Global health burden and cost of lead exposure in children and adults: a health impact and economic modelling analysis

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Summary

Background Lead exposure is a worldwide health risk despite substantial declines in blood lead levels following the leaded gasoline phase-out. For the first time, to our knowledge, we aimed to estimate the global burden and cost of intelligence quotient (IQ) loss and cardiovascular disease mortality from lead exposure.

Methods In this modelling study, we used country blood lead level estimates from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019. We estimated IQ loss (presented as estimated loss in IQ points with 95% CIs) in the global population of children younger than 5 years using the blood lead level–IQ loss function from an international pooled analysis. We estimated the cost of IQ loss, which was calculated only for the proportion of children expected to enter the labour force, as the present value of loss in lifetime income from the IQ loss (presented as cost in US dollars and percentage of gross domestic product with a range). We estimated cardiovascular deaths (with 95% CIs) due to lead exposure among people aged 25 years or older using a health impact model that captures the effect of lead exposure on cardiovascular disease mortality that is mediated through mechanisms other than hypertension. Finally, we used values of statistical life to estimate the welfare cost of premature mortality (presented as cost in US dollars and percentage of GDP). All estimates were calculated by World Bank income classification and region (for low-income and middle-income countries [LMICs] only) for 2019.

Findings We estimated that children younger than 5 years lost 765 million (95% CI 443–1098) IQ points and that 5 545 000 (2 305 000–8 271 000) adults died from cardiovascular disease in 2019 due to lead exposure. 729 million of the IQ points lost (95·3% of the total global IQ loss) and 5 004 000 (90·2% of total) cardiovascular disease deaths due to lead exposure occurred in LMICs. IQ loss in LMICs was nearly 80% higher than a previous estimate. Cardiovascular disease deaths were six times higher than the GBD 2019 estimate. The global cost of lead exposure was US$6·0 trillion (range 2·6–9·0) in 2019, which was equivalent to 6·9% (3·1–10·4) of the global gross domestic product. 77% (range 70–78) of the cost was the welfare cost of cardiovascular disease mortality, and 23% (22–30) was the present value of future income losses from IQ loss.

Interpretation Our findings suggest that global lead exposure has health and economic costs at par with $PM_{2·5}$ air pollution. However, much work remains to improve the quality of blood lead level measurement data, especially in LMICs.

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Introduction

Although global lead exposure has declined substantially since the phasing out of leaded gasoline,[1] sources of lead exposure remain plentiful, especially in low-income and middle-income countries (LMICs).[2,3] Lead is one of WHO's ten chemicals of major public health concern,[4] and lead exposure is ranked fourth among major environmental health risk factors after ambient particulate matter air pollution, household air pollution from solid fuels, and unsafe household drinking water, sanitation, and handwashing according to the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019.[5,6] Lead is the single chemical with by far the largest quantified health effects globally,[7] which could be influenced by research so far and data availability.

Health effects caused by lead exposure included by GBD 2019[6] are cardiovascular disease, chronic kidney disease, and idiopathic developmental intellectual disability. Cardiovascular disease accounted for 94% of mortality and 82% of disability-adjusted life-years (DALYs). However, the estimate of cardiovascular disease mortality in the GBD studies is limited to the effect of lead exposure through increased blood pressure, and the idiopathic developmental intellectual disability estimate does not account for effects on the intelligence quotient (IQ) of the vast majority of children.[8,9]

In this study, we aimed to provide a new estimate of global cardiovascular disease mortality attributable to lead exposure using an alternative method to GBD studies to capture effects that could be mediated through mechanisms other than blood pressure. We also

Research in context

Evidence before this study

We searched PubMed, BioMed Central, JSTOR, and other reference databases for research articles on lead exposure as a worldwide environmental health risk published in English between inception and March 23, 2023. We used the search terms "blood lead", "lead exposure", "health effects/burden", "IQ loss", "cardiovascular disease", "economic cost", "IQ and earnings", "systematic review", "meta-analysis" "low- and middle-income countries", and combinations of these terms. We found blood lead level measurement studies in low-income and middle-income countries (LMICs) summarised in a systematic review; neuropsychological impairment in young children, as evidenced by international pooled analyses of the effects of blood lead levels on intelligence quotient (IQ); and cardiovascular disease mortality in adults, as evidenced by an assessment of cardiovascular disease mortality and blood lead level studies. Despite this evidence, no previous research was identified that has quantified the global health burden and cost of IQ loss in young children and cardiovascular disease mortality in adults from lead exposure. Previous research that has estimated IQ loss in young children and its cost is limited to LMICs, has not included high-income countries as a group, is based on blood lead level estimates that are well over a decade old, and includes blood lead level estimates from very few low-income countries. Previous research that has estimated the global cardiovascular disease burden has captured only the effect of lead exposure on cardiovascular disease mortality that is mediated through blood pressure and has not captured more direct effects on cardiovascular health.

Added value of this study

This study applied complete global blood lead level estimates from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019 to estimate IQ loss in the child population aged 0–4 years and cardiovascular disease mortality in adults aged 25 years or older in both LMICs and high-income countries; it used an alternative methodology to the one used in GBD 2019 to estimate cardiovascular disease mortality that is mediated through other mechanisms than increased blood pressure; and estimated for the first time the global cost of IQ loss and cardiovascular disease mortality from lead exposure.

