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Neurodevelopmental and behavioral manifestations of lead toxicity in children

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***Abstract*---**Lead in any form is harmful for the human body. It is dispersed into the environment through battery manufacturing, foundry, ammunition, lead paint, water pipes and other manmade products. It can enter the body through various pathways such as, air, water, soil, food, and dust. Concern arises, as no amount of lead is safe for the human body. The detrimental effect is higher when children get exposed, as it can interfere with the neonatal neurobehavioral development, and can also lead to low IQ, low birth weight, and fetal death. This review assesses the risk factors of lead toxicity in children, trends in childhood lead poisoning, pediatric burden in low-income countries, and its prevention, intervention, and management in children.

***Keywords*---**lead toxicity, lead exposure, lead poisoning, blood lead levels.

Introduction

Lead is naturally present in the environment. Traces of lead are present naturally in the soil, plants and water (Needleman, 1999). Naturally found traces of lead are practically not harmful. Toxicity begins when the lead is mined and transformed into manmade products (Needleman, 1999). It is by this process that the lead is dispersed in the environment and lead to harmful effects (Needleman, 1999). Shortly lead toxicity has become a global issue. Mostly because lead remains persistent in the environment and its potential toxicity never decreases (Needleman, 1999). As per the Centers for Disease Control and Prevention, "A child's environment is full of lead" (CDC, 2015). The various sources of lead from where children get exposed are gasoline, solder, water pipes, consumer products, artificial turf, candy, folk medicine, top jewelry, toys etc. (CDC, 2015). Also, from "manufacture of batteries, crystal glass, lead paint, repair of automobile radiators, moonshine, Leaded gasoline, lead glazed earthenware, ammunition (and eating food from animals killed by bullets), construction/demolition, plant roots,

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electronic waste processing, imported cosmetics and spices" (Persky, 2017, lead exposure, slide 33).

The children can get exposed to lead by several pathways such as air, water, soil, food and dust. (CDC, 2015). Generalized sources of lead are petrol, lead based paints and pigments, solder in food cans, ceramic glazes, incineration of lead containing waste, electronic wastes, "lead in the food chain, via contaminated soil and lead contamination as a legacy of historical contamination from former industrial sites" (WHO, 2010, pp. 11). "The toxicity of lead depends on the dose, the duration of exposure, and the developmental and nutritional susceptibility of the child" (Valerie B Haley, 2004).

Unusual Lead Exposures in Children

In recent years, in US children have been exposed to lead by various unusual measures (NCPC, 2012-2017). Children's jewelry containing lead, tamarind candy and candy wrappers from Mexico, acidic food served on imported ceramic dishware and pitchers, breathing fumes from melted lead for fishing weights, bullets (there had been a case where the mother and the infant got exposed to lead from the bullet in mother's spine, "she had been shot fifteen years earlier") etc. (NCPC, 2012-2017)

There is no safe exposure of lead. (Vorvolakos et al, 2016). According to an article by Vorvolakos on lead exposure, lead has a significant neurotoxic potential and it is still not known that what is the safe blood lead level concentration (Vorvolakos et al, 2016). At blood level concentrations 80-100$\mu l/dl$ lead causes acute encephalopathy in children which is one of the most serious complication of lead toxicity (Vorvolakos et al, 2016). "Early symptoms of lead neurotoxicity include irritability, headaches and difficulties in concentration in both children and adults" (Vorvolakos et al, 2016). If the exposure to lead remains continuous it leads to neurobehavioral symptoms in children like attention deficit, learning disability, low IQ and behavioral changes even at very low doses say 10-35$\mu l/dl$. (Vorvolakos et al, 2016, Mark Johnson et al, 2017). According to CDC's level of concern/reference neurobehavioral symptoms in children may also develop at doses as low as 5-10$\mu l/dl$ (CDC, 2017). Chronic exposures of medium level concentrations of lead might be related to depression, anxiety and behavioral disorder (Vorvolakos et al, 2016). Whereas psychotic disorders might be associated with high blood lead level concentrations (Vorvolakos et al, 2016).

Lead effects at blood lead level <10$\mu l/dl$: According to an international pooled analysis, "environmental lead exposure in children who have maximum blood lead levels < 7.5 µg/dl is associated with intellectual deficits" (Lanphear et al, 2005, vol 13, pp. 894). To examine the association of test intellectual scores and blood lead concentration for children with maximum blood lead levels <10$\mu l/dl$ they collected the data from "1,333 children who participated in seven international population-based longitudinal cohort studies, followed from birth or infancy until 5–10 years of age" (Lanphear et al, 2005, vol 13, pp. 894). The collected data was then examined. The primary outcome measure was the full-scale IQ score (Lanphear et al, 2005, vol 13, pp. 894). "244 (18%) children had a maximal blood lead concentration < 10 µg/dl, and 103 (8%) had a maximal blood lead concentration <

7.5 µg/dl" (Lanphear et al, 2005, vol 13, pp. 894). An inverse relationship between blood lead concentration and IQ score was found when the covariates were adjusted (Lanphear et al, 2005, vol 13, pp. 894). With an increase in blood lead concentration from 2.4 to 30 µg/dl there was a remarkable 6.9 decrement in IQ [95% confidence interval (CI), 4.2–9.4]. Decrease in IQ was associated with an increase in the Blood lead level (Lanphear et al, 2005, vol 13, pp. 894). "The estimated IQ point decrements associated with an increase in blood lead from 2.4 to 10 µg/dl, 10 to 20 µg/dl, and 20 to 30 µg/dl were 3.9 (95% CI, 2.4–5.3), 1.9 (95% CI, 1.2–2.6), and 1.1 (95% CI, 0.7–1.5), respectively. For a given increase in blood lead, the lead-associated intellectual decrement for children with a maximal blood lead level < 7.5 µg/dl was significantly greater than that observed for those with a maximal blood lead level ≥ 7.5 µg/dl (p = 0.015) (Lanphear et al, 2005, vol 13, pp. 894). Therefore, the blood lead concentrations < 7.5 µg/dl is associated with intellectual.

