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Prenatal lead exposure modifies the effect of shorter gestation on increased blood pressure in children

Alison P. Sanders[a,b,c,*], **Katherine Svensson**[a], **Chris Gennings**[a], **Heather H. Burris**[d], **Emily Oken**[e], **Chitra Amarasiriwardena**[c], **Priyanka Basnet**[c], **María Luisa Pizano-Zarate**[f], **Lourdes Schnaas**[f], **Marcela Tamayo-Ortiz**[g,i], **Andrea A. Baccarelli**[h], **Lisa M. Satlin**[b], **Robert O. Wright**[a,b,c], **Martha M. Tellez-Rojo**[i]

[a] Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[b] Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[c] Lautenberg Environmental Health Sciences Laboratory, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[d] Department of Pediatrics, Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

[e] Department of Population Medicine, Harvard Medical School, Harvard Pilgrim Health Care Institute, Boston, MA, USA

[f] Division of Community Interventions Research, National Institute of Perinatology, Mexico City, Mexico

[g] National Council of Science and Technology (CONACYT), Mexico City, Mexico

[h] Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY, USA

[i] Center for Nutrition and Health Research, National Institute of Public Health, Cuernavaca, Morelos, Mexico

Abstract

Background: High blood pressure (BP) in childhood is frequently renal in origin and a risk factor for adult hypertension and cardiovascular disease. Shorter gestations are a known risk factor for increased BP in adults and children, due in part to a nephron deficit in children born preterm. As nephrogenesis is incomplete until 36 weeks gestation, prenatal lead exposure occurring during a susceptible period of renal development may contribute to programming for later life renal disease. The relationship between shorter gestation and children's BP has not yet been explored to

* Corresponding author at: Departments of Pediatrics & Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1057, New York, NY 10029, USA. alison.sanders@mssm.edu (A.P. Sanders).

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identify i) critical windows using nonlinear piecewise models or ii) combined with other early life risk factors such as prenatal lead exposure.

Objectives: (1) To evaluate the nonlinear relationship between lower gestational age and childhood BP measured at 4–6 years of age, and (2) to investigate modification by prenatal lead exposure.

Methods: In a prospective longitudinal birth cohort, we assessed 565 children between 4 and 6 years of age (mean: 4.8 years) in the PROGRESS cohort in Mexico City, Mexico. Gestational age at delivery was calculated using maternal report of last menstrual period (LMP) and confirmed with Capurro physical examination at birth. We measured pregnant women's blood lead levels (BLLs) in the second trimester via inductively coupled plasmamass spectrometry and children's BP using an automated device. We performed both linear and nonlinear piecewise regression analyses to examine associations of gestational age with children's BP adjusting for children's age, sex, height, prenatal exposure to smoke, and maternal socioeconomic status. We stratified to assess modification by prenatal lead exposure, and used a data-adaptive approach to identify a lead cutpoint.

Results: Maternal second trimester BLLs ranged from 0.7 to 17.8 μg/dL with 112 (20%) women above the CDC guideline level of 5 μg/dL. In adjusted linear regression models, a one week reduction in gestational age was associated with a 0.5 mm Hg (95%CI: 0.2, 0.8) increase in SBP and a 0.4 mm Hg (95%CI 0.1, 0.6) increase in DBP. Our nonlinear models suggested evidence for different magnitude estimates on either side of an estimated join-point at 35.9 weeks' gestation, but did not reach statistical significance. However, when stratified by prenatal lead exposure, we identified a cutpoint lead level of concern of 2.5 μg/dL that suggested an interaction between gestational age and blood lead. Specifically, for BLLs ≥ 2.5 μg/dL, SBP was 1.6 (95%CI: 0.3, 2.9) mm Hg higher per each week reduction in gestational age among children born before 37.0 weeks; and among children born after 37.0 weeks, this relationship was attenuated yet remained significant [β: 0.9, 95%CI (0.2, 1.6)]. At BLLs below 2.5 μg/dL, there was no appreciable association between lower gestational age and SBP.

Conclusions: Our findings suggest that shorter gestation combined with higher prenatal lead exposure contributes to a higher risk of increased SBP at 4–6 years of age, particularly among infants born < 37 weeks gestation. Our results underscore the importance of preventing prenatal lead exposure - even levels as low as 2.5 μg/dL - especially among pregnant women at risk for preterm birth. Given that high BP in childhood is a risk factor for adult hypertension and cardiovascular disease later in life, these results may have implications that extend across the life span.

Keywords

Lead; Gestational age; Preterm birth; Blood pressure; Systolic; Diastolic; Childhood

1. Introduction

High blood pressure (BP) in childhood can lead to adult hypertension (Belsha et al., 1998; Berenson et al., 1998; Chen and Wang, 2008; Hanevold et al., 2004; Sorof et al., 2003). Elevated BP in childhood, in the absence of congenital heart disease, is nearly always

renal in origin (Boubred et al., 2013). While some studies have examined the effect of environmental nephrotoxic exposures during susceptible windows of renal development on elevated childhood BP, none has examined the effect of environmental exposure as a modifier of the effect of shorter gestation.