Implications of all the available evidence

The estimate of the global health burden of lead exposure in this study places lead exposure as an environmental risk factor at par with $PM_{2·5}$ ambient and household air pollution combined, and ahead of unsafe household drinking water, sanitation, and handwashing. This finding is in contrast to that of GBD 2019, which ranked lead exposure as a distant fourth environmental risk factor, due to not accounting for IQ loss in children, other than idiopathic developmental intellectual disability in a small subset of children and reporting a substantially lower estimate of adult cardiovascular disease mortality. A central implication for future research and policy is that LMICs bear an extraordinarily large share of the health and cost burden of lead exposure; consequently, improved quality of blood lead level measurements, lead exposure identification, research, policies, and practices are very urgently needed to address that burden.

estimated global IQ loss due to lead exposure in the entire child population aged younger than 5 years both in LMICs and high-income countries, and we estimated the economic cost of both of these health effects. Consequently, this study presents an alternative to GBD 2019's estimate of global cardiovascular disease mortality, an update of the estimate of children's IQ loss in LMICs by Attina and Trasande,[10] an extension of estimated IQ loss to the global level by including high-income countries, and, to our knowledge, for the first time, an estimate of the global economic cost of cardiovascular disease mortality and IQ loss due to lead exposure.

See Online for appendix

For **blood lead levels from GBD 2019** see https://leadpollution.org

Methods

Data sources and study population

The most common indicator used to estimate global lead exposure is blood lead level.[11] We considered two sets of global blood lead level estimates. Ericson and colleagues[12] estimated mean blood lead levels in children younger than 18 years in 34 LMICs and in adults 18 years or older in 37 LMICs from their systematic review of 520 blood lead level measurement studies published between 2010 and 2019. These countries account for 80% of the population in all LMICs. GBD 2019 estimated mean blood lead levels in 183 LMICs and high-income countries for the year 2019,[6] accounting for 99·9% of the global population. The blood lead level estimates are based on a combination of 554 studies in 84 countries from 1970 to 2017 and modelling of blood lead levels. The modelling used covariates with blood lead level predictive ability. These covariates included urban population share, number of road vehicles per capita, year of leaded-gasoline phase-out, and the Socio-demographic Index, reflecting total fertility, education level of the population aged 15 years and older, and income per capita.[6] Ericson and colleagues[12] report somewhat higher population-weighted mean blood lead levels than GBD 2019 (appendix p 1).

We used mean blood lead levels from GBD 2019 by country, as this set of estimates is the most complete on a global scale. These blood lead level estimates are for children up to the age of 18 years, and whether they also pertain to adults is unclear. We applied the blood lead level estimates to both children and adults because the difference in blood lead level estimates in the study by Ericson and colleague[12] for children and adults was only 5% in the ten countries with the most blood lead level measurement studies. These ten countries account for

60% of the population in LMICs. In the sensitivity analysis, we also report estimates of global health effects by using blood lead levels from the study by Ericson and colleagues[12] for the ten countries with six or more blood lead level measurement studies.

We calculated that population-weighted mean blood lead level was 4·6 µg/dL in LMICs and 1·3 µg/dL in high-income countries in 2019 from the country estimates by GBD 2019.[6]

Mean blood lead levels without information about the blood lead level distribution hide the extent of elevated blood lead levels in a population. However, SDs are not reported at https://leadpollution.org. Therefore, we estimated each country's SD from the mean blood lead levels and SDs reported by Ericson and colleagues[12] (appendix p 2) and undertook sensitivity analyses of the impact of changes in SD on our estimated global health effects.

One issue is the extent to which blood lead level distributions implied by the mean blood lead levels and SDs account for subpopulations in hot spots with high lead exposure and with high occupational exposures. Mean blood lead levels by Ericson and colleagues[12] are based on studies of background blood lead levels that exclude hot spots and groups with identified occupational exposures to provide estimates of the general population's blood lead levels. Ericson and colleagues therefore conclude that their mean blood lead level estimates are conservative.[12] GBD 2019 appears to follow a similar approach.[6] Nevertheless, by characterising blood lead level distributions with the log-normal distribution function, as we did, the implied populations with highly elevated blood lead levels could represent those in geographical hot spots of lead exposure or with occupational exposures. To assess the impact of potentially underestimating the population with highly elevated blood lead levels on our estimates of global health effects, we did a sensitivity analysis of health effects for the population with blood lead levels greater than 10 µg/dL and greater than 20 µg/dL.

Health effects

We drew on four bodies of literature to estimate the major global health effects of lead exposure and their cost: IQ loss in children younger than 5 years; cardiovascular disease mortality in adults aged 25 years or older; lifetime income effects of IQ loss at ages younger than 5 years; and valuation of adult premature mortality. We relied on literature reviews, meta-analyses, and pooled analyses for estimating health effects; on commonly applied income effects of IQ loss; and on a commonly applied benefit-transfer method for the value of statistical life to estimate the welfare cost of premature mortality.

Neuropsychological effects in children

A major measurable neuropsychological effect of lead exposure in early childhood is IQ loss. GBD 2019 included the effect of lead exposure on idiopathic developmental intellectual disability in children in terms of IQ declining below a particular threshold due to lead exposure.[6] GBD 2019 did not account for the effect of lead exposure on children whose IQ did not decline below that threshold, which is the case for the vast majority of children.[6] Bellinger[8] argues that the effect on this majority of children who do not fall below that intellectual disability threshold probably contributes more to the total burden of lead exposure than the increase in incidence of idiopathic developmental intellectual disability.