Table 1: Summary of blood lead levels by month

Month	Number Tested	Percent ≥10 µg/dl	Geometric Mean
January	21,122	4.2	3.96
February	20,380	4	3.87
March	22,713	3.8	3.76
April	22,231	3.7	3.75
May	22,871	4	3.82
June	22,713	5.2	4.08
July	22,368	5.8	4.26
August	21,695	6.4	4.43
September	23,204	6.1	4.4
October	23,060	5.3	4.15
November	20,534	5	4.07
December	19,796	4.5	3.92
Total	2,62,687	4.8	4.04

Lead in maternal bone: According to a prospective study, "maternal bone lead is an independent risk factor for fetal neurotoxicity" (Gomaa et al, 2005). Lead stored in the tissue stores in the maternal bone is now recognized as a potential risk factor for fetal neurotoxicity (Gomaa et al, 2005). In this prospective study, women who were giving birth were recruited from 3 different hospitals in Mexico. They measured the umbilical cord blood level and within four weeks of giving birth maternal lead levels in cortical (tibia) and trabecular (patellar) bone were also measured (Gomaa et al, 2005). "At 24 months of age, each infant was assessed using the Bayley Scales of Infant Development-II (Spanish Version)" (Gomaa et al, 2005, pp.1). "After adjustment for other well-known determinants of infant neurodevelopment, including maternal age, IQ, and education; paternal education; marital status; breastfeeding duration; infant gender; and infant illness, lead levels in umbilical cord blood and trabecular bone were significantly,

independently, and inversely associated with the Mental Development Index (MDI) scores of the Bayley Scale. A 2-fold increase in cord blood lead level (e.g. from 5 to 10 micro g/dl) was associated with a 3.1-point decrement in MDI score" (Gomaa et al, 2005, pp.1). "Higher maternal trabecular bone lead levels constitute an independent risk factor for impaired mental development in infants at 24 months of age" (Gomaa et al, 2005, pp.1).

Seasonality and trends in blood lead level in children: Even though the trends in childhood lead exposure are declining the seasonal variation persists (Valerie B Haley, 2004). During summers children get exposed to lead through soil (Valerie B Haley, 2004). Suggested explanation was large amounts of lead dust on floors and windowsills (as measured by researchers during summer) (Valerie B Haley, 2004). Lead in the floors might come from shoes and appear in the windowsills due to repeated opening and closing of the windows. One main reason might be more outdoor activities playing etc. done by children in summer. As per the study when the trends and the recent data on seasonality of BLLs in New York State children were compared, it was found that the "children's blood lead values showed a distinct seasonal cycle on top of a long-term decreasing trend" (Valerie B Haley, 2004). Children have a high risk of lead exposure due to several reasons for example, mouthing activity, lead intake as a proportion of body mass and higher absorption as compared to adults (Valerie B Haley, 2004). "The prevalence of elevated BLLs in two-year-old was almost twice that in one-year-old over the time" (Valerie B Haley, 2004). "Nearly twice as many children had elevated BLLs in the late summer compared to late winter/early spring" (Valerie B Haley, 2004).

New York State children born between 1994 and 1997 and screened for blood lead within 2 weeks of their first birthday or second birthday (Haley et al, 2004). "Figure 1 shows a more detailed picture of the prevalence of elevated BLLs. The curves show a marked seasonal cycle over a slow exponential decline. The curves have a sharper profile in the summer compared to the winter. They peak around August, and dip in March/April each year "(Valerie B Haley, 2004).