Lower gestational age is a well-established risk factor for increased systolic blood pressure (SBP) in early life (Johansson et al., 2005; Keijzer-Veen et al., 2010) and even among adults (Raju et al., 2017). For example, a meta-analysis of 10 studies of former low birth weight or preterm infants compared to term controls found a pooled estimate of 2.5 mm Hg (95% CI: 1.7, 3.3) higher SBP later in life (average age = 17.1 years) (de Jong et al., 2012). Infants born prior to 36 weeks' gestation, the time by which nephrogenesis (the formation of new nephrons) is complete (Benz and Amann, 2010; Solhaug et al., 2004), represent a particularly susceptible population for altered renal function. Based on the timing of in utero nephron development, we hypothesize that a nonlinear model would more appropriately examine critical windows of renal development. By comparing associations before and after 36 weeks, we hypothesize that there would be a stronger association with increased children's BP among shorter gestations since this is coupled with renal immaturity.

Moreover, we speculate that nephrotoxic exposures during perinatal life in combination with shorter gestation could alter kidney growth/ developmental trajectories and program adult diseases of renal origin. Gestation and early childhood are potential susceptibility windows for nephrotoxic metals, as these life stages are associated with development of glomerular filtration and maturation of tubular function (e.g. absorption and secretion) (Gubhaju et al., 2014; Luyckx et al., 2013; Sutherland et al., 2014). Relatively minor insults can offset the normal developmental trajectory towards a hypertensive phenotype in later life, as BP will increase with age. Lead is a common nephrotoxicant in adults (Chiu and Yang, 2005; Hellstrom et al., 2001; Loghman-Adham, 1997; Sommar et al., 2013). Specifically, in the US, lead accounts for 5% of the population attributable risk for hypertension in adults participating in National Health and Nutrition Examination Survey (NHANES) from 2009 to 2012 (Shiue and Hristova, 2014). Previously, we have shown sex-specific associations between prenatal lead levels and elevated BP in children in Mexico City (Zhang et al., 2012). Other studies have shown links between lead and children's elevated SBP or diastolic blood pressure (DBP) (Gump et al., 2005; Gump et al., 2007; Hawkesworth et al., 2013; Sorensen et al., 1999). However no studies to-date have examined the interaction of prenatal lead exposure in combination with shorter gestation on childhood BP.

We sought to understand whether the association between shorter gestation and increased childhood BP was modified by prenatal lead exposure, selected a priori as a prevalent nephrotoxic metal. To assess effects on BP at 4–6 years of age in a prospective cohort of 565 mother-child dyads, we examined the relationship between gestational age and BP using linear and nonlinear piecewise models. To investigate the modification effect of lead exposure, we used a data driven approach to assess 1) a change point in gestational age associated with SBP; and 2) a cutpoint level of 'high' or 'low' lead that might exacerbate developmental nephrotoxic exposure. This study expands our understanding of the early origins of adult cardiovascular disease, a leading cause of mortality and morbidity in the US

(Heron, 2013), and provides suggestive evidence for the role of prenatal lead exposure in the developmental programming childhood BP.

2. Methods

2.1. Study design

This study was conducted using mother-child pairs participating in the longitudinal cohort study called Programming Research in Obesity, GRowth, Environment, and Social Stress (PROGRESS) based in Mexico City. Full details of enrollment for the parent cohort are published elsewhere (Burris et al., 2013; Renzetti et al., 2017; Sanders et al., 2015). Briefly, women in their second trimester were recruited between 2007 and 2011 through the Mexican Social Security System (Instituto Mexicano del Seguro Social), which is the second largest health provider in the country. Women were considered eligible for enrollment if they were over 18 years of age, at fewer than 20 weeks gestation, free of heart and kidney disease, did not use anti-epilepsy drugs or steroids, and did not consume alcohol daily (Burris et al., 2013). There were 948 women who delivered a live-born infant into the cohort. For this analysis, we included pairs who had maternal blood lead measured in the 2nd trimester, delivery before 42 weeks of gestation, and child BP measured at 4–6 years of age (n = 565 out of 609 children with followup at this stage). No children were excluded from the analysis based on existing renal or cardiovascular conditions. We performed a sensitivity analyses to ensure that including the 10 infants < 34 weeks of gestation did not affect our results. The IRBs of the participating institutions approved this study: Icahn School of Medicine human subjects management #12–00751 and Instituto Nacional de Salud Pública project #560.

2.2. Participant data collection

Demographics and medical data were collected as part of the parent study including maternal age and socioeconomic status (SES), as well as gestational age at delivery, birth weight, age at BP measurement, as well as height and sex. Gestational age was calculated in units of days starting with the maternally reported last menstrual period (LMP) to the date of delivery. The Capurro method (i.e. an infant physical exam) was used as a secondary confirmatory estimate of gestational age and in instances where the gestational age estimated from the LMP differed by more than three weeks from the Capurro method, the Capurro methodderived estimate was used (n = 19) (Sanders et al., 2015). Capurro method estimates were converted from weeks into days, by using week gestation × 7 days/week + 3.5 days (imputed days mid-week). Staff conducted in-person interviews, which included a question about household smoke exposure. Household environmental tobacco smoke exposure was dichotomized as yes/no based on the mother's report that at least one household member smoked during the pregnancy. Very few participants reported smoking during pregnancy (n = 4). The SES index during pregnancy was calculated based on 1994 Mexican Association of Intelligence Agencies Market and Opinion (AMAI) rule 13 * 6. The index classifies families into 6 levels based on 13 questions related to the characteristics of the household. The 6 resultant levels were then collapsed into 3 SES categories: low, medium, and higher.