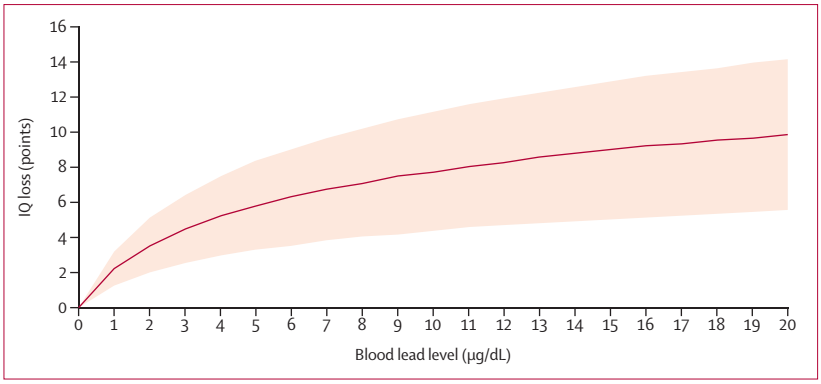

Figure 1: **IQ loss from lead exposure in early childhood**
Blood lead level IQ loss function from Crump and colleagues.[13] The blood lead level is mean lifetime blood lead level in children younger than 5 years. The solid line is the central estimate and the shaded area is the 95% CI as per the study by Crump and colleagues.[13] IQ=intelligence quotient.

We estimated IQ loss (presented with 95% CIs) in the entire child population younger than 5 years in each country from the blood lead level–IQ loss function in the study by Crump and colleagues[13] (appendix p 2). The loss function is estimated from a pooled analysis of seven cohort studies from Australia, Mexico, the USA, and former Yugoslavia with a wide range of blood lead levels from 2·4 µg/dL to 49·3 µg/dL.[14] Children were followed up from infancy to the age of 5–10 years, with periodic measurements of blood lead levels and IQ tests administered when the children were aged about 5 years (10 years in one of the studies).[14,15] We note that the IQ loss function is for IQ loss during the first 5 years of a child's life. Further loss of IQ from lead exposure that could occur after the age of 5 years is therefore not captured.

Figure 1 presents IQ loss from blood lead level during the first 5 years of life from the study by Crump and colleagues[13] with the solid line showing the central estimate and the shaded area showing the 95% CI. As no safe blood lead level has been established, we applied a theoretical minimum risk exposure level (TMREL) of 0 µg/dL with a sensitivity analysis for the TMREL of 1 µg/dL. The US Environmental Protection Agency in a 2020 economic analysis of lead abatement used three alternative IQ loss models, two of which applied a zero blood lead level threshold.[16]

We estimated lost IQ points (ΔIQ) from lead exposure in each country in 2019 by:

$$\Delta IQ = \sum_{i=0}^{n}[\beta \ln(\frac{x_i + x_{i+1}}{2} + 1) P_i]\ C_k/k$$

in which the first two terms are the IQ loss function from the study by Crump and colleagues[13] with β=3·246 (95% CI 1·88–4·66), P_i is the proportion of children with blood lead concentration in the range x_i to x_{i+1} calculated from the log-normal distribution function,[17] and C_k is the child population below k years of age (appendix p 3).

We define C_k/k as the population of children younger than 5 years in 2019 with k=5 for consistency with the age of blood lead level measurements and IQ tests in the studies of the pooled analyses. Alternatively, C_k can be defined as the birth cohort in 2019 adjusted for the mortality rate of children younger than 5 years with k=1. However, the choice of C_k makes very little difference to estimated global IQ loss. Globally estimated IQ loss is 2·5% less for C_k/k with k=1 than for k=5.

We estimated the cost of IQ loss in US dollars and purchasing power parity-adjusted international dollars in 2019 as the present value of loss in lifetime income from the IQ loss. We chose a lifetime income effect of 2·0% per IQ point. The effect size is the same as used by the study by Attina and Trasande[10] and between the size settled for by the study by Grosse and Zhou,[18] and the recent estimate by the US Environmental Protection Agency.[16] Lifetime income is estimated based on an assumed future annual income growth rate of 1·5% in high-income countries and 2·5% in LMICs, and a discount rate twice the rate of income growth as proposed by the World Bank for project economic analysis.[19] Cost of IQ loss was calculated only for the proportion of children expected to enter the labour force. Income for a person in the labour force in 2019 was calculated as the labour compensation share of gross domestic product (GDP) multiplied by GDP and divided by the total labour force (appendix pp 3–4).

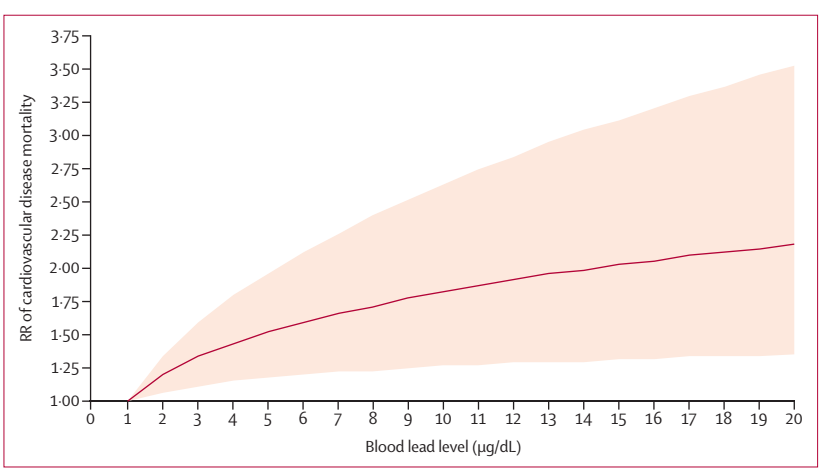

Figure 2: **Relative risk of cardiovascular disease mortality from blood lead level of 0–20 μg/dL**
Blood lead level cardiovascular disease mortality risk function from Ruiz-Hernandez and colleagues[23] and Lanphear and colleagues[24].The solid line is the average of the central estimates of relative risk from the studies by Ruiz-Hernandez and colleagues[23] and Lanphear and colleagues[24] and the shaded area is the 95% CI from the same studies.

