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A meta-analysis of blood lead levels in India and the attributable burden of disease

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ABSTRACT

Multiple studies in India have found elevated blood lead levels (BLLs) in target populations. However the data have not yet been evaluated to understand population-wide exposure levels. We used arithmetic mean blood lead data published from 2010 to 2018 on Indian populations to calculate the average BLLs for multiple subgroups. We then calculated the attributable disease burden in IQ decrement and Disability Adjusted Life Years (DALYs). Our Pubmed search yielded 1066 articles. Of these, 31 studies representing the BLLs of 5472 people in 9 states met our study criteria. Evaluating these, we found a mean BLL of 6.86 μg/dL (95% CI: 4.38–9.35) in children and 7.52 μg/dL (95% CI: 5.28–9.76) in non-occupationally exposed adults. We calculated that these exposures resulted in 4.9 million DALYs (95% CI: 3.9–5.6) in the states we evaluated. Population-wide BLLs in India remain elevated despite regulatory action to eliminate leaded petrol, the most significant historical source. The estimated attributable disease burden is larger than previously calculated, particularly with regard to associated intellectual disability outcomes in children. Larger population-wide BLL studies are required to inform future calculations. Policy responses need to be developed to mitigate the worst exposures.

1. Introduction

Lead is a naturally occurring metal with a range of industrial applications and well-documented adverse health effects when human exposure occurs (ATSDR, 2007). Its widespread use has resulted in significant contamination of natural and human environments (Needleman, 2004; Prüss-Üstün et al., 2010). Chronic lead exposure, even at very low levels, is associated with cognitive impairment, cardiovascular effects, anemia and low birth weight, among other adverse health outcomes (Budtz-Jørgensen et al., 2013; Lanphear, 2015; National Toxicology Program, 2012; United Nations Environment Programme, 2010). Lead exposure has been associated with decreased economic output, lower life expectancy and increased societal violence (Demayo et al., 1982; Landrigan and Goldman, 2011; Mielke and Zahran, 2012; Prüss-Üstün et al., 2010; Taylor et al., 2016).

The 2016 Global Burden of Disease, Injuries and Risk Factors Study by the Institute for Health Metrics and Evaluation (IHME) estimated that lead exposure resulted in 13.9 million Disability-Adjusted Life Years (DALYs) and 540,000 deaths in 2016 globally. The DALY metric is used in quantifying the burden of disease and is intended to capture morbidity and mortality attributable to a given disease or risk factor in a population (World Health Organization, 2016). In India alone, IHME found 4.6 million lead-attributable DALYs and nearly 165,000 deaths (IHME, 2017a).

The most significant historic source of global lead exposure was the use of tetraethyl lead in petrol in the 20th century (Bollhöfer and Rosman, 2001, 2000; Flegal et al., 1984; McConnell et al., 2015; Schwikowski et al., 2004; Véron et al., 1999). In cities where it was used, leaded petrol accounted for 80 to 90% of airborne lead pollution (Lovei, 1999). High-income countries began banning the use of lead in most fuels, as well as in paints, in the 1970s, resulting in significant declines in societal blood lead levels (BLLs) (Needleman, 2004). Leaded

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petrol was phased out in India from 1996 to 2000 and was similarly followed by BLL declines (Singh and Singh, 2006). Nichani et al. (2006), for instance, documented a 60% decrease in BLLs among residents of Mumbai from 1997 to 2002, following the full adoption of unleaded petrol. Similarly, Singh and Singh (2006) found a mean BLL decrease of 33% following the leaded petrol phase out in the urban centers of Mumbai, Chennai, Bangalore, Amritsar and Lucknow.

Despite these substantial improvements in exposure reduction, studies conducted more than a decade after the Indian phase out of leaded petrol continue to report elevated BLLs, often associated with proximity to lead smelting sites (Bellinger et al., 2005; Ghose et al., 2005; Sharma et al., 2005). Other sources of lead exposure to the Indian public have included ayurvedic medicine, cosmetics (kohl/surma) and contaminated foodstuffs (Goswami, 2013; Raviraja et al., 2010; Singh et al., 2010; Singhal, 2016). In some cases these exposures have found severely elevated levels in both occupational and non-occupational settings (Ghanwat et al., 2016; Goswami, 2013). Studies of environmental media have reported elevated lead concentrations in tube wells, rivers, and soil, among other media (Borah et al., 2010; Chatham-Stephens et al., 2013; Lokhande et al., 2012). With regard to lead-based paint, India currently maintains one of the stricter global limits of 90 ppm soluble lead (UNEP, 2017). However a 2015 study that assessed store-bought cans of enamel paint found that 46% of those tested contained > 10,000 ppm lead (Toxics Link, 2015). Additionally, some studies have posited lead-based paint as a possibly significant source of exposure (Ahamed et al., 2009; Khan et al., 2010).

Few studies have attempted to calculate population-wide mean BLLs in low- and middle-income countries (LMICs), with most focusing on discrete cohorts of exposed individuals (Olympio et al., 2017). Caravanos et al. (2014) conducted a meta-analysis of BLLs in Mexico, finding a mean concentration of 5.36 μg/dL in urban areas after the phase out of leaded petrol. A 2009 study of Chinese BLLs reviewed published papers and found a mean BLL of 7.93 μg/dL for male children and 7.69 μg/dL for female children living in urban areas (He et al., 2009).