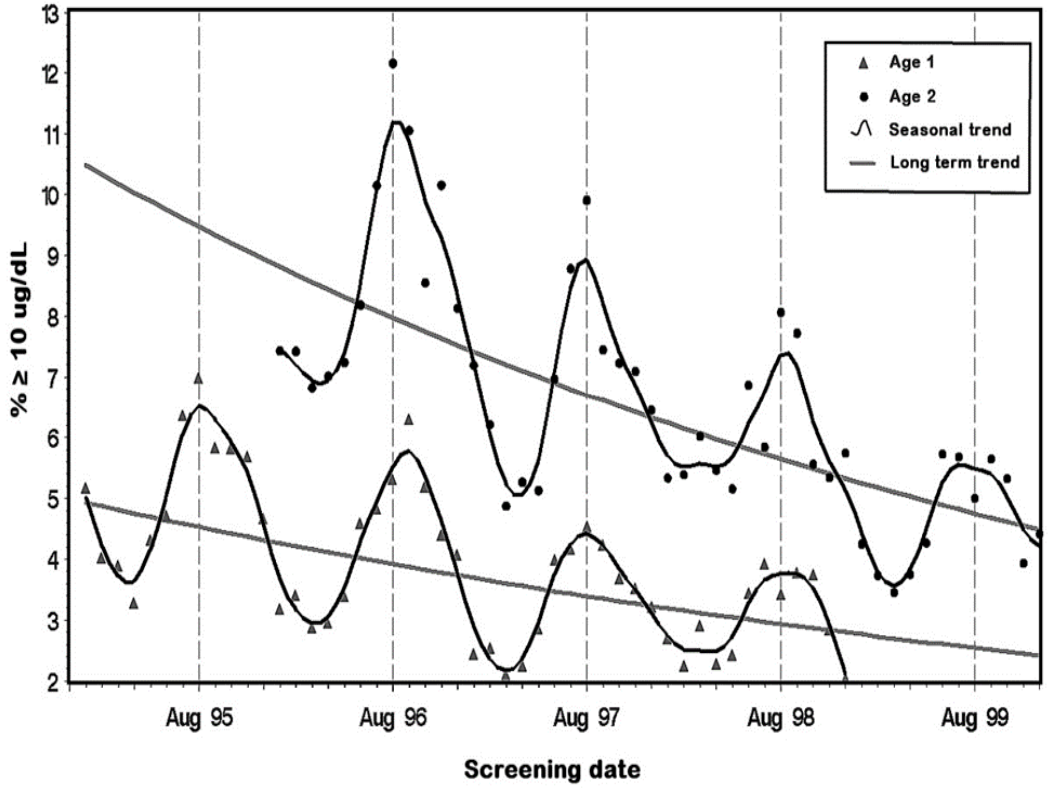


Figure 1: Percent of children with elevated blood lead levels over time, by age (Haley et al, 2004).

Exposure to lead and health effects in children

Fetal Death and low Birth Weight associated with lead contaminated drinking water. (Edwards, 2013). According to an ecologic study done during Washington DC lead crisis (200-2004) fetal deaths peaked in 2001 when the lead levels were highest and then started declining after 2004 when various public health interventions were implemented (Edwards, 2013). The goal was to protect the pregnant women (Edwards, 2013). The results showed that when the fetal death rates in Washington DC (2001-2004) were compared to fetal death rates in the neighboring Baltimore county there was a significant increase in fetal death rates in Washington DC (R^2 = 0.72). And after the intervention programs to prevent lead exposure to pregnant woman were implemented in 2004-2006, there was a significant rise in birth rates in Washington DC versus Baltimore County. The results of the ecologic study are shown in figure 2

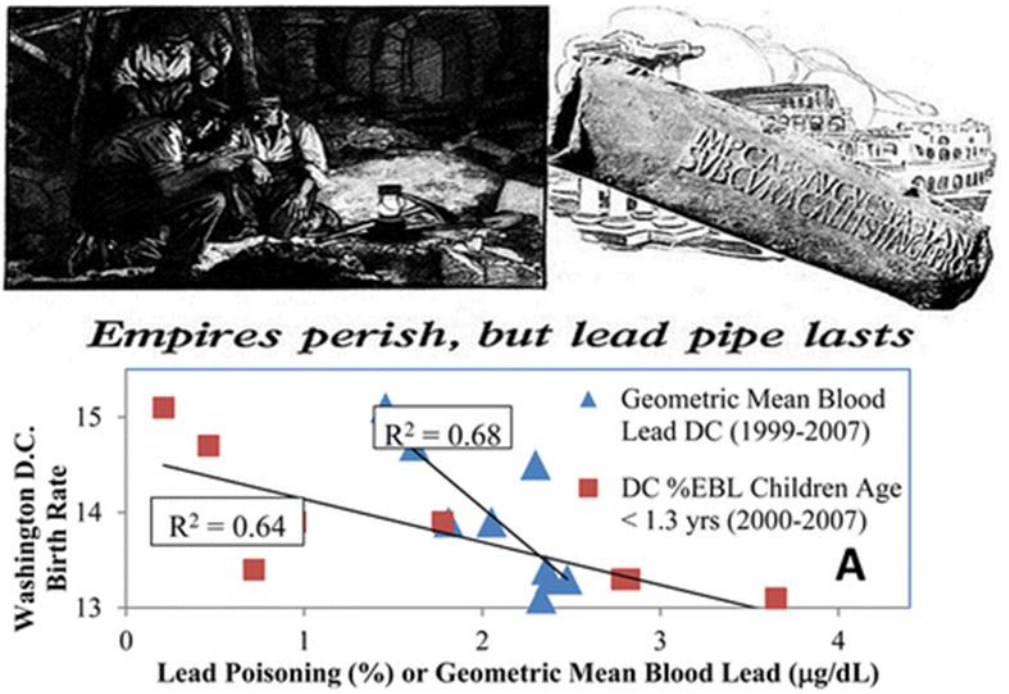


Figure 2 Environ. Sci. Technol., 2014, 48 (1), pp 739–746

Prenatal Lead Exposure and Impaired Neonatal Neurobehavioral Development

According to a study done by Ren LH, "Prenatal lead exposure results in poor neonatal neurobehavioral development and cord blood BDNF is negatively correlated with neonatal neurodevelopment" (Ren LH et al, 2016, pp.1). 120 mother and infants were selected based on the lead concentration in the cord blood. (Ren LH et al, 2016). They were then divided into two groups based on their cord blood lead concentration. The first group had a cord blood lead concentration above 0.48 µmol/L and the second group had a cord blood lead concentration below 0.48 µmol/L. (Ren LH et al, 2016). The results displayed inverted correlation between cord blood lead level concentration and neurobehavioral development in the infants. (Ren LH et al, 2016). "The level of BDNF in umbilical cord blood of high-lead group was (3.538 ± 1.203) ng / ml, which was higher than that of low-lead group (2.464 ± 0.918) ng / ml, the difference of BDNF between the two groups was statistically significant (t =7.60, P < 0.001). The level of BDNF in Umbilical cord blood and the level of BDNF in cord blood were analyzed, and r =0.286, p<0.00, there was a linear correlation. With the increase of cord blood lead concentration, BDNF level increased." (Ren LH et al, 2016).