Cardiovascular disease mortality in adults

GBD 2019 estimated cardiovascular disease mortality from lead exposure through the effect on blood pressure.[6] However, studies have found that lead exposure has cardiovascular effects beyond effects mediated through blood pressure.[9,20–22] One approach to capture these effects is to rely on studies that directly estimate cardiovascular disease mortality from lead exposure. Brown and colleagues[11] present four such studies with a continuous blood lead level–cardiovascular disease mortality response function.[23–26] All four studies analysed blood lead levels in the adult US population from one or more of the nationally representative National Health and Nutrition Examination Surveys from 1988 to 2010.

Brown and colleagues[11] derived the relative risk (RR) of cardiovascular disease mortality from lead in blood from the four studies:

$$RR = e^{\beta \log x}(\frac{BLL_1}{BLL_0}) \text{ for } BLL_1 \geq BLL_0 \geq 1$$

which we transform to natural logarithm and arrive at:

$$RR = BLL^{\beta_T} \text{ for } BLL = BLL_1 \geq 1 \text{ μg/dL and } BLL_0 = 1 \text{ μg/dL}$$

with β_T ranging from 0·104 to 0·35 (appendix pp 4–5) and BLL representing the blood lead level. Of the four studies, the blood lead level distributions in the sample used by Ruiz-Hernandez and colleagues[23] and in the unrestricted sample used by Lanphear and colleagues[24] are closest to the distributions in LMICs. We therefore chose these two studies for estimating global cardiovascular disease deaths from lead exposure. Figure 2 presents the RR of cardiovascular disease mortality that we applied to estimate global cardiovascular disease deaths from lead exposure. The solid line is calculated from β_T=0·261, which is the average of the central β_T in the study by Ruiz-Hernandez and colleagues[23] (0·245) and in the study by Lanphear and colleagues[24] (0·278). The shaded area is 95% CI with the lower bound (β_T=0·1019) and upper bound (β_T=0·421) from the studies by Ruiz-Hernandez and colleagues[23] and Lanphear and colleagues.[24] No safe amount of lead exposure has been established for cardiovascular disease in previous research articles. We therefore adjusted the RR function with a linear relationship for blood lead levels in the range of 0–2 μg/dL with a TMREL of 0 μg/dL and used the unadjusted function for the sensitivity analysis (appendix p 5).

Cardiovascular disease mortality with 95% CIs from lead exposure in each country in 2019 was estimated by the population attributable fraction (PAF) of baseline cardiovascular disease mortality, approximated by:

$$PAF = \sum_{i=0}^{n} P_i[RR(\frac{x_i + x_{i+1}}{2}) - 1] / \sum_{i=0}^{n} P_i[RR(\frac{x_i + x_{i+1}}{2}) - 1] + 1)$$

where RR is from equation 3 with β_i=0·261 (0·101–0·421), and P_i is the proportion of adults with blood lead level in the range x_i to x_{i+1} calculated from the log-normal distribution function[17] (appendix p 6). We also calculated the cardiovascular disease mortality rate from lead exposure as cardiovascular disease deaths from lead exposure in 2019 per 100 000 population.

Using the studies by Ruiz-Hernandez and colleagues[23] and Lanphear and colleagues[24] to estimate global cardiovascular disease mortality in 2019 based on estimated blood lead level in 2019, as we did, entails an assumption of steady-state blood lead levels over a period of time preceding death. The studies used a one-time measurement of blood lead level from the National Health and Nutrition Examination Surveys from 1988 to 2004. However, lifetime lead exposure was substantially higher for most of the adult participants in the studies than the blood lead levels measured at the time of the surveys.[27] Therefore, it remains uncertain whether the effect sizes for cardiovascular disease mortality from lead exposure estimated by the studies reflect the high lead exposures early in life, or whether the effect sizes are mainly associated with the relative steady blood lead levels in the decade (or decades) just preceding death. None of the studies provide a definite answer to this question, but Lanphear and colleagues[24] extended the follow-up period to a median of 19·3 years from the time of blood lead level measurement, or three decades from the high lead exposures in the 1970s, and still found that the one-time blood lead level measurement is a significant predictor of cardiovascular disease mortality.