2.3. Lead exposure assessment

Maternal venous whole blood samples were collected at the second trimester visit. Blood samples were drawn in trace metal free tubes and stored at 2–6 °C until analysis. Samples were prepared and analyzed for lead levels using the Agilent 8800 ICP Triple Quad (ICP-QQQ) in MS/MS mode at the Lautenberg Environmental Health Sciences Laboratory at the Icahn School of Medicine at Mount Sinai in New York (Renzetti et al., 2017). The limit of detection was 0.02 μg/dL; only one sample was below the LOD and was imputed to 0.02 divided by $\sqrt{2}$.

2.4. Blood pressure measurement

Children's resting BP was measured using a Spacelabs Healthcare automated oscillometric device (Ambulatory BP 90207 monitor, WA, USA). After 3–5 min of rest, BP was measured using the automated Spacelabs system with a child-sized cuff, taking two measurements as per the standard PROGRESS protocol. SBP, DBP, and mean arterial pressure (MAP) are estimated directly by the instrument; although MAP can be calculated using the equation (SBP-DBP)/3 + DBP, we analyzed MAP estimated by the instrument via a proprietary method. The Spacelabs system has a number of advantages over standard sphygmomanometer measurement, including the elimination of observer bias and reduction of White Coat Hypertension (anxiety induced from visiting the doctor's office and BP measurement) (Gillman and Cook, 1995; Mattu et al., 2001).

2.5. Statistical analysis

2.5.1. Linear model—To examine the associations between continuous gestational age and BP at 4–6 years, we first used linear regression. Models estimated the mean change in BP associated with weeks' shorter gestation. We investigated SBP and DBP, primarily, as well as pulse pressure (PP) and mean arterial pressure (MAP) as separate outcomes. We chose covariates a priori including child sex, height, and age at the time of BP measurement, as well as maternal SES and environmental tobacco smoke exposure inside the home. Prenatal smoke exposure and maternal SES were categorized as described above. Both adjusted and unadjusted regression models were performed. The reported beta coefficients represent the change in BP (mm Hg) per week change in gestation. In secondary analyses, we calculated children's z-scored DBP and SBP based on sex, age and height, calculated according to the updated American Academy of Pediatrics guidelines (Flynn et al., 2017). However, because the reference population derives from US children participating in NHANES, we presented main analyses as the non-z-scored BP outcomes adjusted for sex, age and height. In analyses of SBP and DBP z-score outcomes, the model adjusted only for maternal SES and prenatal smoke exposure to prevent over adjustment for height, age, and sex. We identified cases of "high" BP using updated terminology for pediatric BP as defined in the 2017 report by the AAP Subcommittee On Screening Management Of High Blood Pressure In Children and Adolescents wherein "high" BP refers to both hypertensive (stages 1 and 2) and elevated BP (formerly called "prehypertension") together and we refer the reader to the AAP report for details (Flynn et al., 2017). Because casual BP was obtained in this study visit, we cautiously interpret the classification of "high" BP individuals since the BP collection protocol was designed prior to the revised AAP clinical guidelines.

2.5.2. Nonlinear piecewise model—To evaluate our data for evidence of a nonlinear association between gestational age at birth (GA) and SBP, we selected a piecewise model parameterized as:

$$\mu = \begin{Bmatrix} \beta_0 + \beta_1 GA, & GA < \delta \\ \gamma_0 + \gamma_1 GA, & GA \geq \delta \end{Bmatrix},$$

with the continuity constraint at the join-point, δ; i.e., $\beta_0 + \beta_1 \delta = \gamma_0 + \gamma_1 \delta$. This model allows for a different slope between GA and SBP on either side of the join-point. A test for a difference in the slopes and the 95% confidence interval (CI) on δ was conducted. When the estimate for the join-point is at the boundary of the observed data, the model is over-parameterized and we instead fit a linear model: $\mu = \beta_0 + \beta_1 GA$. We anticipated negative slope estimates indicating shorter GA would be associated with higher SBP at 4–6 years of age. The join-point of gestational age was identified as the value where the slope of the relationship between GA and SBP changes. When the slope associated with shorter GA (i.e., $GA < \delta$) was more negative than that associated with typical GA (i.e., $GA \geq \delta$), we cautiously interpret this as evidence of increased risk of higher BP with shorter GA at birth. We assessed gestational age within the range of weeks of gestation at birth in the PROGRESS cohort: 29.0 up to 42.0 weeks using intervals of 0.5 weeks. While both SBP and DBP are important risk factors for later life hypertension, nonlinear models assessing the relationship between GA and DBP were over parameterized, suggesting the relationship modeled with linear regression was more appropriate; therefore only linear models with DBP are presented. We performed a sensitivity analysis excluding the 10 infants < 34 weeks of gestation using identical methods.

2.5.3. Lead-modified nonlinear piecewise model—To evaluate whether lead modified the effect of gestational age and SBP, we used nonlinear piecewise models stratified by different BLLs. A sensitivity analysis excluding the 10 infants < 34 weeks of gestation used identical methods as described below. Selection of BLL for stratification was determined using a data-adaptive approach and not selected a priori. It was hypothesized that when lead was 'high' the relationship between gestational age and SBP would be represented by the piecewise model (Eq. (1)), but when lead is 'low' this relationship is different (Eq. (2)).

$$\mu = \begin{Bmatrix} \beta_{0,H} + \beta_{1,H} GA, & GA < \delta_H \\ \gamma_{0,H} + \gamma_{1,H} GA, & GA \geq \delta_H \end{Bmatrix} \quad (1)$$

$$\mu = \begin{Bmatrix} \beta_{0,L} + \beta_{1,L} GA, & GA < \delta_L \\ \gamma_{0,L} + \gamma_{1,L} GA, & GA \geq \delta_L \end{Bmatrix} \quad (2)$$

with the continuity constraint in both. When the estimated join-point parameter (δ) was at the boundary of the observed data, the model is over-parameterized, and we instead fit a linear model. To optimize our model required two stages: i) identification of lead cutpoint (π) and ii) identification of gestational age join-point (δ), in relation to SBP.