Congenital Lead poisoning: Lead accumulates in the blood, soft tissues and bone mainly by ingestion or inhalation routes (Mazumdar et al, 2014). Lead is not only associated with various acquired disorders in children but also with congenital disorders (Mazumdar et al, 2014). Lead intoxication in the fetus may occur if the mother is suffering from chronic lead toxicity. Lead may get

transferred to the infant's system by feto maternal circulation causing congenital disorders in children or it may get transferred from the breast milk (Mazumdar et al, 2014). Breast milk consumed after birth is the other main sources by which infants get intoxicated if the mother suffering from chronic lead toxicity (Mazumdar et al, 2014). "Lead affects the hemopoietic system, central and peripheral nerves, renal function, vascular system and the gastrointestinal tract causing anemia, kidney impairment, nephropathy and gastrointestinal symptoms including impairment of liver function. Anemia (Hb level 5.4 gm/dl), abnormal liver enzymes (including elevated transaminase activity) and high blood lead value (83 µg/dl)" are also revealed in lad investigations in children as small as 6 months old. (Mazumdar et al, 2014, pp.2)

Lead exposure and Low IQ: Environmental lead exposure affects children's IQ even at very low doses. Hispanic children in Chicago public school were tested for Blood lead levels and their performance in the standardized test (Blackowicz et al, 2016). Children's with "BLLs below 10 µg/dl (0.483 µmol/L) were inversely associated with reading and math scores in all Hispanic subgroups" (Blackowicz et al, 2016). Adjusted Relative Risks and 95% confidence intervals (CI) for reading and math failure were 1.34 (95% CI = 1.25, 1.63) and 1.53 (95% CI = 1.32, 1.78), respectively, per each additional 5 µg/dl of lead exposure for Hispanic children; RR adjusted did not differ across subgroups (Blackowicz et al, 2016). It was estimated that 7.0% (95% CI = 1.8, 11.9) of reading and 13.6% (95% CI = 7.7, 19.2) of math failure among Hispanic children can be attributed to exposure to BLLs of 5-9 µg/dl (0.242 to 0.435 µmol/L) vs. 0-4 µg/dl (0-0.193 µmol/L). The RR adjusted of math failure for each 5 µg/dl (0.242 µmol/L) increase in BLL was notably (p = 0.074) stronger among black Puerto Rican children (RR adjusted = 5.14; 95% CI = 1.65-15.94) compared to white Puerto Rican children (RR adjusted = 1.50; 95% CI = 1.12-2.02)." (Blackowicz et al, 2016, pp.1). The study stated that the "early childhood lead exposure is associated with poorer achievement on standardized reading and math tests in the 3rd grade for Mexican, Puerto Rican, and Other Hispanic children enrolled in Chicago Public Schools" (Blackowicz et al, 2016, pp.1).

Table 2. Population attributable fractions (PAFs) for elevated Blood Lead Levels and Reading/Math ISAT Failure among Hispanic children.

Hispanic Subgroup	**Reading Failure**		**Math Failure**	
	PAF (%)	**95% CI**	**PAF (%)**	**95% CI**
All Hispanics [a]	7.0	1.9, 11.9	13.7	7.8, 19.2
Mexican-American [b]	7.4	2.0, 12.5	14.5	8.2, 20.3
Puerto Rican [b]	6.4	1.7, 10.9	12.6	7.1, 17.7
Other Hispanic [b]	5.8	1.5, 9.8	11.3	6.3, 16.0

Table 2. Population attributable fractions (PAFs) for elevated Blood Lead Levels and Reading/Math ISAT Failure among Hispanic children.

Hispanic Subgroup	Reading Failure		Math Failure	
	PAF (%)	95% CI	PAF (%)	95% CI

[a"] For All Hispanic Children, model used to calculate PAF includes elevated blood lead level (5–9 vs. 1–4 µg/dL), gender, mother's education, low-income, small for gestational age, preterm birth, child's age at time of BLL, ISAT vs. Iowa, and Hispanic subgroup (Mexican-American vs. other Hispanic and Puerto Rican vs. Other Hispanic); [b] for individual Hispanic subgroups, model used to calculate PAF includes elevated blood lead level (5–9 vs. 1–4 µg/dl), gender, mother's education, low-income, small for gestational age, preterm birth, child's age at time of BLL, and ISAT vs. Iowa." (Blackowicz et al, 2016).

Risk Factors in Children:

Young Age: As per a "population based study of demographic risk factors for elevated lead in Texas children" (Kurtin et al, 1997) Children 25-36 months of age have higher percentage (14.3%) of elevated blood lead concentration (Kurtin et al, 1997). Younger children 19-24 months of age have slightly lower percentage (13%) of elevated blood lead concentrations and older children 37-48 months have even lower percentage (12%) of blood lead concentrations (Kurtin et al, 1997). Younger children are more at risk for elevated blood lead levels (Kurtin et al, 1997).