In this assessment we reviewed existing studies on BLLs to infer broader conclusions about the population of a subset of India. We first conducted a literature review and meta-analysis of Indian BLLs published between 2010 and 2018. We then used the results to quantify the disease burden in terms of IQ decrement and attributable DALYs. The objective of this study was to quantify the potential public health impacts of lead exposure in India and to stimulate policies, education, and, where appropriate, remediation of contaminated sites.

2. Methods and approach

2.1. Literature review and data selection

We conducted a PubMed search in April 2018 using the terms blood (subheading, all fields, MeSH terms) lead (all fields, MeSH terms), and India (all fields, MeSH terms, abstract text) between 1 January 2010 and 1 January 2018 (National Library of Medicine (US), 1946). We then assessed each article by a the following 6 criteria: 1) the study published BLL data from human populations residing in India; 2) the study included at least 30 participants; 3) BLL data were derived from venous, capillary, or umbilical cord samples (bone, organ or tissue samples were excluded); 4) the utilized data were collected after 2005; 5) the study was published in English; 6) the study contained a statistical mean and standard deviation (SD) or standard error (SE) for the original data set. Articles that did not meet one or more of the above criteria were excluded from the meta-analysis.

2.2. Subgroup rational

The BLL data for each study were analyzed by certain demographic categories following the literature review. Where possible samples were disaggregated by the following four subgroups: gender, age, urbanicity, and occupation.

Age categories were defined using United Nations Children's Fund's parameters outlined in the Convention on the Rights of the Child. An individual was considered a “child” if he or she was at or below the age of 17 at the time of the original study, and an “adult” if he or she was identified as at or above 18 (United Nations General Assembly, 1989). Gender was stratified into four different categories: female, male, both and unspecified. Urbanicity was determined by a review of studies for ‘urban’ or ‘rural’ keywords. If this was not indicated in the article, the study location was used to make this determination. The Census of India classification of 400 people per square kilometer was used as the threshold for an urban area (India, 2011). Finally samples were coded as occupational if the relevant occupation substantively involved lead and therefore a higher risk of elevated BLLs. Samples comprised of battery recyclers for instance were coded as occupational, while studies of teachers were coded as non-occupational.

2.3. Identification and use of sample means

Where possible, the mean and SD/SE were derived for our specific subgroups. In cases where the subgroups used by study were incongruous with our own, the mean and SD/SE were taken for a larger subset, such as the study population.

If the same population was assessed multiple times, and treatment was not provided in between assessments, the mean for all analyses was used. In cases where the mean for all analyses could not be taken, the most conservative value (i.e. lowest) value was used. If treatment was provided to the patients with the intent of lowering BLLs, pre-treatment values were used.

Three studies assessed the BLLs of the same large cohort of untreated children at different points (Palaniappan et al., 2011; Roy et al., 2013, 2009). In this case, one study had a slightly larger sample size than the other two and all presented similar overall results with regard to BLLs. The study with the largest population was thus included and the other two were excluded.

In one case, BLLs were assessed at the same point using multiple methods having different results (Reddy et al., 2014). In this case we selected the most conservative (i.e. lowest) value.

Some studies segregated the sample exclusively based on the results of the BLL test (e.g. high and low subgroups). In these cases we took the pooled BLL for the study. In one study (Ravibabu et al., 2015), the pooled mean was not available. We therefore used both subgroups as discrete samples. Other studies disaggregated the sample by health outcome. Tiwari et al. (2012), for instance analyzed BLLs for three groups of anemic women (mild, moderate, severe) and one control group. A pooled mean was not available for the study as a whole, so we used the means for each subgroup and presented them as discrete samples.

Two studies, Goswami et al. (2013) and Chaudhary et al. (2017), found exceptionally high BLLs in children. While the exposures that result in these BLLs were not occupational they do represent an acute scenario that is not representative of the general population, thus justifying their exclusion. Goswami et al. (2013) looked at children that apply surma (kohl) as a cosmetic, which has long been identified as an acute source of lead exposure, and a control group of children that do not apply surma (Ali et al., 1978; Gogte et al., 1991). In this case a study mean was not available, so we utilized the control group and excluded the exposed group. Chaudhary et al. (2017) assessed the BLLs of 260 children (age 6 months to 12 years) attending the pediatrics outpatient department at a hospital in Lucknow, Uttar Pradesh. The study reported a mean BLL of 55.7 μg/dL (SD: 227.38). We were unable to identify a comparably high value of a general population in the literature. Other studies in Lucknow have found much lower levels. Ahamed et al. (2011) assessed the BLLs of 68 children (age 3–12 years) in Lucknow, finding BLLs of 4.23–9.86 μg/dL. An earlier study by the same authors

evaluated 200 children (age 3–12 years) finding a mean BLL of 9.3 μg/dL (range: 1.0–27.9 μg/dL) (Ahamed et al., 2009). A separate study of study of 500 pregnant women in 1996 before the phase-out of leaded petrol found an average BLL of 14.3 μg/dL (Awasthi et al., 1996). In addition to being significantly higher than other studies of Lucknow populations, the BLLs identified by Chaudhary et al. (2017) are inconsistent with the other studies we assessed from elsewhere in the country. The next highest BLL for a sample of children was 11.8 μg/dL, while half of the studies of occupationally exposed adults found lower mean BLLs. Thus this study was assumed to represent an acute exposure and was excluded from the pooled studies of children's BLLs.

The following data were extracted for each identified sample: study authors; publication date; sex of sample; state of India; age category (adult/child); urbanicity; arithmetic mean BLL; subgroup rationale (e.g. surma users, mechanics); number of participants; SD or SE; age if children.

