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Global burden of intellectual disability resulting from prenatal exposure to methylmercury, 2015

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ABSTRACT

We describe analyses to estimate the global burden of disease associated with methylmercury (MeHg). An intelligence quotient < 70, indicating intellectual disability (ID), was selected as the critical disease, maternal hair Hg concentration during pregnancy selected as the critical exposure biomarker, and a dose-effect relationship of an 0.18 point IQ reduction per μg/g increase in maternal hair Hg was assumed, based on a meta-analysis. A systematic review was conducted to obtain country-specific data on the distribution of maternal hair Hg concentrations. The country-specific incidence of MeHg-associated ID was calculated, and a random effects model was used to impute the incidence for countries for which no exposure data could be found. The global burden of MeHg-associated ID was quantified in terms of Disability-Adjusted Life Years (DALYs) using the World Health Organization (WHO) Global Health Estimates methodology, and presented by 14 subregions. In 2015, the global total for MeHg-associated cases of ID was 226,655; 210,074 of these cases (93%) were mild cases of ID. The highest rate of ID (6 cases per 100,000 population) was found in the Americas D subregion. The global DALY estimate was 1,963,869. The Western Pacific B subregion contributed the most to this total (696,417), although the Americas D subregion had the greatest rate (54 DALYs per 100,000 population). The burden of disease associated with MeHg is therefore highly subregion-dependent even in areas that are geographically related. The priority given to reducing this burden can therefore be expected to vary considerably by subregion depending on other health needs.

1. Introduction

The neurodevelopmental toxicity of methylmercury (MeHg) is well-known (Karagas et al., 2012). Neurodevelopmental toxicity is considered to be the most sensitive outcome of methylmercury exposure and the development *in utero* the most sensitive period of exposure (Joint FAO/WHO Expert Committee on Food Additives, 2007). Ingestion is the primary pathway of exposure, and contaminated seafood and rice are the most important components of the diet with regard to MeHg.

Recently, the World Health Organization (WHO) published first-ever estimates of the global and regional burden of foodborne disease (Havelaar et al., 2015). The study showed that the 31 considered foodborne hazards caused 600 million illnesses, resulting in 420,000 deaths and 33 million Disability-Adjusted Life Years (DALYs). The burden estimates for the foodborne chemicals however only revealed the tip of the iceberg, as only three chemicals and toxins could be included, i.e., aflatoxins, cassava cyanide, and dioxins (Gibb et al., 2015). In this paper, we add to this work by quantifying the contribution of exposure to MeHg to the global burden of disease, expressed as DALYs.

2. Materials and methods

Several inputs were combined to estimate the disease burden

Abbreviations: AFR, African Region; AMR, Region of the Americas; ASGM, Artisanal and small scale gold mining; DALY, Disability-adjusted life year; EMR, Eastern Mediterranean Region; EUR, European Region; ID, Intellectual disability; MeHg, Methylmercury; SEAR, South-East Asia Region; WHO, World Health Organization; WPR, Western Pacific Region

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associated with MeHg: the target disease caused by MeHg, the critical biomarker of exposure, the dose-effect relationship between the target disease and the critical biomarker concentration, the distribution of the critical biomarker concentration in the target population of each country, the incidence of the target disease in each country, disease features including age at onset, case fatality rate, and duration, and the disability weight(s) associated with the disease. The rationale for the decisions reached about each of these inputs is described in the following sections.

2.1. Critical disease

The evidence supporting a causal role for MeHg in human health outcomes varies substantially across organ systems and health endpoints (World Health Organization, 2004). There is robust evidence that children's cognitive development is the most sensitive endpoint, and that gestation is the critical exposure window (Rice et al., 2003; World Health Organization, 2004; ATSDR: Toxicological Profile for Mercury, 1999). We selected loss of full-scale IQ points as the critical endpoint with regard to MeHg toxicity. The estimation of a global burden of disease requires that a disease or diseases be specified. For methylmercury, the disease is “intellectual disability” (ID). To estimate the burden of disease associated with methylmercury, we estimated the numbers of children whose IQ scores would be expected, as a result of prenatal MeHg exposure, to fall within the categories of intellectual disability (ID) specified in the International Classification of Disease-9th Revision Clinical Modification: mild (IQ 50–69), moderate (IQ 35–49), severe (IQ 20–34), and profound (IQ < 20) (World Health Organization, 2017).