We estimated the cost of cardiovascular disease mortality by using the value of a statistical life estimated for each country, as in the World Bank[28] and the *Lancet* Commission on pollution and health[29] (appendix p 7). The value of a statistical life is on average 58 times GDP per capita in low-income countries, 75 times GDP per capita in lower-middle-income countries, 90 times GDP per capita in upper-middle-income countries, and 97 times GDP per capita in high-income counties. The cost of cardiovascular disease mortality estimated by the value of a statistical life is a welfare cost and not economic productivity cost. We compared the size of the welfare cost to GDP (in US and international dollars and as a percentage of GDP) simply to illustrate the magnitude of the cost. However, premature mortality also has a productivity cost. A quarter of the individuals estimated to die from cardiovascular disease due to lead exposure are of working age younger than 65 years according to GBD 2019.[6,30]

We estimated the total cost of lead exposure as the sum of the cost of IQ loss and the cost of cardiovascular disease mortality.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	Mean blood lead level (µg/dL)
World Bank income classification	
Low income	6·6
Lower-middle income	5·4
Upper-middle income	3·3
Low income and middle income	4·6
High income	1·3
Worldwide	4·1
World Bank regions	
East Asia and Pacific	3·4
Europe and central Asia	2·3
Latin America and Caribbean	3·6
Middle East and north Africa	5·2
South Asia	6·2
Sub-Saharan Africa	5·1

The mean blood lead level was calculated using the the Global Burden of Diseases, Injuries, and Risk Factors Study 2019.[6] Only low-income and middle-income countries are included in the World Bank regions.

Table 1: **Population-weighted mean blood lead levels in 2019**

Results

Mean blood lead levels were highest in low-income countries and declined with income per capita as per our calculations based on the country estimates by the GBD 2019.[6] Regionally in LMICs, mean blood lead levels were lowest in Europe and central Asia and highest in south Asia, Middle East and north Africa, and sub-Saharan Africa (table 1).[6] We characterised the blood lead level distribution by a log-normal distribution function[17] and estimated that 47% of children in LMICs have blood lead levels higher than 5 µg/dL and 28% higher than 10 µg/dL. This finding is similar to Ericson and colleagues' estimates.[12] By contrast, an estimated 5% of children in high-income countries had blood lead levels higher than 5 µg/dL and 1% higher than 10 µg/dL. The situation was similar for adults.

We estimated that the global IQ loss in children younger than 5 years due to lead exposure was 765 million (95% CI 443–1098) IQ points in 2019. 95·3% (729 million of 765 million IQ points) of the loss was in LMICs (table 2).

The IQ loss is estimated to have cost US$1·4 trillion (range 0·8–2·0) or international $2·4 trillion (1·4–3·5). The cost is the present value of future income losses from the IQ loss in 2019. The size of the cost is equivalent to 1·6% (range 0·9–2·3) of the 2019 global GDP (table 2), or 1·8% (1·1–2·6) of purchasing power parity-adjusted GDP. The cost increases as a share of GDP from 1·2% (range 0·7–1·7) in high-income countries to 8·3% (4·8–11·9) in low-income countries.

The cost of IQ loss is for loss in 2019 only. The IQ loss that children experienced over the first 5 years of life was five times larger than the loss experienced in the single year of 2019. The average IQ loss over these first years of life is 5·9 (95% CI 3·4–8·5) IQ points per child in

	Million IQ points lost (95% CI)	Cost of IQ loss as percentage of GDP
World Bank income classification		
Low income	155 (90–222)	8·3% (4·8–11·9)
Lower-middle income	388 (224–556)	3·8% (2·2–5·5)
Upper-middle income	186 (108–267)	1·7% (1·0–2·5)
Low income and middle income	729 (422–1046)	2·2% (1·3–3·2)
High income	36 (21–52)	1·2% (0·7–1·7)
Worldwide	765 (443–1098)	1·6% (0·9–2·3)
World Bank regions		
East Asia and Pacific	137 (79–197)	1·7% (1·0–2·5)
Europe and central Asia	23 (13–33)	1·4% (0·8–2·0)
Latin America and Caribbean	50 (29–72)	2·1% (1·2–2·9)
Middle East and north Africa	54 (31–77)	2·9% (1·7–4·2)
South Asia	230 (133–330)	3·5% (2·0–5·0)
Sub-Saharan Africa	235 (136–337)	6·3% (3·7–9·1)
Low income and middle income	729 (422–1046)	2·2% (1·3–3·2)

Point estimates and 95% CIs of IQ points lost are calculated from the IQ loss function in figure 1. Point estimates and ranges (in parentheses) of cost are calculated based on the point estimates and 95% CIs of IQ points lost. Cost as percentage of GDP is the total cost of IQ points lost in countries in income group or region divided by total GDP in the same countries. Only low-income and middle-income countries are included in the World Bank regions. GDP=gross domestic product. IQ=intelligence quotient.

Table 2: **Estimated IQ loss in children younger than 5 years in 2019 and associated cost by country-income classification and for low-income and middle-income countries by region**

	Cardiovascular disease deaths (95% CI)	Cost of cardiovascular disease mortality as percentage of GDP
World Bank income classification		
Low income	345 000 (149 000–493 000)	3·0% (1·3–4·3)
Lower-middle income	2 081 000 (884 000–3 034 000)	5·6% (2·4–8·2)
Upper-middle income	2 577 000 (1 058 000–3 888 000)	8·5% (3·5–12·8)
Low income and middle income	5 004 000 (2 092 000–7 415 000)	7·8% (3·2–11·8)
High income	542 000 (214 000–856 000)	3·8% (1·5–6·0)
Worldwide	5 545 000 (2 305 000–8 271 000)	5·3% (2·1–8·2)
World Bank regions		
East Asia and Pacific	2 004 000 (827 000–3 008 000)	8·7% (3·6–13·1)
Europe and central Asia	542 000 (218 000–834 000)	13·8% (5·6–21·3)
Latin America and Caribbean	327 000 (135 000–490 000)	4·6% (1·9–7·0)
Middle East and north Africa	339 000 (144 000–495 000)	6·8% (2·8–9·9)
South Asia	1 393 000 (599 000–2 005 000)	5·6% (2·4–8·1)
Sub-Saharan Africa	399 000 (169 000–583 000)	2·6% (1·1–3·8)

Point estimates and 95% CIs of cardiovascular disease mortality are calculated from the cardiovascular disease mortality function in figure 2. Point estimates and ranges (in parentheses) of cost are calculated based on the point estimates and 95% CIs of cardiovascular disease mortality. Cost as percentage of GDP is total cost of cardiovascular disease mortality in countries in income group or region divided by total GDP in the same countries. Only low-income and middle-income countries are included in the World Bank regions. GDP=gross domestic product.