2.4. Meta-analysis of BLLs

We pooled the arithmetic mean BLLs from each study using a Random Effects (RE) meta-analysis model. Meta-analyses are typically conducted using either an RE or Fixed Effects (FE) model. Fixed effects models are concerned with within-study variability only and do not account for variability between studies. An FE model is appropriate when the effect size for all studies is assumed to have one true value and any variance that occurs is due to sampling error (Borenstein et al., 2010). Random effects models, by contrast, assume that studies represent a random sampling of different populations within a larger 'super' population (DerSimonian and Kacker, 2007; Hedges, 1992). Thus in an RE model variance observed in the evaluated studies is assumed to be due in part to true variance between the sampled groups (Borenstein et al., 2010). Effectively this method weights each sample's effect size by its inverse variance in pooling effect sizes and confidence intervals.

In the present effort we evaluated studies drawn from discrete populations across India; each with different lifestyles and exposure scenarios. We therefore assumed that variance reflected in the samples was due, at least in part, to true differences in mean BLL concentrations. Accordingly we took the mean BLL and standard error from each sample and pooled them using a RE model. We used the metan tool in Stata 15.1 for the analysis (StataCorp. LP, 2017). The metan tool utilizes the DerSimonian and Laird method (1986) for RE and a method taken from Mantel and Haenszel (1959) to assess heterogeneity (Sterne, 2009). In addition to a pooled effect size and confidence intervals, the metan tool generates q, I^2, and tau^2 statistics. We present these in the relevant figures below. In all but one of our evaluated subgroups the p-value of the q-statistic is below 0.000, confirming heterogeneity and further indicating that an RE model was appropriate.

2.5. Calculating IQ decrement

We calculated IQ decrement resulting from pediatric lead exposure using the log-linear model described in Budtz-Jørgensen et al. (2013). The authors used internationally pooled data from seven cohorts of children to calculate a benchmark dose of 0.1–1.0 μg/dL for the loss of a single IQ point. Budtz-Jørgensen et al. (2013) re-evaluated the data and approach of Lanphear et al.'s (2005) study of low level environmental lead exposure (defined as < 7.5 μg/dL) and its impact on the developing brain. The cohorts used in both studies are comprised of school-age children (age 5–10 years) with chronically elevated BLLs. Verbal and performance tests were conducted to determine the extent of intellectual impairment and those results are compared with BLL measurements from the following four periods: early childhood (age 6–24 months); average lifetime; maximum lifetime; and concurrent (at the time of the IQ test). Lanphear et al. (2005) found that concurrent BLL measurements had the strongest relationship with IQ decrement. Budtz-Jørgensen et al. (2013) accordingly applied concurrent geometric mean BLLs to both log-linear and two-piece linear models, and found the log-linear to be the best fit. Here, we used the log-linear model presented and input the arithmetic mean BLL for the subgroup children in India to determine IQ points lost for children age 10 years and under.

2.6. Calculating DALYs

We used the meta-analysis results for non-occupationally exposed adults and children to calculate DALYs. DALYs are a metric intended to represent the disease burden in a given population and the relative contribution of disparate health outcomes to it. They are the sum of two other metrics, Years of Life Lost (YLL) and Years Lived with Disability (YLD). YLL represents early attributable mortality while YLD represents the severity and duration of a given health outcome (World Health Organization, 2016). DALYs are employed most notably by the World Health Organization (WHO) and IHME in their respective periodic global burden of disease reports (Forouzanfar et al., 2016; World Health Organization, 2016).

Lead exposure results in a number of quantifiable adverse health outcomes, however methods for integrating those outcomes into DALY calculations, as with other chemical exposures, are somewhat limited (Grandjean and Bellanger, 2017). We therefore calculated DALYs for two sequelae only: cardiovascular disease (CVD) and intellectual disability. We followed the approach outlined by Ericson et al. (2016, 2018a) and described below. DALY calculations for both sequelae utilized the total population of the all states where the individual studies were conducted.

To calculate DALYs resulting from cardiovascular disease in 2013 we used a prevalence rate calculator developed by the WHO for BLLs (Fewtrell et al., 2003). The calculator requires the geometric mean BLL and standard deviation for a given population to determine the lead-attributable fraction of CVD in that population. Values are returned for four classifications of CVD: ischemic, cerebrovascular, hypertensive, and other heart diseases. In the absence of a population-wide geometric mean, we input the pooled arithmetic mean and standard deviation for non-occupational exposures for adults to determine the attributable fraction for each case. We then applied these attributable fractions to the most recent (2013) WHO CVD DALY estimates for India to determine the number of DALYs and deaths attributable to lead exposure (WHO, 2014). We further proportionately reduced the national number of DALYs for India to the population of those states from which studies were drawn.

To calculate DALYs resulting from lead induced intellectual disability in 2012 we used the WHO calculator described above to determine a prevalence of Mild Mental Retardation (MMR) in a given population of 0–4 year olds with a given geometric mean BLL. We again input the arithmetic mean and standard deviation for children in our study (all non-occupational). As above, we used the total population of the states where studies were conducted rather the national population to develop our estimates.

The WHO calculator was developed in 2003 and uses the now antiquated classification of MMR and its associated disability weight. These values have since been revised to more accurately capture a gradient of intellectual disability. While MMR was previously quantified with a disability weight of 0.361, the revised disability weights for intellectual disability are as follows: borderline (0.0034), mild (0.1270), moderate (0.30), severe (0.3830) and profound (0.4440) intellectual disability (Colin et al., 2004; WHO, 2013). To determine the proportional composition of these subgroups, we assumed MMR was analogous to mild intellectual disability and calculated the prevalence of the remaining subgroups by extrapolating from that value. To do so, we used relative proportions provided by the WHO (2013). We then determined the number of DALYs attributable to each sequalae using the following equation:

Table 1
Mean values and relevant statistics of Indian blood lead levels by subgroup.

