologic studies have found correlations between metals in environmental matrices and dentine levels (Gunier et al., 2013; Johnston et al., 2019; Gunier et al., 2014).

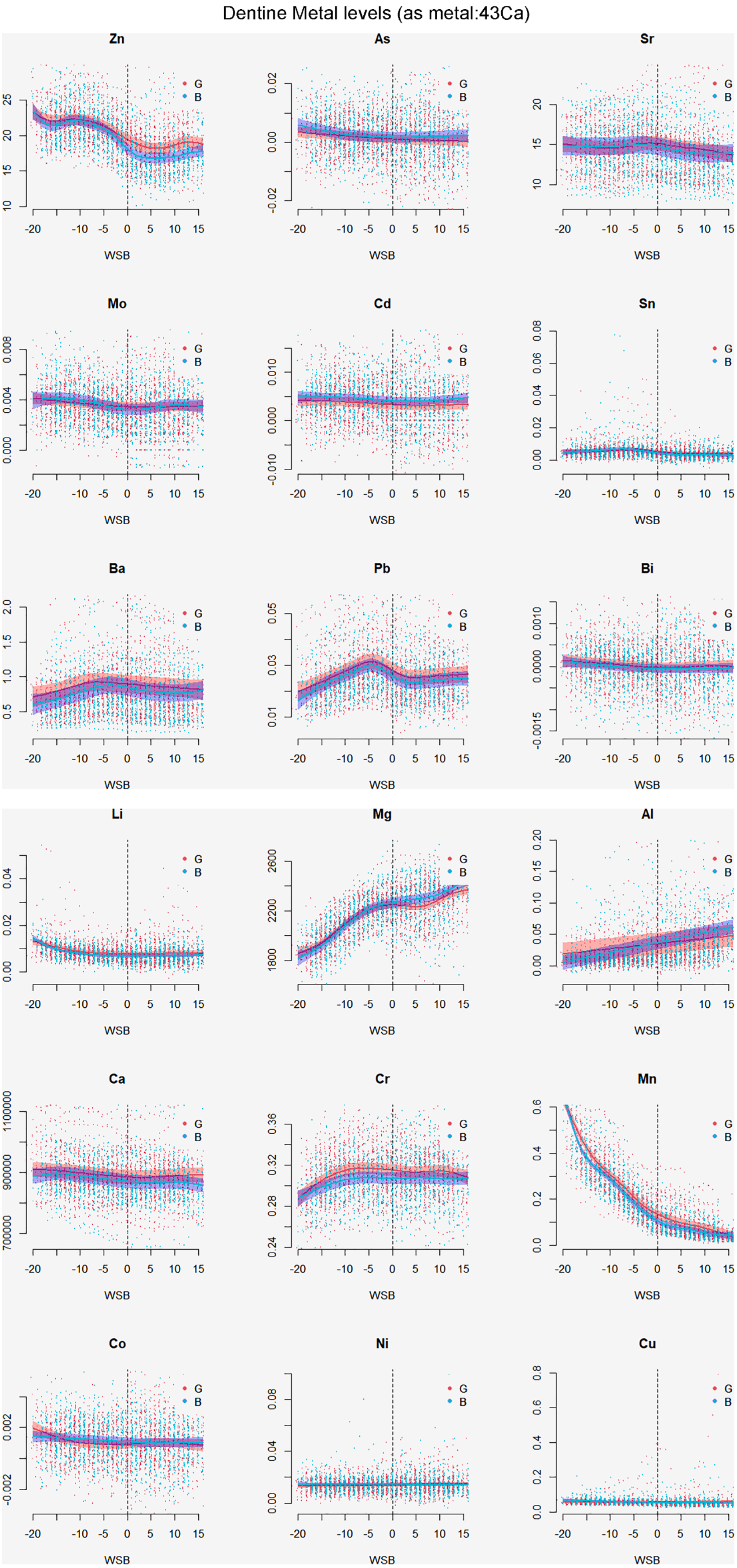

Fig. 1. Dentine metal levels as ln metal:^{43}Ca ratio from early second trimester (20 weeks before birth) until 4 months after birth (16 weeks), stratified by child sex. WSB: Weeks since birth. Dots represent individual dentine metal measurements for 94 children, with a range of 24-37 measurements per participant. Metals ordered by atomic number. Boys are blue and girls are red. Vertical line at week 0 indicates birth. Line represents Loess smoother. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