Using our data-adaptive approach to find a cutpoint value of lead, the piecewise models were stratified by BLLs across a range of exposure in the PROGRESS cohort defined as the mean BLL ± one standard deviation (1.0 to 6.5 μg/dL using intervals of 0.1) (Supplemental material, Fig. S1). Simultaneously applying the stratified piecewise models, total sum of squared errors (SSE) was calculated as the sum of SSE between the two strata and plotted to find the best-fit model with the overall lowest total SSE and identify a cutpoint BLL. We required that the identified smallest total SSE met the following criteria: (1) the iterative estimation algorithm converged to solutions; and (2) the estimated cutpoint was within the observed gestational age range.

2.5.4. Sensitivity analyses—We performed three sensitivity analyses for the nonlinear models which included: i) excluding the 10 infants < 34 weeks of gestation using identical methods, ii) excluding 19 infants with Capurro-reassigned gestational age and iii) including adjustment for weight in addition to child sex, height, and age at the time of BP measurement. We conducted each sensitivity analysis using identical nonlinear piecewise methods as described above. Furthermore, to examine the association between lead exposure and SBP at 4–6 years, we used linear regression and adjusted for the same covariates as the nonlinear model including child sex, height, and age at the time of BP measurement.

3. Results

3.1. Characteristics of study participants

Demographics of the 565 mother-child pairs participating in this subcohort of the PROGRESS study at 4–6 years of age are presented in Table 1. The average maternal age was 28 years and ranged from 18 to 44. Half of the women were within the two lowest SES categories (51%), and the majority reported no tobacco smoke exposure in the home (70%). Gestational age ranged from 29 to 41.9 weeks; 59 children (10%) were born preterm. Maternal second trimester BLLs ranged from 0.7 to 17.8 μg/dL with 112 (20%) above the CDC guideline level of 5 μg/dL. Five of the children in this study met the criteria for high BP as defined by the Subcommittee on Screening Management of High BP in Children and Adolescents (Flynn et al., 2017).

3.2. Association between gestational age and SBP at 4 years

Linear examination of the relationship between gestational age and SBP showed that a one week reduction in gestational age was associated with a 0.5 mm Hg (95%CI: 0.2, 0.8) increase in SBP and a 0.4 mm Hg (95%CI: 0.1, 0.6) increase in DBP, adjusted for child's sex, age, height, maternal SES, and prenatal exposure to smoke (Table 2). Likewise, a one week reduction in gestational age was associated with a 0.4 mm Hg (95%CI: 0.2, 0.7) increase in MAP (Table 2). The estimates were relatively unchanged when adjusted for covariates, and similar relationships were observed with z-scored SBP and DBP (Table 2). No significant relationship was identified between gestational age and PP in adjusted or unadjusted models.

Examination of the relationship between gestational age and SBP using nonlinear piecewise models suggested evidence of different effect estimate magnitudes, depending on gestational

age at delivery (Fig. 1) though these did not reach statistical significance. Our piecewise model demonstrated evidence of a join-point δ at 35.9 weeks' (95%CI: 28.8, 43.0). Among children born before 35.9 weeks, SBP was 0.9 (95%CI: −0.5, 2.3) mm Hg higher per one week reduction in gestational age; and among children born later than 35.9 weeks, SBP was 0.4 (95%CI: −0.06, 0.9) mm Hg higher. While we are intrigued by the estimated join-point δ and potential indication of a nonlinear association, we cautiously interpret these findings and note the wide confidence interval and that a test comparing the difference in slopes β1 and γ1 had a *p*-value > 0.05.

3.3. Prenatal lead modifies the association between shorter gestation and higher SBP

Using the data-driven SSE best-fit model approach, we identified the cutpoint BLL, π, of 2.5 μg/dL. When BLLs were < 2.5 μg/dL, evidence for nonlinearity was not present, therefore a linear model showed that each week reduction in gestational age was associated with a 0.4 mm Hg (95%CI: −0.9, 0.01) decrease in SBP (Fig. 2a). We note that for BLLs below 2.5 μg/dL this relationship was not statistically significant. However, when BLLs were ≥2.5 μg/dL, the data showed evidence of nonlinearity with the join-point δ estimated as 37.0 (95%CI: 32.1, 41.9) (Fig. 2b). Specifically, when BLLs were ≥2.5 μg/dL, SBP was 1.6 (95%CI: 0.3, 2.9) mm Hg higher per each week reduction in gestational age among children born before 37.0 weeks of gestation; and among children born after 37.0 weeks of gestation, this relationship was attenuated yet remained significant [β: 0.9, 95%CI (0.2, 1.6)] (Fig. 2b). However, the slopes β1 and γ1 were not statistically different. The overall *p*-value for the nonlinear model was $p < 0.0001$; however, the goodness of fit test comparing the piecewise model to a linear model (with high lead) was not significant.