Subgroup	Number of samples	Mean BLL (μg/dL)	LCI	UCI	CHI^2	p	I^2	TAU^2
Occupational adults								
Female	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Male	14	48.65	38.74	58.56	12,593.47	0.000	99.9%	336.62
Non occupational								
Adult female	9	4.32	3.41	5.23	413.71	0.000	98.1%	1.62
Adult male	8	7.23	4.52	9.94	375.19	0.000	98.1%	14.66
All adults	28	7.52	5.28	9.76	29,841.92	0.000	99.9%	23.21
Unspecified	3	9.62	6.25	12.96	17.13	0.000	88.3%	7.54
Children	17	6.86	4.38	9.35	7135.25	0.000	99.8%	26.89
Urban adults	19	6.69	4.89	8.48	5642.36	0.000	99.7%	15.50
Rural adults	1	10.90	9.34	12.46	0.00	N/A	N/A	N/A
Urban children	16	6.92	4.35	9.50	7051.37	0.010	99.8%	27.19
Rural children	1	5.90	4.82	6.98	0.00	N/A	N/A	N/A

$$YLD = DW \times p$$

where:

p = prevalence
DW = disability weight

Adapted from WHO (2013).

2.7. Sensitivity analysis

To assess the sensitivity of the meta-analysis, we employed two distinct approaches. In the first we simply ran the analysis using a FE model (Bown and Sutton, 2010). In the second we utilized "leave-one-out" cross validation. In this approach, we ran the RE model successively removing a single study from the sample in each run (Arlot and Celisse, 2010). We took the squared error for each run (actual minus predicted value) and calculated the mean squared error for all runs.

To assess the sensitivity of the DALY model parameters, we calculated DALYs using IHME disability weights for intellectual disability. In our study we utilized the following WHO weights: borderline (0.0034), mild (0.1270), moderate (0.30), severe (0.3830) and profound (0.4440) (WHO, 2013). In our sensitivity analysis we used the following IHME weights: borderline (0.011), mild (0.043), moderate (N/A), severe (0.16) and profound (0.2) (Global Burden of Disease Collaborative Network, 2017).

3. Results

3.1. Results

Our PubMed search yielded 1066 studies. Of these 979 did not contain BLL data on human populations within India and were excluded. A further 56 studies did not meet one or more of the remaining criteria and were excluded. The remaining 31 studies contained 67 samples for use in our study (marked with an asterisk in the references). The 67 samples represented a population of 5472 people in 9 different Indian states (Andhra Pradesh, Karnataka, Maharashtra, Punjab, Rajasthan, Tamil Nadu, Telangana, Uttar Pradesh, and West Bengal). These states had an approximate population of 717 million people representing 56% of India's national population in 2011 (India, 2011).

3.2. Blood lead levels

Seventeen of the 67 samples were comprised of children representing 2009 individuals in 6 different states. These states had an estimated population of 560,190,596 at the time of the most recent census (India, 2011). All childhood exposures were identified as non-occupational. The samples utilized in this study were normally distributed as assessed with the Shapiro-Wilk test ($p > 0.6$). The pooled arithmetic mean for all children was 6.86 μg/dL (95% CI: 4.38–9.35).

All children in all studies were < 14 years of age. Most studies included age ranges covering multiple years and provided limited detail on the composition of the those groups. Thus, a mean age for the study population could not be determined. Of those children included in the samples, at least 24% (n = 486) were ≤2 years of age, at least 66% (n = 1318) were ≤7 years of age, at least 80% (n = 1618) were ≤10 years of age, and at least 90% (n = 1814) were ≤12 years of age. Samples comprised exclusively of children ≤2 years of age had a mean BLL of 8.49 μg/dL (95% CI: 6.18–10.8), those ≤7 years of age had a mean BLL of 6.9 μg/dL (95% CI: 2.70–10.67), those ≤10 years of age had mean BLL of 6.52 μg/dL (95% CI: 3.24–9.8), and those ≤12 years of age had a mean BLL of 6.73 μg/dL (95% CI: 4.17–9.28). It therefore appears that a younger age was associated with a higher BLL, though given the lack of specificity in the data this observation cannot be properly evaluated.

A forest plot of all samples of children is presented as Fig. 2. Mean BLLs and related statistics (confidence interval, p-value, q, I^2, and tau^2) for subgroups are presented below in Table 1. A forest plot of all samples and studies used in the analysis are presented in Fig. 1.

Fifty of the samples were comprised of adults representing 3463 individuals in nine states. These states had an estimated population of 717,577,668 at the time of the most recent census (India, 2011). Of these 22 samples were made up of 1499 individuals with occupational exposures, while the balance (n = 28) were comprised of 1964 individuals with non-occupational exposures. The pooled arithmetic mean for non-occupationally exposed adults in the study was 7.52 μg/dL (95% CI: 5.28–9.76). The samples utilized were normally distributed as assessed with the Shapiro-Wilk test ($p > 0.05$). A forest plot of all samples of adults used in the analysis is presented as Fig. 3.