Table 3: **Estimated cardiovascular disease deaths and associated cost by country-income classification and for low-income and middle-income countries by region in 2019**

LMICs at the mean blood lead level in LMICs in 2019, as can be seen from figure 1. The cost of this loss is as high as 11·8% (6·8–17·0) of lifetime income for children who will participate in the labour force, as each lost IQ point reduces income by 2%. We estimated 5 545 000 (95% CI 2 305 000–8 271 000) cardiovascular deaths in adults from lead exposure in 2019 (table 3). By contrast, GBD 2019[6] estimated 0·85 million cardiovascular disease deaths in 2019 due to lead exposure. As many as 5 004 000 (90·2%) of the estimated 5 545 000 global cardiovascular disease deaths were in LMICs, of which 4 658 000 (93·1%) were in lower-middle-income and upper-middle-income countries. Of the estimated 5 004 000 cardiovascular deaths in LMICs, 3 397 000 (67·9%) were in east Asia and Pacific and south Asia (table 3).

Deaths from cardiovascular disease from lead exposure per 100 000 population in 2019 were lowest in high-income countries (44·8 per 100 000) and low-income countries (51·6 per 100 000), followed by lower-middle-income countries (71·5 per 100 000) and upper-middle-income countries (90·4 per 100 000). Regionally, in LMICs, the rate was 36·1 per 100 000 population in sub-Saharan Africa, 53·3 per 100 000 thousand in Latin America and Caribbean, 75·9 per 100 000 in south Asia, 86·9 per 100 000 in Middle East and north Africa, 95·8 per 100 000 in east Asia and Pacific, and 136·9 per 100 000 in Europe and central Asia.

The cost of global cardiovascular disease mortality from lead exposure was US$4·6 trillion (range 1·9–7·1) in 2019, or international $7·9 trillion (3·2–12·1). The cost was US$2·5 trillion (range 1·0–3·8) or international $5·3 trillion (2·2–8·0) in LMICs. The estimated cost is equivalent to 5·3% (range 2·1–8·2) of the global GDP in 2019, or 5·9% (2·4–9·1) of purchasing power parity-adjusted GDP. The estimated cost was 7·8% (range 3·2–11·8) of GDP in LMICs, increasing as a share of GDP from 3·0% (1·3–4·3) in low-income countries to 8·5% (3·5–12·8) of GDP in upper-middle-income countries. It was highest in LMICs in Europe and central Asia at 13·8% (range 5·6–21·3) of GDP and lowest in sub-Saharan Africa at 2·6% (1·1–3·8) of GDP (table 3).

The total global cost of lead exposure—ie, the cost of IQ loss and cardiovascular disease mortality combined—was estimated at US$6·0 trillion (range 2·6–9·0) in 2019, or international $10·4 trillion (4·6–15·6). 77% (range 70–78) of this cost is the welfare cost of cardiovascular disease mortality and occurred in 2019, whereas 23% (22–30) is the present value of future income losses from IQ loss in 2019. The cost in LMICs was estimated at US$3·2 trillion (range 1·5–4·8), or international $7·0 trillion (3·2–10·5). Globally, the estimated cost was equivalent to 6·9% (range 3·1–10·4) of the 2019 global GDP. The estimated cost was 10·1% (range 4·5–15·0) of GDP in LMICs, increasing as a share of GDP from 5·0% (2·2–7·7) in high-income countries to 11·3% (6·1–16·2) of GDP in low-income countries. The estimated cost was highest

in the LMICs of Europe and central Asia at 15·2% (6·4–23·2) and lowest in Latin America and the Caribbean at 6·7% (3·1–9·9) of GDP (table 4).

Sensitivity analyses indicated that our estimates of global health effects are robust with respect to a change in the TMREL from 0 to 1 µg/dL, a change in the SD of mean blood lead levels of 35% for LMICs and 15% for high-income countries, the use of mean blood lead levels from Ericson and colleagues[12] for the ten countries with six or more blood lead level measurement studies, and truncating the lead exposure–response functions for IQ and cardiovascular disease mortality from blood lead level of 20 µg/dL. The latter implies the assumption that there is no incremental effect on IQ or cardiovascular disease risk of blood lead levels beyond 20 µg/dL. The estimates of global health effects are sensitive to a change in the TMREL to 1 µg/dL for high-income countries, which reduced estimated cardiovascular disease mortality and IQ loss by 17–20% in this group of countries. Truncating the exposure–response functions from 10 µg/dL reduced estimated IQ loss and cardiovascular disease mortality by 11% in LMICs and minimally in high-income countries. The cost of IQ loss was very sensitive to the choice of discount rate relative to the rate of future income growth. Our estimated cost of IQ loss is conservative compared with most of the alternative income growth and discount rates we considered. For example, reducing the discount rate from 2 to 1·5 times the rate of income growth increased estimated cost of IQ loss by 54% in LMICs (appendix pp 7–8).