Older Housing and poor neighborhood a risk factor: According to U.S. Environmental Protection Agency (EPA), more than 80% of housing before 1978 still have lead based paints which is one of the major sources of lead exposure in children especially those living in poor neighborhoods (MDH,2014) Children living in older housing and those in poverty have a greater risk for lead exposure (Minnesota Department of Health, 2014)

Hand to mouth Behavior a risk factor: Children are at high risk of exposure because of their innate curiosity and age appropriate hand to mouth behavior. Due to this behavior, they bring lead coated objects to their mouth. This coating may contain lead contaminated soil or dust which increases their risk of exposure. "This route of exposure is magnified in children who engage in pica. The amount of soil and house dust that a typical 1–6-year-old child ingests is said to be 100 mg/24 h, but a more conservative estimate of 200 mg/24 h with an upper percentile of 400 mg/24 h has also been suggested. Children in the United States who engage in pica may ingest as much as 10 g/24 h" (WHO, 2010, pp. 18) (EPA, 2002)

Protective effect of thymoquinone: Some of the animal studies show that thymoquinone has a protect effect on lead induced hepatic toxicity. As per a randomized control trial "adult male rats were randomized into four groups.: Control group received no treatment, Pb group was exposed to 2000 ppm Pb acetate in drinking water, Pb-TQ group was cotreated with Pb plus TQ (5 mg/kg/day, per orally), and TQ group receiving only TQ. All treatments were applied for 5 weeks. Results indicated that Pb exposure increased hepatic Pb content, damaged hepatic histological structure (necrotic foci, hepatic strands disorganization, hypertrophied hepatocytes, cytoplasmic vacuolization, cytoplasmic loss, chromatin condensation, mononuclear cell infiltration, congestion, centrilobular swelling), and changed liver function investigated by plasma biochemical parameters (AST, ALT, ALP, γ-GT, LDH)." (Mabrouk et al, 2016). Treatment with lead resulted in increased lipid peroxidation in liver. It also significantly reduced the antioxidant level in liver. (Mabrouk et al, 2016). Pb-induced adverse effects were improved with supplementation of TQ (Mabrouk et al, 2016). Results indicate, TQ has a protective effect against Pb-induced hepatotoxicity and might be useful in Pb intoxication in human beings. (Mabrouk et al, 2016)

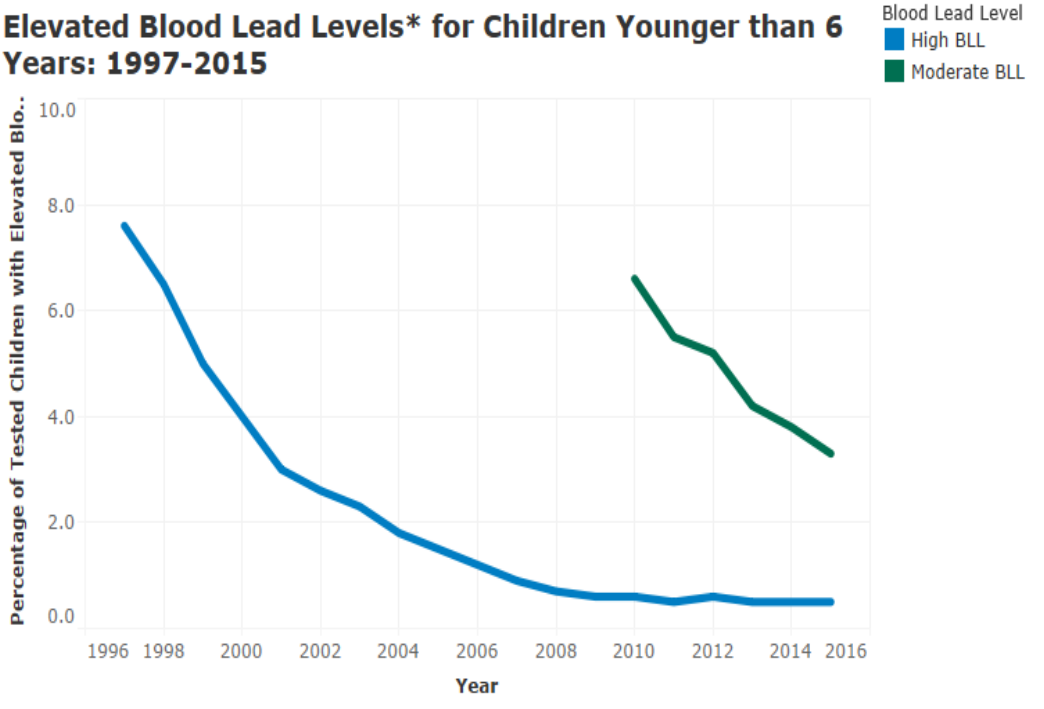
Protective effect of 17-β-estradiol: Developing nervous system is the primary target of heavy metals such as lead (Chetty et al, 2007). "Pb-exposure causes cognitive dysfunction, growth retardation, hyperactivity and neurochemical deficits in animals and humans" (Chetty et al, 2007, pp.1). 5 μM Pb can cause 50% inhibition in the proliferation of the neuroblastoma cells. Some of it is related to apoptotic cell death caused by lead in a concentration dependent manner. If the neuroblastoma cells are exposed to lead for 48 hours there is a significant increase (+732% of control) in caspase-3 activity, an indicator of apoptosis (Chetty et al, 2007). The effects of lead on caspase-3 activity can be blocked by 17-β-estradiol (10 nM) (pretreatment). (Chetty et al, 2007)

Protective effect of Vitamin E: Animal studies suggest that Vitamin E has a protective effect on lead induced toxicity (Salehi et al, 2015). Lead poisoning impairs the central nervous system and memory whereas the Vitamin E counteracts this effect by acting as a memory enhancer (Salehi et al, 2015). Vitamin E can reverse learning and memory deficits in pre, post or co- exposure with Pb ($P < 0.001$) (Salehi et al, 2015). According to one of the animal study 48 rats were given water containing 0.2% lead for 1 month and then post treated with vitamin E for the other two months (Salehi et al, 2015). Passive avoidance learning was then assessed. "The results showed that Pb caused impairment in acquisition and retrieval processes in passive avoidance learning" (Salehi et al, 2015). Vitamin E can counteract the negative effects of lead on the Central Nervous System such as disability in learning and memory deficits (Salehi et al, 2015). But to extrapolate these findings to human, future studies are needed to be done.