With regard to subgroups, occupationally exposed adults had significantly higher BLLs than any other group. Fourteen samples (all men) represented individuals from this group and had a mean BLL of 48.65 μg/dL (95% CI: 38.74–58.56). By contrast mean BLLs for all other subgroups ranged from 4.32 to 10.9 μg/dL.

3.3. IQ decrement

Within the study population, children had an arithmetic mean BLL of 6.86 μg/dL (95% CI: 4.38–9.35). Using the log-linear model described in Budtz-Jørgensen et al. (2013) we determined that this BLL would result in an average decrement of 4 IQ points (95% CI: 2.5–4.7) for children under age 10.

3.4. Disability Adjusted Life Years (DALYs)

We calculated that cardiovascular disease attributable to lead exposure resulted in 2.7 million DALYs (95% CI: 2.3–3) in 2012 in the 9 states we reviewed. We further found that intellectual disability in

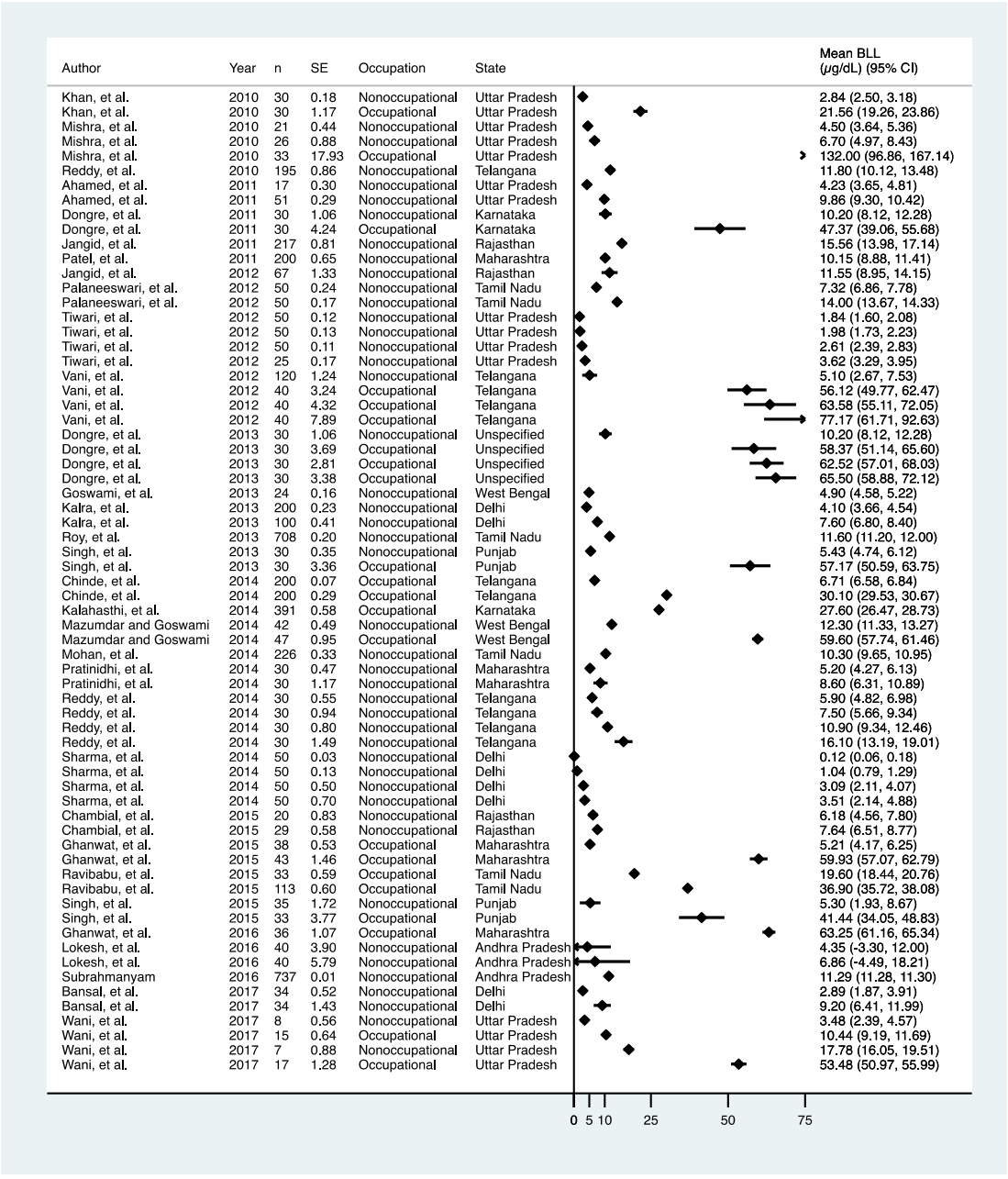

Fig. 1. Forest plot of all samples and studies used in the analysis.

children (age 0–4 years) attributable to lead exposure resulted in 2.2 million DALYs (95% CI: 1.6–2.6) in the same year in the 6 states we reviewed. Altogether we calculate 4.9 million DALYs (95% CI: 3.9–5.6) attributable to lead exposure in the geography we reviewed in 2012. Tables 2–4 summarize attributable DALYs by sequelae and calculated BLLs.

3.5. Results of the sensitivity analysis

Conducting the analysis with an FE model yielded a mean BLL of 0.87 μg/dL (95% CI: 0.81–0.93) in children and a mean BLL of 11.18 μg/dL (95% CI: 11.17–11.2) in non-occupationally exposed adults. In the case of children, a single study with both a low mean BLL (0.12 μg/dL) and a low standard error (0.126) disproportionately influenced the effect size with a weighting of 88.92%. Similarly in non-occupationally exposed adults, a single study with a mean BLL of 11.29 μg/dL and low standard error (0.0058) received a weighting of 98.58%. The RE method used here accounts for heterogeneity between samples, while the FE model does not. Thus to some extent our approach mitigates this issue.