2.2. Critical biomarker of exposure

Mercury has been measured in a variety of biological matrices, including hair, blood (including cord blood), urine, and nails (toenail, fingernail). The concentration of mercury in hair is the exposure metric that is most frequently measured in epidemiological and surveillance studies. Speciation studies have shown that 80–90% of the total mercury in hair is MeHg (National Research Council, 2000), and most studies report total hair mercury concentrations. We selected maternal hair mercury concentration during pregnancy or at birth as the critical biomarker.

2.3. Dose-effect relationship

To relate maternal hair mercury concentration to ID, we selected the result of a meta-analysis of data from the three major prospective studies of prenatal MeHg exposure and children's cognitive development (Faroe Islands, Seychelles Islands, New Zealand studies) reported by Axelrad et al. (2007). This analysis estimated that a child's IQ score declines 0.18 points (95% CI: -0.38, -0.01) for each μg/g increase in maternal hair mercury concentration during pregnancy.

2.4. Country-specific estimates of MeHg exposure

We conducted a systematic review in order to identify studies that provide data on the distributions of the mercury biomarker concentrations in different countries or regions of countries (see Bellinger et al., 2016, for details of the search process). In the 305 papers identified, mercury biomarker data (hair or blood) were reported for 80 countries.

We abstracted the following information from each paper: country, the population sampled (e.g., miners, residents near a mining site, coastal, urban/rural, subsistence fisherman, general population, etc.), the biological matrix measured (hair, blood, cord blood), total number of individuals sampled, age, sex, mercury biomarker concentrations (including measure of central tendency, dispersion, and range, if available). (See Supplementary Tables in Bellinger et al., 2016 for the raw data).

For countries for which multiple studies provided information, one study was chosen as most representative. We favored studies with the following characteristics:

1) a nationally-representative sample
2) described how the study sample was drawn from the base population
3) the study sample was not occupationally-exposed to mercury, did not live in an area likely to be polluted with mercury (i.e., a region of artisanal gold mining), and was not selected based on clinical status, i.e., a disease potentially related to MeHg exposure)
4) measured hair mercury concentration; if blood mercury was measured but the study was selected, on the basis of other characteristics, as the most representative study, hair mercury concentration was estimated from blood mercury concentration using a conversion factor (250:1) (ATSDR: Toxicological Profile for Mercury, 1999). If cord blood mercury concentration was measured, it was first transformed to maternal blood concentration using a conversion factor (1.7:1) (Stern and Smith, 2003)
5) provided information about both the central tendency and variability of the biomarker distribution (e.g., standard deviation, interquartile range, centile values, etc.)
6) provided information specifically about prenatal mercury exposure. Priority of subgroups in terms of relevance to prenatal exposure to mercury: pregnant women, women of reproductive age, adult women, adult males, children

2.5. Country-specific incidence of intellectual disability

In the absence of methylmercury exposure, we assume that IQ scores in each country have a mean of 100 and a standard deviation of 15. Assuming that 0.18 IQ points are lost per μg/g increase in maternal hair mercury during pregnancy, we used the distribution of hair mercury concentrations to calculate the percentages of children in each country whose IQ scores would be shifted, as a result of MeHg exposure, into the four categories of ID (i.e., mild, moderate, severe, profound). For most countries, limited data were available on the hair mercury distribution. Therefore, it was assumed that hair mercury levels were normally distributed, and the Microsoft Excel function NORMDIST was used to determine the proportion of the population with hair mercury levels above specified levels based on the reported mean and standard deviation (Poulin and Gibb, 2008). Finally, the incidences of different levels of severity of MeHg-associated ID in a country (i.e., number per 100,000 births) were calculated using birth rate data (www.cia.gov/library/publications/the-world-factbook/rankorder/2054/html). The Supplementary Tables in Bellinger et al. (2016) present the data used to estimate incidence rates.