3.4. Sensitivity analyses

A sensitivity analysis using nonlinear piecewise models further excluding infants born prior to 34 completed weeks showed an estimated join-point δ at 34.9 weeks (95%CI: 33.7, 36.2). Among children born before than 34.9 weeks, SBP was 8.1 (95%CI: −14.2, 30.3) mm Hg higher per one week reduction in gestational age; and among gestations longer than 34.9, SBP was 0.4 (95%CI: −0.02, 0.8) mm Hg higher. While we are intrigued by the estimated join-point δ and potential indication of a nonlinear association, we cautiously interpret these findings and note the wide confidence interval and that a test comparing the difference in slopes β1 and γ1 had a *p*-value > 0.05.

A sensitivity analysis examining nonlinear piecewise models with lead modification restricting to infants between 34 and 42 weeks of gestation yielded the BLL cutpoint, π, of 2.9 μg/dL. When BLLs were < 2.9 μg/dL, shorter gestation was marginally linearly associated with lower SBP [β: 0.2, 95%CI (−0.3, 0.7)]. When BLLs were ≥2.9 μg/ dL, the join-point δ was estimated as 37.0 (95%CI: 35.7, 38.3). Among children born before 37.0 weeks of gestation, each one week reduction in gestational age was associated with 3.9 (95%CI: 0.8, 6.9) mm Hg higher SBP, and among children born after 37.0 weeks this relationship was attenuated yet remained significant [β: 0.9, 95%CI (0.1, 1.6)]. A test comparing the difference in slopes β1 and γ1 on either side of the join-point was $p = 0.05$. The overall model *p*-value was $p < 0.0001$. The goodness of fit test comparing the piecewise

model to a linear model (with high lead) was $p = 0.09$, suggesting potential evidence of a nonlinear relationship.

Two additional nonlinear sensitivity analyses that i) excluded 19 infants with reassigned gestational age or, ii) adjusting for weight in addition to other covariates, resulted in an estimate for the join-point δ near 29 weeks', the extreme of the data range. These models did not meet our criteria for inclusion as specified in the methods.

In additional sensitivity analyses using linear models, we observed a null relationship between lead and SBP adjusted for age, sex and height (β: −1.3, 95%CI: −3.2, 0.6). Similarly, a null relationship between lead and gestational age (β: 0.03, 95%CI: −0.02, 0.08) was previously reported in the PROGRESS cohort (Renzetti et al., 2017).

4. Discussion

Results from our nonlinear model suggest that lower gestational age combined with higher prenatal lead exposure contributes to a higher risk of elevated BPs at 4–6 years of age among infants born < 37 weeks of gestation. We propose that the most appropriate interpretation of these data is that infants below this gestational age are more susceptible to the effects of in utero lead exposure due to the immaturity of renal development at the time of transition to extrauterine life. We identified a BLL cutpoint in our analyses as 2.5 μg/dL, a relatively low lead level, suggesting even low-level prenatal lead exposure that may have implications for later life renal health with far ranging public health significance. This is particularly important as current practice uses 5 μg/dL as the level of concern. Our statistical approach demonstrates the utility of nonlinear modeling for identifying i) critical windows of susceptibility (e.g. the joint point δ) and ii) threshold exposure levels (e.g. cutpoint BLL π). These data inform issues of temporality and dose related to early life lead exposure and contribute to the limited existing literature on the adverse cardiorenal effects of metals in children (Sanders et al., 2018; Zheng et al., 2017).

To avoid methodological concerns introduced by stratifying on preterm vs. term status or adjusting for gestational age (e.g., collider bias) (Wilcox et al., 2011), we explored the nonlinear piecewise model as a method to more appropriately examine critical windows of in utero renal development. Further, we observed a null relationship between lead and gestational age as previously reported (β: 0.03, 95%CI: −0.02, 0.08) (Renzetti et al., 2017). Similarly, the relationship between lead and SBP in this study demonstrated a null relationship with the inverse direction (β: −1.3, 95%CI: −3.2, 0.6). Our findings are intriguing as we identified an estimate for δ at 35.9 weeks, which closely aligned with our hypothesis of an expected δ near the time of complete nephron formation: 36 weeks. Our model demonstrates a novel statistical approach because methodologically accounting for gestational age as a known risk factor is difficult, and builds upon existing literature that shorter gestations as a risk factor for higher BP. Moreover, due to concern of prenatal lead exposure as a paradigm nephrotoxicant in the study population, we then explored the nonlinear piecewise model combined with lead stratified by 'high' and 'low' levels derived using a data-adaptive approach. Since a low nephron number alone may not predict increased BP, a kidney with fewer nephrons could be less able to withstand additional toxic

injury (Luyckx and Brenner, 2015; Luyckx et al., 2017). Intriguingly, our results from the nonlinear piecewise model with lead exposure ≥ 2.5 μg/dL support this hypothesis. These findings have potential far-ranging public health significance as childhood renal health predicts adult renal health (Gluckman et al., 2008; Huang et al., 2009; Luyckx et al., 2013).