Protective Effect of Vitamin C, B12 and Omega-3: Animal studies done on rats reveal that Vitamin C, B12 and Omega-3 might have a protective effect on lead induced memory impairment in rats (Moosavirad et al, 2016). Cognitive impairment is induced by lead poisoning whereas Vitamin C (120 mg/kg/day) or Vitamin B12 (1 mg/kg/day) or ω-3 (1000 mg/kg/day) or their combination may

have a possible protective effect on lead induced cognitive loss. (Moosavirad et al, 2016)

Trends childhood lead poisoning: Childhood lead poisoning was extensive in 1970's. The two major sources of lead poisoning in children were airborne lead, which was derived from combustion of gasoline containing tetraethyl lead; and leaded chips and dust, from deteriorating lead paint (Pediatrics, 2005, volume 116, Issue 4). The blood lead level of the American population declined between 1975 and 1980 from 14.6 µg/dl to 9.2 µg/dl and this occurred because of removal of lead from gasoline (Piomelli, 2002). By 1994 blood lead level concentration declined to 3.2 µg/dl as per the NHANES data (Piomelli, 2002). The mean BLL of children declined by about 24% born between 1994 and 1997 (Haley et al, 2004). As per first NHANES survey the blood lead level of 14 million children between 1975-1980 (Age: 6months- 5 years of age) was 30 µg/dl (Piomelli, 2002). The second NHANES survey revealed a dramatic decline in blood lead levels between 1991-1994 (Piomelli, 2002). In 1994, it was 10 µg/dl which is still associated with neurotoxicity (Piomelli, 2002). Elevated blood lead levels for children younger than 6 years from 1997- 2005 are shown in Figure: 2 (CDC's National Surveillance data)



defined as greater than or equal to 5 µg/dL.
Source: Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Environmental Health. (2016). CDC's national surveillance data (1997-2015): Tested and confirmed elevated blood lead lev..

Figure 3: shows elevated blood lead levels for children younger than 6 years. (1997-2015) (CDC's National Surveillance data).

Pediatric Burden of lead toxicity in low income countries: A study done by chatham-stephans et al evaluated impact of lead from toxic waste sites on children in low and middle income countries (chatham-stephans et al, 2014). They evaluated 200 lead contaminated sites of 31 countries and "779,989 children younger than 4 years of age potentially exposed to lead. Environmental lead levels produced a range of BLLs from 1.56 to 104.71 µg/dl. These BLLs equated to an estimated loss of 5.41-8.23 IQ points." (chatham-stephans et al, 2014). Table 1 shows "countries with lead-contaminated sites evaluated by the Blacksmith Institute Toxic Sites Identification program" and Table 2 shows "pediatric blood lead levels at lead- contaminated sites in low and middle income countries." (chatham-stephans et al, 2014). The study shows significant decrease in the intelligence Quotient (IQ) of children in relation to increased blood lead levels, exposed to lead from soil and water at toxic waste sites. (chatham-stephans et al, 2014)

Table 3: Countries with lead-contaminated sites evaluated by the Blacksmith Institute's Toxic Sites Identification Program

Country	Region	Income	Number of sites
India	South Asia	Lower-middle	32
Philippines	East Asia & the Pacific	Lower-middle	27
Indonesia	East Asia & the Pacific	Lower-middle	26
China	East Asia & the Pacific	Upper-middle	19
United Republic of Tanzania	Sub-Saharan Africa	Low	17
Argentina	Latin America & the Caribbean	Low	9
Pakistan	South Asia	Lower-middle	9
Uganda	Sub-Saharan Africa	Low	9
Peru	Latin America & the Caribbean	Upper-middle	7
Bangladesh	South Asia	Low	6
Remainder of countries			39

Table 4: Predicted pediatric blood lead levels at lead-contaminated sites in low and middle income countries

Age (months)	Median BLL[a] (µg/dL)
6–12	17.5
12–24	22.2

Age (months)	Median BLL[a] (µg/dL)
24–36	21.2
36–48	20.8

Blood lead levels were calculated using the U.S. EPA IEUBK Model, which resulted in a mean BLL for each age group at each of 200 sites. We present the median BLL for each age group across 200 sites.