In line with the WHO estimates of the global burden of foodborne disease, we aggregated our country-level estimates into global, regional, and subregional estimates. There are six WHO regions, including the African Region (AFR), the Region of the Americas (AMR), the Eastern Mediterranean Region (EMR), the European Region (EUR), the South-East Asia Region (SEAR), and the Western Pacific Region (WPR). Countries within a region are further classified into subregions by mortality levels: A: Very low child, very low adult mortality; B. Low child, low adult mortality; C. Low child, high adult mortality; D High child, high adult mortality; and E: High child, very high adult mortality (Ezzati et al., 2002). The countries included in each subregion are provided in Devleesschauwer et al. (2015).

2.6. Imputation

For countries for which no studies could be found that provided information on population MeHg biomarker concentrations and for

which an incidence rate of MeHg-associated ID could not be calculated, a log-Normal random effects model was used to impute it, as described by Devleesschauwer et al. (2015). Briefly, the model was fitted to the available data, and incidence values for countries with no data were imputed based on the resulting posterior predictive distributions. For countries in a subregion where none of the countries had data, the incidence was imputed as 10,000 random draws from a log-Normal distribution reflecting a "random" country within a "random" subregion, with the uncertainty interval describing the variability between and within regions. For countries in a subregion where at least one of the other countries had data, the incidence was imputed as 10,000 random draws from a log-Normal distribution reflecting a "random" country within the concerned subregion, with the uncertainty interval describing the variability within regions.

2.7. Disability-adjusted life years

The case fatality rate of ID was assumed to be zero, therefore only years lived with disability contributed to the DALYs associated with prenatal MeHg exposure. Years lived with disability for a given health state are given by the product of the number of incident cases with the health state's duration and disability weight. In this study, the two considered health states were mild and moderate ID. The age-of-onset of MeHg-associated ID was assumed to be zero (i.e., birth), and the disease was assumed to be life-long; the duration was therefore given by the life expectancy at age of birth. Life expectancies at birth by country for the year 2015 were derived from the 2017 revision of the United Nations World Population Prospects (https://esa.un.org/unpd/wpp/Download/Standard/Population/). Disability weights reflect on a scale from 0 to 1 the relative reduction in quality of life associated with the health state. The WHO Global Health Estimates disability weights for ID were used: 0.127 for mild ID and 0.293 for moderate ID (World Health Organization, 2017).

The DALY calculations were implemented in a probabilistic framework, using 10,000 Monte Carlo simulations to propagate uncertainty from the incidence estimation process (Devleesschauwer et al., 2015). The resulting uncertainty distributions were summarized by their median and a 95% uncertainty interval defined as the distribution's 2.5th and 97.5th percentile. As for incidence, country-level DALY estimates were aggregated into global, regional, and subregional estimates and presented as such. Population estimates for the year 2015 from the United Nations World Population Prospects 2017 Revision were used to calculate incidence and DALY rates per 100,000 population.

3. Results

The median estimates of the numbers of incident cases of MeHg-associated ID by each of the 14 considered subregions and the corresponding 95% uncertainty intervals are displayed in Table 1. These estimates include only mild and moderate ID, as estimates of the numbers of severe and profound ID associated with MeHg were negligible. Globally, the number of cases of MeHg-associated mild ID greatly exceeded the number of cases of moderate ID. Within WPR, the number of mild ID cases exceeded the number of moderate cases by more than 20-fold.

Table 2 presents the median rates per 100,000 population separately for mild ID and moderate ID. Within AMR, the range of the rate of MeHg-associated intellectual disability was almost an order of magnitude (0.7 and 6.0 per 100,000 for AMR A and AMR D, respectively). The median rate per 100,000 of mild and moderate ID combined was ≥ 5 cases per 100,000 in AFR D, AMR D, and WPR B.