To our knowledge, our study is the only study to-date to examine the joint effects of lower gestational age and lead exposure. However, three previous studies evaluated the linear association between prenatal lead exposure and childhood BP with inconsistent results. Inconsistent associations reported across populations may be due to variations in the timing exposure or outcome assessment. In a prospective study of 690 Bangladeshi children, Skroder et al. (2016) identified no significant relationship with maternal blood erythrocyte lead measured in the second or third trimesters (14 or 30 weeks gestation) and SBP at 4.5 years of age. We note that Skroder et al. observed an inverse relationship between maternal blood lead and child kidney volume measured by ultrasound in a subset of 117 dyads. Zhang et al. (2012) in a prospective birth cohort of 457 mother-child pairs in Mexico, reported that an interquartile range (IQR) increase of prenatal lead measured in maternal tibia 1-month postpartum (reflecting prenatal exposures) resulted in a 2.1 mm Hg higher SBP (95% CI: 0.7, 3.5) and 1.6 mm Hg higher DBP (95% CI: 0.3, 2.9) among girls only at 10 years of age. No associations were observed in boys, or for lead measured in cord blood or patella. And lastly, Gump et al. (2005) showed in a retrospective study of 122 US children that higher cord blood lead levels were associated with significantly higher SBP ($\beta = 12.16$, $p = 0.02$) at 9.5 years of age. Prior studies that observed relationships between lead and BP were conducted later in childhood (9.5 years as compared to 4–6 years of age in our study) and assessed lead exposure via bone or cord blood rather than prenatal BLLs. Critical windows during pregnancy may reflect more sensitive timings during nephron development and subsequent studies in PROGRESS will examine relationships with BP at 7–10 years of age. Our study contributes to the body of literature suggesting that prenatal lead exposure contributes to altered BP in childhood, particularly among infants born preterm. Future studies should consider the potential interaction effect of gestational age and other nephrotoxicant exposures as well. Finally, these data may indicate that lead plays a role in the development of hypertension in adults born prematurely.

Our study builds on existing findings by highlighting the multifactorial effects of adverse birth outcome and prenatal lead exposure, as possible mechanisms of developmental BP programming. Nephrogenesis, the precise and complex programming of nephron formation in the metanephric kidney, generally begins at ~5 weeks of gestation and is complete by 36 weeks in the human infant (Benz and Amann, 2010; Solhaug et al., 2004). After birth, both renal blood flow and glomerular filtration, major determinants of renal function, continue to mature until approximately 2 years of age (Calcagno and Rubin, 1963; Veille et al., 1998). Infants born with low birthweight or born preterm have interruptions in normal development and significantly reduced kidney volume and final nephron number compared to normal weight or full term babies (Kandasamy et al., 2013; Luyckx et al., 2013). Mechanistic studies in mice implicate the mammalian target of rapamycin (Mtor) signaling pathway and the inhibitory protein Hamartin play a role in the duration of nephrogenesis and risk of subsequent kidney disease (Volovelsky et al., 2018). Indeed, the Barker hypothesis sprung from the observation that lower birthweight infants were more likely to develop

later life hypertension (Barker et al., 1989). While several mechanisms of developmentally programmed hypertension and renal disease have been proposed (Baum, 2010; Block et al., 2015; Schreuder and Nauta, 2007), a consensus document by the Low Birth Weight and Nephron Number working group highlighted “the need to act early to prevent CKD and other related noncommunicable diseases later in life by reducing low birth weight, small for gestational age, prematurity, and low nephron numbers at birth through coordinated interventions” (Low Birth and Nephron Number Working, 2017).

There are a number of potential mechanisms that might explain our results. While speculative, metals including lead are well known to induce oxidative stress through a number of pathways. One mechanism by which preterm infants may be particularly susceptible to the effects of lead on the later development of higher BP may be the added impact of lead induced oxidative stress and the reactive oxygen species that arise from birth on the developing kidney. Indeed, several recent studies and reviews of lead toxicity proposed that the many health effects of lead on different tissues could be explained by oxidative stress, and that free radical damage could be a unifying mechanism to explain these pleiotropic effects (Corsetti et al., 2017; Mitra et al., 2017; Rehman et al., 2018). Future research should not exclude other mechanisms of action, but given the well-known relationship between lead and oxidative stress, this particular mechanism merits future study. Furthermore, when infants are born, at any gestational age, the partial pressure of oxygen rises from in utero levels of 40–50 mm Hg just prior to birth to 60–90 mm Hg within hours (Fanaroff et al., 2006). This increase, especially when combined with any additional supplemental oxygen, which is more commonly administered to preterm infants, can result in an excess of reactive oxygen species (Auten and Davis, 2009). In rats, lead exposure can reduce the ability to excrete reactive oxygen species (Vaziri et al., 1999) suggesting that the combined extra-uterine exposure to oxygen and higher lead concentrations in the setting of incomplete renal development may lead to direct tissue damage and subsequent susceptibility to hypertension. While epidemiological studies cannot determine mechanism, future investigations may aim to address redox and non-redox mechanisms underlying the observations.

Our study has several strengths. First, PROGRESS is a prospective study, with carefully collected covariate data, birth outcomes, and simultaneous exposures. Lead exposure was assessed years prior to BP and cannot be biased with respect to BP. We enrolled women during pregnancy and followed mother-child dyads to 4–6 years of age. Given our cohort design, we adjusted for potential confounding variables and analyzed gestational age as a continuous outcome. In linear models, we analyzed SBP and DBP as the primary outcomes collected using automated state of the art equipment. While residual confounding may limit our study, in general the effect estimates were markedly unchanged after covariate adjustment indicating little confounding. Moreover, similar results were observed with BP measures adjusted for key covariates (height, age, and sex) as observed with z-scored DBP and SBP outcomes that account for height, age, and sex using the new American Academy of Pediatrics guidelines (Flynn et al., 2017). We note that while the observed effect estimates (ranging from 0.4 to 1.6 mm Hg increased BP per each week shorter gestation) were not clinically relevant, even small changes in early life BP have been shown to impact an individual’s trajectory for later life hypertension (de Jong et al., 2012). Furthermore, the

Prevention Paradox suggests that shifting the blood pressure of a whole population, even slightly, can affect the incidence or prevalence of a common disease such as hypertension (Rose, 2001).