"Lead Screening and Prevalence of Blood Lead Levels in Children Aged 1–2 Years Child Blood Lead Surveillance System, United States, **2002–2010** and National Health and Nutrition Examination Survey, United States, **1999–2010**" (MMWR, 2014, September 12) According to NHANES data (2007–2010) 3.1% of children aged 1–2 years had BLLs ≥5 µg/dl (CDC, Raymond et al, 2014). "Among non-Hispanic black children aged 1–2 years, 7.7% had BLLs ≥5 µg/dl compared with 1.6% of Mexican-American children aged 1–2 years (95% CI = 0.7–3.0)" (CDC, Raymond et al, 2014). Prevalence of BLLs ≥5 µg/dl varied with different poverty levels; "6.0% of children living in a household with a poverty-to-income ratio of <1.3 had BLLs ≥5 µg/dl, compared with 0.5% of children living in a household with a poverty-to-income ratio of ≥1.3 had BLLs ≥5 µg/dl" (CDC, Raymond et al, 2014). These findings indicate that the blood lead levels in children significantly vary by poverty levels. (table 5) (CDC, Raymond et al, 2014)
As per the NHANES data, "the percentage of children aged 1–2 years living in pre-1950 housing remained steady from 1999 to 2010 (Table 6) (CDC, Raymond et al, 2014). The greatest decline in the percentage of children having BLLs ≥5 µg/dl from 1999 to 2010 occurred among children living in pre-1950 housing (25.9% versus 3.7%, respectively; $p<0.05$) (Table 6) (CDC, Raymond et al, 2014). However, children living in pre-1950 housing were 10 and four times more likely to have BLLs ≥5 µg/dl compared with children living in homes built after 1978 during the NHANES 1999–2002 and 2007–2010 cycles, respectively (Table 6) (CDC, Raymond et al, 2014).

TABLE 5. Number and percentage of children aged 1–2 years with blood lead levels ≥5 µg/dL, by selected demographic characteristics — National Health and Nutrition Examination Survey, United States, 2007–2010

Chacteristic	**No.**	**%**	**(95% CI)**
Sex			
Male	410	3.1	(1.6–5.0)
Female	383	3.2	(1.8–4.9)
Race/ethnicity			
Black, non-Hispanic	164	7.7	(4.0–12.4)
Mexican-American	238	1.6	(0.7–3.0)*

White, non-Hispanic	252	3.2	(1.2–6.0)*
Poverty-to-income ratio†			
<1.3	430	6.0	(3.7–8.9)
≥1.3	309	0.5	(0.1–1.2)*
Medicaid status			
Yes	326	5.3	(3.2–7.8)
No	467	2.1	(1.1–3.4)
Total	**793**	**3.1**	**(2.1–4.4)**

Abbreviation: CI = confidence interval.
* Relative standard error ≥30.
† Income-to-poverty ratios represent the ratio of family or unrelated individual income to their appropriate poverty threshold. (Source: US Census Bureau. Current population survey [CPS] – definitions. Washington, DC: US Census Bureau; 2014. Available at http://www.census.gov/cps/about/cpsdef.html.)

Centers for Disease Control and Prevention (MMWR), (Raymond et al, 2014)

TABLE 6. Percentage of children aged 1–2 years with blood lead levels ≥5 μg/dl, predicted by age of housing — National Health and Nutrition Examination Survey, United States, 1999–2010

Housing	%	(95% CI)	%	(95% CI)	%	(95% CI)
After1978	2.5	(0.7–5.4)*	2.7	(1.1–5.1)*	1.0	(0.2–2.4)*
1950–1977	8.9	(5.0–13.9)	3.0	(1.1–5.7)*	1.1	(0.1–3.0)*
Before 1950†	25.9	(16.3–36.9)	12.5	(6.1–20.8)	3.7	(1.6–6.7)*
Refused to say or did not know	17.7	(12.0–24.5)	8.2	(4.5–12.8)	7.5	(4.6–11.1)

Abbreviation: CI = confidence interval.
* Relative standard error ≥30.
† The percentage of children living in any housing built before 1950 was 13.7% for 1999–2002, 13.9% for 2003–2006, and 13.9% for 2007–2010.

Centers for Disease Control and Prevention (MMWR), (Raymond et al, 2014)

Lead Poisoning Prevention in Children

1) Screening for lead poisoning: Screening includes determining the child's risk for high-dose lead exposure through a questionnaire (CDC guidelines, 1991). Measuring blood lead levels of children at 6 months of age (at high risk for high dose lead poisoning) (CDC guidelines, 1991). Measuring blood lead levels of children at 12-15months of age (at low risk for high dose lead poisoning) (CDC guidelines, 1991). Conducting blood lead testing follow-up for children. Screening of lead poisoning is established by the pediatric health care provider (CDC guidelines, 1991). "They Interpret blood lead results, educate parents about reducing blood lead levels and ensure that poisoned children receive appropriate medical, environmental, and social service follow-up" (CDC guidelines, 1991). A more careful follow-up for children with blood lead level **15-19 µg/dl, a full medical evaluation for children with blood lead level 20-69 µg/dl and emergency treatment for children with blood lead level > or = to 70 µg/dl is recommended** (CDC guidelines, 1991)**.**

2) Parents Education: Parents can be educated to prevent exposure to lead to reduce blood lead level in children (CDC guidelines, 1991). For example, they can be educated about "housekeeping interventions to reduce exposure to dust, interventions to reduce exposure to other sources of lead and attention to nutrition" (CDC guidelines, 1991). House intervention measures include keeping child away from access to peeling paint, window sills or chewable surfaces painted with lead based paint (CDC guidelines, 1991). For houses built before 1960, wet mop the floor once a week with a high phosphate solution (5-8% phosphate) (CDC guidelines, 1991). Do not vacuum surfaces like window sills which can disperse lead based dust. Wash toys frequently and wash their hands frequently before eating (CDC guidelines, 1991). Other interventions include planting grass around the home or other ground cover if the surrounding soil is contaminated with lead (CDC guidelines, 1991). Do not use inadequately fired pottery. Store food in the closed cans. Run cold water 5-10minutes before drinking if you are living in old housing conditions which have old or corroded pipe lines (CDC guidelines, 1991). Nutrition includes giving child diet rich in calcium and iron and to make sure they are not empty stomach as more lead is absorbed in an empty stomach (CDC guidelines, 1991).