Table 3 shows the DALYs associated with MeHg-associated ID. Globally, the median estimate of the total was 1,963,869. As would be expected from the numbers of incident cases, the WPR B subregion made the largest contribution to the global total, accounting for more than one third of global DALYs. However, the number of DALYs per 100,000 population was greatest in the AMR D subregion, exceeding by approximately 8-fold the DALYs per 100,000 population in the subregion with the lowest number (AMR A).

4. Discussion

The major findings of these analyses are that, worldwide, prenatal exposure to MeHg accounts for nearly one quarter of a million incident cases of intellectual disability each year, with the vast majority being cases of mild ID (i.e., $50 < IQ < 70$). These cases account for nearly 2 million DALYs. To place this in context, in the Global Burden of Disease (GBD), 2017 study, the global prevalence of developmental intellectual disability in 2015 was calculated to be approximately 190 million cases, resulting in nearly 25 million DALYs (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). Estimates for MeHg-associated ID are however not available from the GBD.

The variability among subregions with respect to the total number of DALYs is substantial with the largest contribution to the DALY total coming from countries in the WPR B subregion (Cambodia, China, Cook Islands, Fiji, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Micronesia (Federated States of), Mongolia, Nauru, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam). This is however in part a reflection of the size of the population in WPR B. When DALYs are expressed on a per capita basis, however, it is countries in the AMR D subregion, consisting of Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, and Peru, that bear the greatest burden of MeHg-associated ID.

Our findings illustrate the importance of conducting the analyses at the subregion level. For both incident case rate and DALYs, the lowest and the highest estimates were for subregions of the Americas making the overall estimates for the Americas region as a whole misleading.

It is important to acknowledge the limitations of estimations of disease burden. These limitations pertain to assumptions and decisions made at each step of the estimation process.

The data on mercury biomarker concentration was based on nationally-representative sampling for only three countries (USA, Republic of Korea, Germany). For some countries large birth cohort studies were available (New Zealand, Faroe Islands, Seychelles Islands), and the distributions of hair mercury concentrations in those cohorts are likely to be good proxies for those that would be obtained in a nationally-representative sample. For each country, we selected the study that seemed to provide data most representative of the exposures within its population, but this was likely more successful for some countries than for others.

Data on biomarker concentrations in a country's population did not always include the concentrations specifically in pregnant women, the population subgroup of greatest concern with respect to MeHg developmental neurotoxicity. In such cases, it was necessary to rely on proxy measures of hair concentration during pregnancy that vary in their suitability, such as hair or blood mercury biomarker concentrations in all adult women or in adult men. Standard conversion factors were applied in translating proxy measures into hair mercury concentrations. These factors necessarily involve some error. Although a ratio of 250:1 is routinely used in risk assessments to convert a hair mercury concentration to a blood mercury concentration, values as high as 344 have been reported (Yaginuma-Sakurai et al., 2012).

When suitable data for a country were not available, they were imputed using mercury biomarker concentrations measured in another country in the same subregion or, failing that, from data at the global level. An alternative strategy would have been to base the imputation on a country within the same Global Environmental Monitoring System (GEMS)/food consumption database (www.who.int/nutrition/landscape_analysis/nlis_gem_food/en). Although the GEMS classification system groups countries with similar consumption patterns, it is

Table 1
Estimated number of incident cases (median and 95% uncertainty interval) of MeHg-associated intellectual disability (ID) by region and subregion, 2015.