Discussion

Although global blood lead levels have declined substantially since the phase-out of leaded gasoline,[1] several sources of lead exposure remain, resulting in adverse health and economic effects, particularly in LMICs. Our total estimated cost of lead exposure is equivalent to 6·9% of the global GDP (central estimate). This cost exceeds the combined cost of $PM_{2·5}$ ambient and household air pollution estimated by the World Bank[28] at 6·1% of the global GDP in 2019.

The highest cost of IQ loss as a share of GDP was in low-income countries and sub-Saharan Africa due to a combination of high blood lead levels and high birth rates.

The highest cost of cardiovascular disease mortality from lead exposure as a share of GDP, and the highest cardiovascular disease mortality rate per 100 000 population due to lead exposure, was in the LMICs of Europe and central Asia region. The high cost and mortality rate is due to the high susceptibility to cardiovascular disease and cardiovascular mortality in these countries' aging populations, whereas the main reason for the low cardiovascular disease mortality rate in sub-Saharan Africa is a young population and low baseline cardiovascular disease rate.

The cost of IQ loss exceeds the cost of mortality only in low-income countries and is about the same in lower-middle-income countries, whereas the cost of mortality exceeds the cost of IQ loss in upper-middle-income countries and high-income countries. The cost shares are greatly influenced by population age distribution. Low-income countries and lower-middle-income countries have higher birth rates; therefore, a larger share of their total population is younger than 5 years than in upper-middle-income countries and high-income countries. A larger share of the population in upper-middle-income countries and high-income countries are older people and more susceptible to cardiovascular mortality than is the case in low-income countries and lower-middle-income countries.

The limitations of this study revolve around the accuracy of global blood lead level estimates, given that blood lead level measurements are absent for many countries, the absence of robust studies of income effects of IQ in LMICs, the uncertainties of lifetime income projections for children younger than 5 years, the uncertainties of applicable discount rate of lifetime income losses, and the uncertainty of the applicability to LMICs of cardiovascular disease mortality effects of blood lead levels estimated from the USA. Some of these limitations are addressed through sensitivity analyses, whereas the last issue can be resolved only through undertaking studies in LMICs. An additional limitation is that our study does not capture the detrimental effects of lead exposure other than IQ loss and cardiovascular

	Total cost as a percentage of GDP
World Bank income classification	
Low income	11·3% (6·1–16·2)
Lower-middle income	9·4% (4·6–13·6)
Upper-middle income	10·2% (4·5–15·3)
Low income and middle income	10·1% (4·5–15·0)
High income	5·0% (2·2–7·7)
Worldwide	6·9% (3·1–10·4)
World Bank regions	
East Asia and Pacific	10·5% (4·6–15·6)
Europe and Central Asia	15·2% (6·4–23·2)
Latin America and Caribbean	6·7% (3·1–9·9)
Middle East and North Africa	9·7% (4·5–14·1)
South Asia	9·1% (4·4–13·1)
Sub-Saharan Africa	8·9% (4·8–12·9)
Low income and middle income	10·1% (4·5–15·0)

Total cost is the sum of the cost of IQ points lost and cardiovascular disease mortality. Cost as percentage of GDP is total cost in countries in income group or region divided by total GDP in the same countries. Only low-income and middle-income countries are included in the World Bank regions. GDP=gross domestic product. IQ=intelligence quotient.

Table 4: **Estimated total cost of lead exposure by country-income classification and for low-income and middle-income countries by region in 2019**

disease mortality. Our estimates of global cost are therefore conservative.

The strengths of our study are that we relied on long-established evidence of IQ loss from lead exposure, estimated IQ loss for the entire child population younger than 5 years rather than only for children at the lower end of the IQ scale in terms of idiopathic developmental intellectual disability, for the first time provided an indication of the possibly very large magnitude of global cardiovascular disease mortality from lead exposure through mechanisms other than blood pressure, and found through sensitivity analyses that our results are robust, with the exception that our estimated cost of IQ loss could indeed be conservative.

We estimated that 90% of cardiovascular disease mortality and 95% of IQ loss from lead exposure in 2019 occurred in LMICs. Consequently, our estimates hinge crucially on the accuracy of estimates of population blood lead levels in LMICs. Globally, we find that our estimates are minimally affected by the use of blood lead level estimates from GBD 2019[6] versus Ericson and colleagues[12] for the ten countries with six or more blood lead level measurement studies. These countries account for as much as 60% of the population in LMICs. However, the correlation between the two sets of blood lead level estimates is low. Therefore, estimates of cardiovascular disease mortality and IQ loss show large differences for separate countries depending on choice of blood lead level estimates. Moreover, few, if any, blood lead level measurement studies in LMICs are nationally representative.

Consequently, there is a risk that blood lead level estimates by Ericson and colleagues[12] and GBD 2019[6] might be biased downwards or upwards. Given the magnitude of our estimates of health effects in LMICs, it is imperative that nationally representative periodic blood lead level measurements be institutionalised. These measurements could, for example, be incorporated into existing household surveys, such as the Demographic Health Surveys or the Multiple Indicator Cluster Surveys, which are routinely administered in most of the LMICs approximately once every 5 years.