This study had several limitations. We assessed BP at one time point, although the assessment was blind to prenatal BLLs. Cross-sectional examination of childhood lead as well as longitudinal follow-up is ongoing and future studies (including assessment of renal function and risk factors including sodium intake) will assess whether the effects of lead exposure on BP persist into adolescence or ultimately lead to hypertension. The PROGRESS cohort is a racially/ethnically homogeneous population, which may limit external generalizability. Although we observed five cases of high BP in this study (< 1%) in children aged 4–6 years, the estimated prevalence of childhood hypertension in Mexico is roughly 10% in adolescents (Cervantes et al., 2000; Juarez-Rojas et al., 2008), about 3-fold higher than the estimates of 3–4% in the US among children age 8–17 (George et al., 2014), albeit these estimates do not reflect the recently updated definition for childhood hypertension. It is possible that while our results suggest some children may be on the trajectory to high BP, assessment at 4–6 years of age is still very early for the development of clinical hypertension. Moreover, casual BP was obtained in this study and averaged from two oscillometric measures; we recommend future studies apply a minimum of 3 measures. The observed lead levels are generally higher among Mexican than US populations, making this an ideal cohort in which to test our hypotheses. There are still many pockets of lead poisoning in both Mexico and the U.S. and while levels are decreasing there are still thousands of adults with BLLs higher than 2.5 μg/dL (Tsoi et al., 2016). We reiterate that our nonlinear results between gestational age and SBP should be interpreted with caution due to limited data at lower gestational ages and the findings should be replicated. The prevalence of preterm birth in this cohort was 10% (59 cases), which while comparable to national estimates, limited sample size contributing to some models. Our intriguing findings suggesting a lead-modification effect of increased BP for children born prior to 37 weeks should be replicated in other larger cohorts. We acknowledge that sensitivity analyses adjusting for weight, and excluding the 19 Capurro-reassigned gestations resulted in unstable models. This is a limitation of our dataset and these results require replication in additional cohorts.

5. Conclusion

We found that higher maternal BLLs in pregnancy modified the association between lower gestational age and increased BP in children, whereby children with combined prematurity and maternal BLL in pregnancy ≥2.5 μg/dL had higher BP at age 4–6, than children who did not have both characteristics. This study contributes to our understanding of the early origins of adult renal or cardiovascular disease, and suggests the role of prenatal lead exposure in the multi-factorial sequela of programmed childhood BP. If replicated in other cohorts and studies, the findings provide further support that prenatal lead exposure, particularly for children born preterm, is a preventable risk factor for altered early life BP with widespread implications for future health and disease. Future studies will assess renal function and molecular changes and indicate whether the observed association with BP persists into adolescence and adulthood. Our results underscore the importance of preventing prenatal

lead exposure, preterm birth, and higher BP in childhood to reduce risk of hypertension and cardiovascular disease later in life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

BLL	blood lead level
BMI	body mass index
BP	blood pressure
DBP	diastolic blood pressure
LMP	last menstrual period
NHANES	National Health and Nutrition Examination Survey
PROGRESS	Programming Research in Obesity, GRowth, Environment, and Social Stress
SBP	systolic blood pressure

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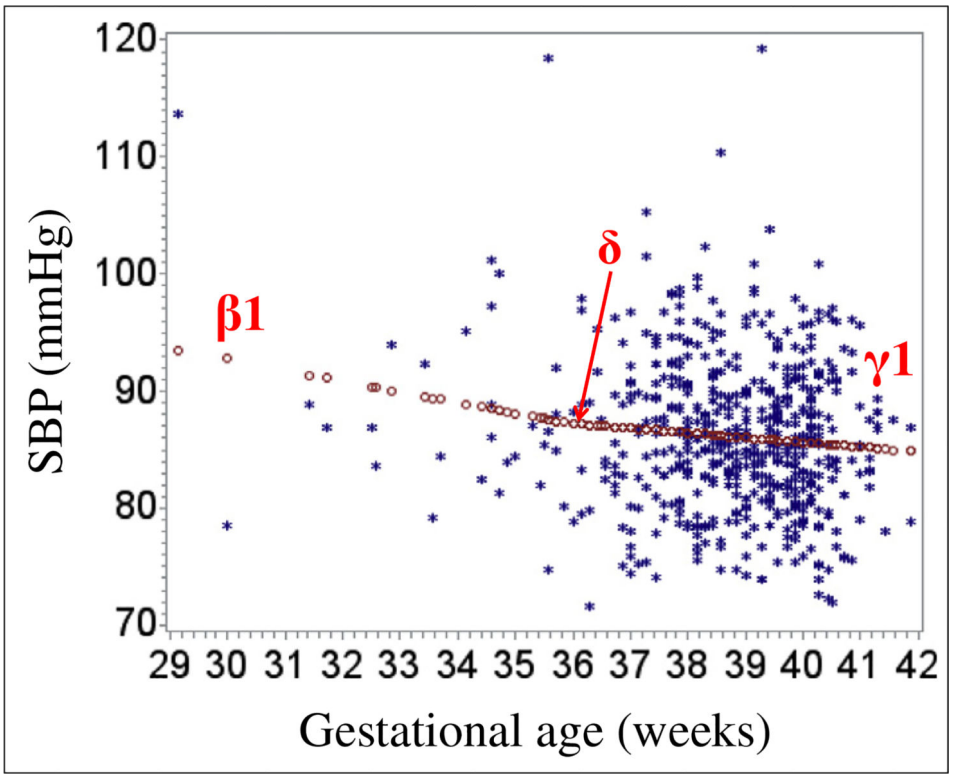

Fig. 1.