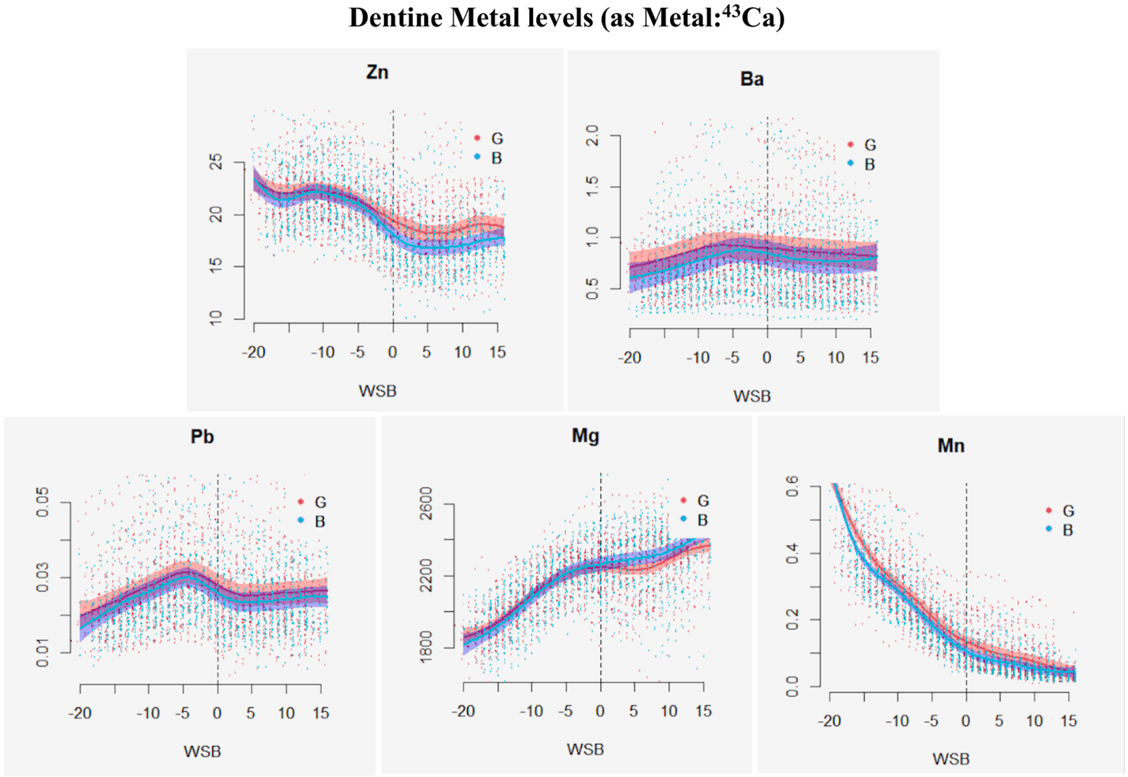

Fig. 2. Dentine Zn, Ba, Pb, Mg and Mn metal levels from early second trimester (20 weeks before birth) until 4 months after birth (16 weeks), as ln metal:^{43}Ca ratio. WSB: Weeks since birth. Dots represent individual dentine metal measurements for 94 children, with a range of 24–37 measurements per participant. Boys are blue and girls are red. Vertical line at week 0 indicates birth. Line represents Loess smoother. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

For all detected trace elements in the primary teeth, the highest level was found for Mg. This is the fourth most abundant cation in the body. It has several functions in the human body, including its role as a cofactor for more than 300 enzymatic reactions and in regulating several fundamental functions such as muscle contraction, glycemic control, myocardial contraction and blood pressure (Al Alawi et al., 2018; Bertinato et al., 2015). Mg also plays an important role in energy production and bone development. Furthermore, lack of Mg has been associated with a wide range of diseases (Bertinato et al., 2015; Grober et al., 2015). In the primary teeth, dentine Mg was lowest in the early prenatal period, and then increased steadily until 4 months of age.

There was an increase in Ba-dentine in the prenatal period until week -4 ($p < 0.001$). Subsequently, the curve flattens postnatally for both genders ($p = 0.205$). An increase in Ba levels after birth is expected, as transfer of Ba from mother to foetus is restricted by the placenta in the prenatal period (Krachler et al., 1999). Previously studies have shown that an increase in Ba levels after birth likely reflect consumption of breastmilk and/or formula (Austin et al., 2013). In Austin et al. (2013), the results demonstrate that the distribution of the isotopes ^{138}Ba:^{43}Ca in teeth accurately reflects the dietary transition from breastmilk to other sources during the weaning process. Furthermore, the study concluded that ^{138}Ba:^{43}Ca ratios were higher in individuals who reported formula use compared to breastfeeding.

5. Conclusions

The present results demonstrate the feasibility of naturally shed primary teeth as a biomarker to understand past chemical exposure in critical developmental periods, both pre-and postnatally. By understanding the precise timing of toxic exposures on vulnerable and susceptible infants and children, it may be possible to decrease exposure during critical developmental windows and prevent development of disease (Selevan et al., 2000; Meredith et al., 2012). This baseline study can be used as a control-group in future case-control-studies to try to understand different health outcomes in children and adolescents and use this information for prevention.

Ethics approval and consent to participants

The establishment of MoBa and initial data collection was based on a licence from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is currently regulated by the Norwegian Health Registry Act. The approval number of the MoBaTooth Biobank from The Regional Committees for Medical and Health Research Ethics is 2007/5697-077.07. This study is also approved by The Regional Committee for Medical Research Ethics, with reference number 140805.

CRediT authorship contribution statement

Synnøve Stokke Jensen: Investigation, Conceptualization, Methodology, Project administration, Validation, Writing – original draft. **Christine Austin:** Formal analysis, Writing – review & editing. **Manish Arora:** Formal analysis, Funding acquisition, Writing – review & editing. **Stein Atle Lie:** Software, Data curation, Writing – review & editing. **Marit Øilo:** Writing – review & editing. **Kristin S. Klock:** Conceptualization, Validation, Funding acquisition, Supervision, Writing – review & editing.

Declaration of Competing Interest

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

Data availability

Data will be made available on request.

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