Using the leave-one-out approach, we found that children's BLLs ranged from 6.55–7.26 μg/dL and had a mean squared error of 0.042. With regard to adults, we found that BLLs ranged from 7.13–7.77 μg/dL and had a mean squared error of 0.031.

Replacing the WHO disability weights with those used by IHME, we calculated 695,068 DALYs (95% CI: 522,191–822,872) for children in our geographic subgroup in 2012, indicating that disability weighting has a significant influence over the results.

4. Discussion

Our analysis of studies of BLLs from a geographic subgroup within India found that 4.9 million DALYs (95% CI: 3.9–5.6) were attributable to lead exposure in 2012. This is somewhat greater than the disease

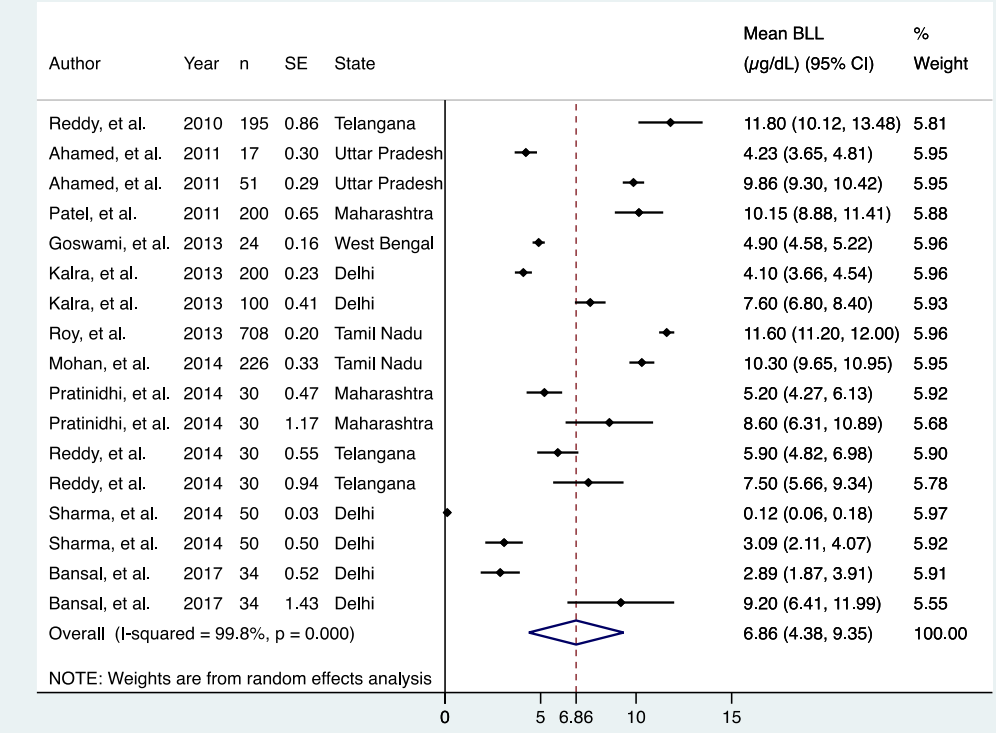

Fig. 2. Forest plot of all samples of children used in the analysis.

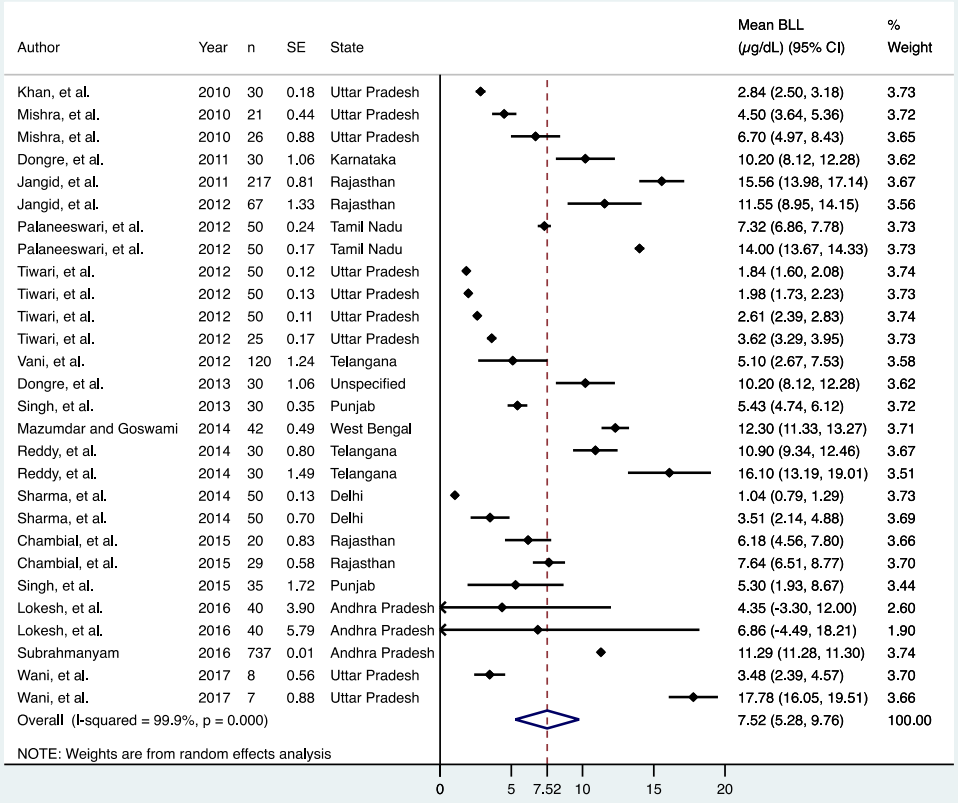

Fig. 3. Forest plot of all samples of non-occupationally exposed adults used in the analysis.