Associations of gestational age and child SBP at 4–6 years using nonlinear piecewise regression (n = 565). Plotted SBP values are residuals accounting for child's age, sex, and height. Red circles are predicted values. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

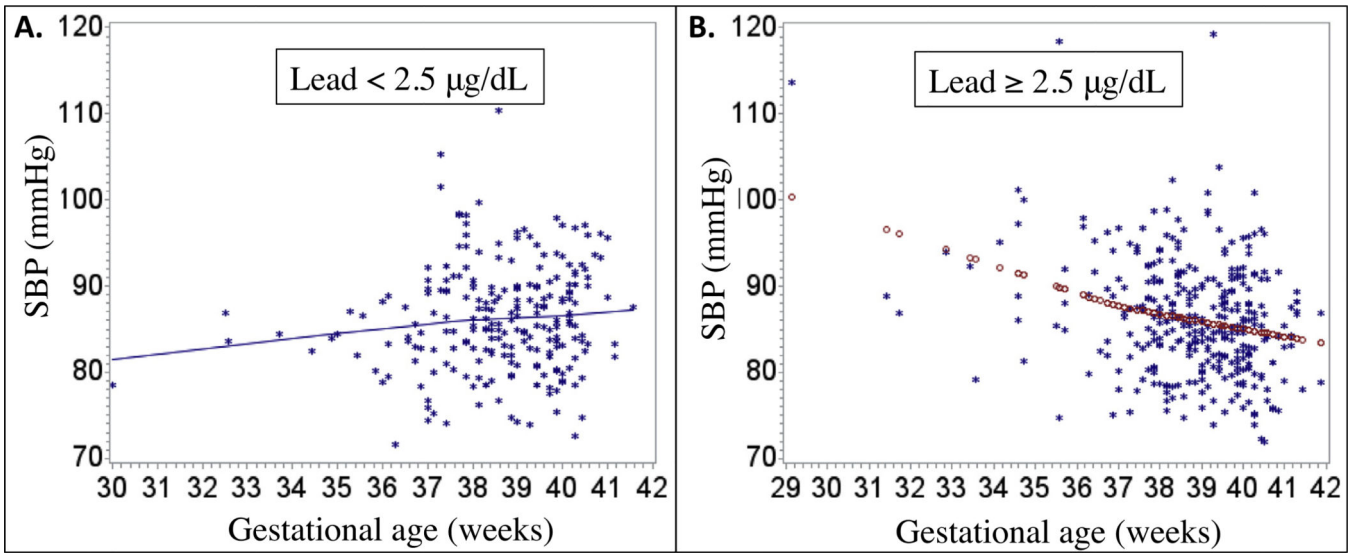

Fig. 2.

The association between lower gestational age and child SBP, when stratified by second trimester blood lead cutpoint **π** as a) BLLs < 2.5 and b) BLLs ≥ 2.5 µg/dL. Plotted SBP values are residuals accounting for child's age, sex, and height. The blue line is a linear regression; red circles are predicted values from the nonlinear piecewise model. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1

Demographics for 565 mother-child dyads participating in the PROGRESS study at 4–6 years.

Demographic	n (%)
SES	
Low	289 (51.2)
Medium	217 (38.4)
High	59 (10.4)
Tobacco smoke exposure in home	
No	394 (70.2)
Yes	167 (29.7)
Sex	
Male	283 (50.1)
Female	282 (49.9)
	Mean ± std (range)
Maternal age (years)	27.6 ± 5.6 (18.0–44.0)
Gestational age (weeks)	38.7 ± 1.7 (29.1–41.9)
Birth weight (kg)	3.1 ± 0.4 (1.1–4.2)
Child age at BP measurement (years)	4.8 ± 0.6 (4.0–6.7)
Child BMI (kg/m^2)	15.7 ± 1.7 (11.4–26.4)
Child BP at 4–6 years (mm Hg)	
SBP	86.2 ± 7.4 (66.5–120.0)
DBP	52.6 ± 5.8 (35.5–76.0)
Blood lead levels (μg/dL)	
2nd trimester pregnancy	3.7 ± 2.7 (0.7–17.8)

Table 2

The relationship between shorter gestation and BP using adjusted and unadjusted linear regression models (n=565).

	Effect estimate[a]		*p*–Value	Effect estimate[b]		*p*–Value
	β	**(95% CI)**		**β**	**(95% CI)**	
SBP	0.45	(0.10, 0.81)	0.01	0.48	(0.15, 0.80)	0.004
DBP	0.34	(0.06, 0.63)	0.02	0.37	(0.10, 0.64)	0.007
PP	0.11	(−0.17, 0.39)	0.45	0.10	(−0.17, 0.37)	0.46
MAP	0.41	(0.12, 0.69)	0.005	0.44	(0.17, 0.70)	0.002
SBP z–score[c]	0.05	(0.02, 0.08)	0.003	0.04	(0.01, 0.07)	0.005
DBP z–score[c]	0.04	(0.01, 0.06)	0.003	0.03	(0.01, 0.06)	0.008

[a] Unadjusted model.

[b] Adjusted for child's age, height, and sex and maternal SES and tobacco smoke in the home.

[c] BP Z–score model adjusted only for SES and tobacco smoke.