Our estimated IQ loss in LMICs is 80% higher than that of Attina and Trasande,[10] despite our study's substantially lower population-weighted mean blood lead level (4·6 µg/dL *vs* 8·1 µg/dL). This is because of differences in the IQ loss function. However, our estimated cost of IQ loss is only slightly higher than the estimate by Attina and Trasande[10] because they applied the lifetime income effect of IQ loss to all children regardless of whether they eventually will join the labour force.

Our estimate of the cost of the IQ loss is equivalent to 2·2% (range 1·3–3·2) of GDP in LMICs in 2019. This estimate might be very conservative due to the sensitivity of the estimate to the discount rate relative to the future growth rate of income. We also noted that although the cost of lead exposure in the single year in 2019 is substantial, the cost of children's lead exposure over their first 5 years of life was much higher. We estimated that children in LMICs on average show a loss of 5·9 IQ points from lead exposure in early childhood, causing an estimated lifetime income loss of nearly 12%. This loss represents a substantial detrimental effect on the human capital value of children in LMICs on top of the cognitive and lifetime income effects of, for example, early childhood undernutrition[31] and inadequate psychosocial stimulation[32] that many children in LMICs still experience. In view of the magnitude of our estimated IQ and lifetime income loss, studies of income effects of IQ loss in LMICs, similar to those on stunting and inadequate psychosocial stimulation,[31,32] are essential. Incorporation of IQ loss of the general child population in future GBD estimates would help to determine the total burden of lead exposure more accurately.[8] One potential approach is to assign disability weight to human capital impairment or by using other options such as noted in the study by Shaffer and colleagues.[9]

Our central estimate of global cardiovascular disease mortality from lead exposure of 5·5 million deaths in 2019 is six times higher than the central estimate (0·85 million) in GBD 2019, close to the number of estimated global deaths from $PM_{2·5}$ ambient and household air pollution combined (6·45 million), and more than three times the number of estimated global deaths from unsafe household drinking water, sanitation, and handwashing (1·66 million).[6] Our estimate of cardiovascular disease mortality from lead exposure could, however, be incomplete. Models by Lanphear and colleagues[23] and Ruiz-Hernandez and colleagues[24] were adjusted for hypertension, which means that our estimate does not include the effect of lead exposure on cardiovascular disease mortality mediated through hypertension. Moreover, studies have found a significant effect (95%) of blood lead level on all-cause mortality.[24–27] Lanphear and colleagues[24] estimate all-cause mortality from lead in blood to be 60% higher than estimated cardiovascular disease mortality, suggesting that total mortality from lead exposure globally could substantially surpass our estimate.

Our estimate strongly suggests that lead exposure in LMICs has cardiovascular effects beyond those mediated through blood pressure, but the applicability to LMICs of effect sizes estimated from the USA remains to be confirmed. 20 years ago, the world faced the same questions regarding estimation of long-term global mortality from $PM_{2·5}$ ambient air pollution from studies primarily from the USA, which helped to initiate such studies in LMICs. Studies of cardiovascular disease mortality from lead exposure are very much needed in LMICs. Moreover, further investigation is needed to assess the extent to which concurrent adult blood lead level is an adequate predictor of cardiovascular disease mortality risk versus bone lead levels. This investigation is especially important given that blood lead levels have

declined substantially in all regions of the world in recent decades[1] and that almost all measurement studies in LMICs are of lead in blood.

With our new estimate of cardiovascular disease mortality, as much as 77% (range 70–78) of our estimated total cost of lead exposure is the welfare cost of cardiovascular disease mortality, whereas 23% (22–30) is the present value of future income losses from IQ loss in 2019. The cost of IQ loss exceeds the cost of mortality only in low-income countries where birth rates are high and baseline cardiovascular disease mortality rates are low. Although the welfare cost of mortality and the productivity cost measure of IQ loss are not directly comparable, the relative magnitudes of cost nevertheless show that cardiovascular disease mortality is a health effect of lead exposure to be taken very seriously. Reducing environmental lead exposure has almost immediate benefits for young children in terms of preventing cognitive impairment. Reducing exposure also has long-term cardiovascular disease benefits in adulthood for children of all ages. However, it remains unknown to what extent reducing exposure can also benefit today's adults who have had lifelong lead exposure. Some relevant studies have shown that EDTA (edetic acid) chelation therapy very effectively removes lead from the body[33] and reduces the risk of adverse cardiovascular events over a 5-year follow-up period in patients with previous myocardial infarction.[34,35] These are encouraging findings that could suggest that reducing lead exposure could benefit the adults of today.

In conclusion, our estimated magnitude of global health effects and costs of lead exposure lends urgency to reducing population exposure to lead. First and foremost, periodic national blood lead level measurements must be institutionalised. These measurements must be accompanied by comprehensive source identification as well as relevant legislative responses in order to effectively combat lead pollution and exposure. It should also be noted that global health effects and costs of other chemicals than lead could also be substantial and largely remains to be quantified at national population levels.

Contributors

BL and ES-T contributed to the conception and design of this work and to the acquisition, analysis, and interpretation of its underlying data. Both authors drafted the work or critically revised it, and both have accessed and verified the data. The authors had final responsibility for the decision to submit the manuscript for publication and agree to be accountable for all aspects of the work.

Declaration of interests

We declare no competing interests.

Data sharing

The data collected and analysed are from the sources identified in the references section and are available in those sources. Requests for further information about the analyses conducted for this Article should be directed to the corresponding author of this Article.

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