Table 2
DALYs from cardiovascular disease attributable to lead exposure in 9 Indian states in 2012.

	Hypertension	Ischemic	Cerebrovascular	Other CVD	Total DALYs (CVD)
Pooled mean (7.52 μg/dL)	93,082	1,146,922	1,199,438	286,028	2,725,470
LCI (5.28 μg/dL)	79,573	983,168	1,033,822	244,882	2,341,444
UCI (9.75 μg/dL)	103,241	1,269,450	1,322,146	316,886	3,011,723

Table 3
DALYs from intellectual disability attributable to pediatric lead exposure in 6 Indian states in 2012.

	Borderline	Mild	Moderate	Severe	Profound	Total DALYS (intellectual disability)
Pooled mean (6.86 μg/dL)	19,935	913,231	777,933	338,963	147,356	2,197,418
LCI (4.38 μg/dL)	14,973	685,936	584,312	254,598	110,680	1,650,500
UCI (9.35 μg/dL)	23,599	1,081,053	920,892	401,253	174,435	2,601,233

Table 4
Calculated DALYs (all sequalae) attributable to lead exposures in the reviewed states in India in 2012.

	Total DALYs (CVD)	Total DALYS (intellectual disability)	Total DALYs (all sequalae)
Pooled mean	2,725,470	2,197,418	4,922,889
LCI	2,341,444	1,650,500	3,991,944
UCI	3,011,723	2,601,233	5,612,955

burden calculated by IHME of 4.6 million DALYs (95% CI: 2.9–6.5) for the country as a whole in 2016 (IHME, 2017b). The discrepancy is most pronounced in children (age 0–4 years) who accounted for 33,264 DALYs (95% CI: 12,428–33,264) in IHME's analysis. In the 6 states included in our review of children's BLLs we found this group incurred more than 2.2 million DALYs (95% CI: 1.6–2.6). This discrepancy is in part due to differences in how IHME weights sequelae related to intellectual disability and how we do so here. In our sensitivity analysis we calculated DALYs using the IHME weights, finding 695,068 DALYs (95% CI: 522,191–822,872). Thus while disability weighting significantly influences the results, it alone insufficiently accounts for the discrepancy.

Looking at ages 15 years and above only, IHME calculates 4.3 million DALYs (95% CI: 2.6–6.3) attributable to lead exposure compared with the 2.7 million DALYs (95% CI: 2.3–3) found by this study. The 9 states covered by this study represent approximately 56% of the national population. Scaling IHME's values to a population of comparable size results in 2.4 million DALYs (95% CI: 1.4–3.5). Thus the results are similar for adults.

It is possible that the 2016 IHME GBD report underestimates the pediatric disease burden from lead exposure in India. In this study, we calculated a mean BLL of 6.86 μg/dL (95% CI: 4.38–9.35) for all children in our geographic subgroup. We further calculated that, using our method, a national mean BLL of < 1 μg/dL would be required to arrive at the 33,264 DALYs (95% CI: 12,428–61,466) estimated by IHME for 2016. While this value has been achieved in the United States, it would seem inconsistent with the recent blood lead exposure data examined here (Center for Health Statistics, 2017).

In the 2004 WHO global burden of disease estimate, average BLLs of 7.4 μg/dL for children and 9.8 μg/dL for adults were used to calculate the attributable burden (Prüss-Üstün et al., 2010). The researchers found a prevalence of 5.5 cases of MMR per 1000 population attributable to lead exposure based on these estimates. This is somewhat less than we found in the present effort (~13 cases of MMR per 1000) however significantly more than the ~0.27 per 1000 prevalence that would be required to reach the 33,264 DALYs calculated by IHME (using our method). Few other studies have calculated the disease burden of chemicals either globally or on a national level for India (Chatham-Stephens et al., 2013; Prüss-Ustün et al., 2011). Therefore, there is a limited basis for assessing the relative accuracy of the estimates provided here and by WHO or IHME. Given the robust literature on the adverse effects of lead on neurological development and the likely elevated BLLs in children in India, the topic could clearly benefit from further study.

A 2015 study by Iyer et al. reports on the blood lead analysis of 222,668 individuals from multiple states in India. The study provides limited statistical information and was therefore not included in the present analysis. Specifically, neither SD nor SE was included with the sample mean. However given the exceptionally large sample size, the study provides useful context for our results. For children under 2 years of age (n = 119), the authors find a mean BLL of 4.91 μg/dL and for children 2–10 years of age (n = 688) the authors find a mean BLL of 4.2 μg/dL. In adults (n = 219,303), the authors find mean BLLs of different age groups ranging from 4.24–4.95 μg/dL. In all cases, the values reported by Iyer et al. (2015) are somewhat lower than our results. Of particular interest are the geographic differences in BLLs identified by Iyer et al. (2015). For instance, the authors define a 'high' BLL as 15 μg/dL and provide the percentage of blood samples from each state that exceed this threshold. In two states, Maharashtra and Bihar, this percentage exceeds 10, while in Gujarat it is 2.5. This indicates that significant differences in BLLs exist between states. Further review of the vast dataset utilized by Iyer et al. (2015) to better understand these differences could greatly benefit other researchers.