3) Role of State and local Public Agencies: The role of the public health agencies is to screen children to assess their blood lead levels (CDC guidelines, 1991). Surveillance and risk assessment to determine the source of lead exposure in the community (CDC guidelines, 1991). To design and implement the prevention programs and to provide appropriate medical and environmental services to poisoned children (CDC guidelines, 1991). The role of the housing agencies is to provide appropriate housing to poisoned children (CDC guidelines, 1991). They are supposed to "enforce code requirements regarding lead hazards and use regulations and policies to increase the amount of safe and effective abatement performed" (CDC guidelines, 1991). Environmental agencies prevent lead poisoning by addressing environmental health hazards by following a multimedia approach (CDC guidelines, 1991). They are also responsible for "monitoring, regulatory, licensing, and enforcement activities to reduce environmental exposure to lead" (CDC guidelines, 1991).

Dietary Intervention: As per the Advisory Committee on Childhood Lead Poisoning Prevention There is no trial data which supports dietary interventions to prevent lead absorption but still Laboratory and clinical data suggests that that adequate intake of iron, calcium, and vitamin C is important for children" (Pediatrics, Volume 116, Issue 4, 2005). Adequate iron and calcium stores may decrease lead absorption, and vitamin C may increase renal excretion (Pediatrics, Volume 116, Issue 4, 2005). Although there is epidemiologic evidence that diets higher in fat and total calories are associated with higher blood lead concentrations at 1 year of age, 57the absence of trial data showing benefits and the caloric requirements of children at this age preclude recommending low-fat diets for them" (Pediatrics, Volume 116, Issue 4, 2005).

Medical Management: For children with blood lead concentration 20 to 44 µg/dl chelation therapy with succimer is a recommended therapy to lower the blood lead concentrations. (Pediatrics, Volume 116, Issue 4, 2005). There is no data supporting its use for blood lead concentrations below 45 µg/dl in children (Pediatrics, Volume 116, Issue 4, 2005). Also, chelation therapy cannot improve the cognitive function, neurodevelopmental deficits in children it can only lower the blood lead concentrations preventing from further toxicity or health complications. (Pediatrics, Volume 116, Issue 4, 2005)

CDC Recommendations for Children with confirmed Elevated Blood Lead Concentrations:

Recommendations for Children with Confirmed (Venous) Elevated Blood Lead Concentrations

Blood Lead Concentration	Recommendations
10–14 µg/dL	Lead education
	Dietary
	Environmental
	Follow-up blood lead monitoring
15–19 µg/dL	Lead education
	Dietary
	Environmental
	Follow-up blood lead monitoring
	Proceed according to actions for 20–44 µg/dL if
	A follow-up blood lead concentration is in this range at least 3 months after initial venous test; or
	Blood lead concentration increases

Blood Lead Concentration	Recommendations
20–44 µg/dL	Lead education
	Dietary
	Environmental
	Follow-up blood lead monitoring
	Complete history and physical examination
	Lab work
	Hemoglobin or hematocrit
	Iron status
	Environmental investigation
	Lead hazard reduction
	Neurodevelopmental monitoring
	Abdominal radiography (if particulate lead ingestion is suspected) with bowel decontamination if indicated
45–69 µg/dL	Lead education
	Dietary
	Environmental
	Follow-up blood lead monitoring
	Complete history and physical examination
	Lab work
	Hemoglobin or hematocrit
	Iron status
	Free EP or ZPP
	Environmental investigation
	Lead hazard reduction
	Neurodevelopmental monitoring
	Abdominal radiography with bowel decontamination if indicated
	Chelation therapy
≥70 µg/dL	Hospitalize and commence chelation therapy

Blood Lead Concentration	Recommendations
	Proceed according to actions for 45–69 μg/dL
Not Recommended at Any Blood Lead Concentration	
Searching for gingival lead lines	
Evaluation of renal function (except during chelation with EDTA)	
Testing of hair, teeth, or fingernails for lead	
Radiographic imaging of long bones	
X-ray fluorescence of long bones	

- ZPP indicates zinc protoporphyrin.

(Center for Disease control and Prevention Recommendations, 2002) (Pediatrics October 2005, VOLUME 116 / ISSUE 4)

Conclusion

In the recent decades, much has been known about the neurodevelopmental and behavioral manifestations of lead poisoning in children (WHO, 2010, pp.54). "At high levels of acute exposure, lead attacks the brain and central nervous system to cause coma, convulsions and even death (WHO, 2010, pp.54). Even if a child survives the acute or chronic poisoning, they are typically left with mental retardation and behavioral disruption (WHO, 2010, pp.54). No safe levels of lead have been discovered yet. We only know that it causes severe health consequences specifically mental effects in children even at very low doses such as <5 $\mu g/dl$. Even though some protective measures have been discovered to counteract the effects of lead poisoning such as Vitamin E, thymoquinone, 17-β-estradiol, Vitamin B12, Omega 3 etc. but we don't have much human evidences to substantiate their protective effects. "Prevention is the best way to deal with lead poisoning" (WHO, 2010, pp.54).

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