4.1. Contemporary sources of lead contamination

A number of possible environmental sources of lead exposure are present in India, including ayurvedic medicine, contaminated food and cosmetics (Goswami, 2013; Raviraja et al., 2010; Singh et al., 2010). Lead contamination as a food safety issue was recently brought to the fore when supplies of a popular noodle product, Maggi, were found to have elevated concentrations of lead (Singhal, 2016). Additionally, lead-based enamel paint evidently remains widely available (Toxics Link, 2015).

Eighty-five percent of global lead production is used in the manufacture of storage, lighting and ignition (SLI), or lead-acid, batteries (International Lead Association, 2016). In India 700–750,000 metric tons of lead are recycled each year with perhaps 50% being recycled in the informal sector (Ericson et al., 2016; Pugazhenthy, 2017). Widespread informal used lead acid battery (ULAB) recycling is perhaps due in part to the confluence of a large informal economy and increased car ownership. Approximately 21% of India's GDP is generated in the informal sector while the number of automobiles in India nearly tripled from 55 million to 159.5 million from 2001 to 2012 (Schneider et al., 2010; Shukla et al., 2015).

Informal ULAB recycling is a prominent source of lead exposure in LMICs where primitive operations of unregulated backyard smelters

cause widespread contamination (Daniell et al., 2015; Ericson et al., 2018a, b, 2016; Haefliger et al., 2009; Prajapati, 2016). One well documented example of an extreme case of poisoning resulting from informal ULAB recycling was the deaths of 18 children in Senegal linked to informal battery smelting (Haefliger et al., 2009). Informal smelters are by definition illegal, and are accordingly particularly vulnerable to regulatory intervention. In response, these low-cost operations are often operated intermittently at different locations in different neighborhoods, resulting in the creation of new hotspots of contamination (Shen et al., 2016). Due to lead's low mobility in the environment, contamination hotspots are likely to pose a risk indefinitely without remediation (Kabala and Singh, 2001). Lead deposited from smelters and other sources, such as leaded petrol, in surface soils is readily re-suspended as dust, presenting an ongoing exposure risk (Laidlaw et al., 2012).

In addition to lead contamination, smelting operations can generate elevated concentrations of other toxic trace metals including arsenic, cadmium and mercury (Roussel et al., 2010; Stafilov et al., 2010). There are limited published studies detailing effective approaches to mitigating the health risks posed at informal ULAB sites. One recent example from Vietnam describes the construction of an industrial zone for informal workers located 1 km from residential areas. The relocation, coupled with community education and soil lead abatement work, resulted in median BLL declines of 67% in children (< 6 years of age) within one year of the intervention (Ericson et al., 2018b).

In India, the product life cycle of lead-acid batteries is regulated under India's *Batteries Management and Handling Rules of 2001*, amended in 2010 (Ministry of Environment and Forests (India), 2001, 2010). The Rules create a deposit refund system in which retailers collect used lead-acid batteries from consumers when they purchase new batteries and offer a rebate for the new purchase. ULABs in turn are required to be sold only to registered recyclers, who transport, handle and recycle the used batteries responsibly. Despite this existing legislation, informal (unregulated) ULAB recycling is widespread. One study found that among major battery manufacturers, few were able to collect > 40% of the used batteries they had produced (Prajapati, 2016).

4.2. Study limitations

The study is most significantly limited by its reliance on a relatively small number of studies (n = 31). As a result, values are inferred for a population of 717 million from the BLL results of only 3973 non-occupationally exposed people. Future studies might endeavor to collect more comprehensive biological data from a more representative cross-section of the country. It should be noted that the US National Health and Nutrition Examination Survey (NHANES) is slightly larger in size, with data collected from approximately 5000 individuals annually, and done with the specific intention of inferring results for the population as a whole (Center for Health Statistics, 2017).

A second limitation is our reliance on an older method for calculating the attributable disease burden. The prevalence rate calculator we used was developed by WHO in 2003 and has been validated, though to the best of the authors' knowledge has not been modified in the intervening years. Significantly, the WHO calculator estimates the prevalence of MMR using an older linear IQ decrement model developed by Schwartz (Schwartz, 1994). Replacing those values with the more recent Budtz-Jørgensen et al. (2013) log-linear model would likely result in a higher estimate of the prevalence of intellectual disability, and thus a higher disease burden (Ericson et al., 2018a). We do not endeavor to do so here.

5. Conclusion

Population-wide BLLs in India remain elevated despite regulatory action to mitigate the most significant sources. The attributable disease burden may be larger than previously calculated, particularly with regard to intellectual disability in children. Larger population-wide BLL studies are required to inform future calculations. Major traditional sources of lead exposure based on leaded petrol emissions and depositions are insufficient to account for the results here. Therefore, the attributable portion of disease associated with lead exposure must involve other sources, with the most likely suspect being ULAB processing. Lead exposure can result in a number of lifelong outcomes with adverse implications for individuals as well as the broader society. Consequently, there are clear societal benefits that could be accrued from more targeted investment in remediation, mitigation and policy development to mitigate the worst exposures.

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Competing interest

BE, RD, JC, SF, MR, PS, AS and RF were employed by Pure Earth while working on this manuscript. Pure Earth is a charity that works on pollution issues in low- and middle-income countries, including India.

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