Region	Mild ID	Moderate ID	Total
Africa (AFR)	41,235 (6965–261,750)	4064 (2325–7204)	45,306 (9276–268,911)
AFR D	21,568 (3858–133,016)	1993 (1165–3480)	23,553 (5018–136,462)
AFR E	19,654 (3070–128,734)	2073 (1161–3727)	21,726 (4230–132,462)
America (AMR)	23,869 (8632–55,527)	1575 (677–3342)	25,482 (9301–58,851)
AMR A	2320 (770–5410)	418 (135–994)	2740 (912–6362)
AMR B	15,700 (5585–35,887)	919 (392–1956)	16,616 (5983–37,740)
AMR D	5677 (2072–15,963)	239 (134–417)	5920 (2209–16,376)
Eastern Mediterranean (EMR)	19,999 (6453–93,035)	1887 (1134–3103)	21,939 (7601–96,318)
EMR B	4746 (1774–12,565)	337 (169–651)	5102 (1943–13,120)
EMR D	15,082 (4207–81,021)	1542 (934–2559)	16,647 (5152–83,474)
Europe (EUR)	11,174 (4135–29,451)	1140 (536–2291)	12,370 (4671–31,375)
EUR A	5828 (2117–13,423)	475 (193–1030)	6307 (2298–14,395)
EUR B	3166 (1069–13,638)	380 (214–659)	3556 (1286–14,141)
EUR C	1901 (688–4396)	286 (108–641)	2189 (795–5015)
Southeast Asia (SEAR)	22,718 (8023–52,049)	3391 (1193–7833)	26,154 (9271–59,646)
SEAR B	6267 (2095–14,589)	563 (195–1309)	6834 (2289–15,832)
SEAR D	16,468 (5848–38,027)	2829 (997–6526)	19,289 (6913–43,989)
Western Pacific (WPR)	81,823 (27,961–188,066)	3827 (1470–8523)	85,643 (29,470–196,380)
WPR A	2199 (805–5572)	147 (73–287)	2349 (878–5826)
WPR B	79,495 (27,218–182,893)	3679 (1395–8237)	83,168 (28,632–191,203)
World	210,074 (78,752–607,928)	16,038 (8435–29,701)	226,655 (87,386–633,509)

Table 2
Estimated incidence rates per 100,000 population (median and 95% uncertainty interval) of MeHg-associated intellectual disability (ID) by region and subregion, 2015.

Region	Mild ID	Moderate ID	Total
Africa (AFR)	4 (0.7–26)	0.4 (0.2–0.7)	5 (0.9–27)
AFR D	5 (0.8–28)	0.4 (0.2–0.7)	5 (1–29)
AFR E	4 (0.6–25)	0.4 (0.2–0.7)	4 (0.8–26)
America (AMR)	2 (0.9–6)	0.2 (0.07–0.3)	3 (0.9–6)
AMR A	0.6 (0.2–1)	0.1 (0.04–0.3)	0.7 (0.2–2)
AMR B	3 (1–7)	0.2 (0.07–0.4)	3 (1–7)
AMR D	6 (2–17)	0.3 (0.1–0.5)	6 (2–18)
Eastern Mediterranean (EMR)	3 (1–14)	0.3 (0.2–0.5)	3 (1–15)
EMR B	3 (1–7)	0.2 (0.09–0.4)	3 (1–7)
EMR D	3 (0.9–17)	0.3 (0.2–0.5)	4 (1–18)
Europe (EUR)	1 (0.5–3)	0.1 (0.06–0.3)	1 (0.5–3)
EUR A	1 (0.5–3)	0.1 (0.04–0.2)	1 (0.5–3)
EUR B	1 (0.5–6)	0.2 (0.09–0.3)	2 (0.5–6)
EUR C	0.8 (0.3–2)	0.1 (0.05–0.3)	0.9 (0.3–2)
Southeast Asia (SEAR)	1 (0.4–3)	0.2 (0.06–0.4)	1 (0.5–3)
SEAR B	2 (0.6–4)	0.2 (0.06–0.4)	2 (0.7–5)
SEAR D	1 (0.4–2)	0.2 (0.06–0.4)	1 (0.4–3)
Western Pacific (WPR)	4 (1–10)	0.2 (0.08–0.5)	5 (2–10)
WPR A	1 (0.5–3)	0.09 (0.04–0.2)	1 (0.5–4)
WPR B	5 (2–11)	0.2 (0.08–0.5)	5 (2–11)
World	**3 (1–8)**	**0.2 (0.1–0.4)**	**3 (1–9)**

based on more than 60 food categories, some of which are informative with regard to intake of MeHg (e.g., cereal grains and flours, marine fish) but most of which are not (e.g., fruiting vegetables, roots and tubers, milks, sugars). Furthermore, because of the greater number of clusters within the GEMS classification system, there would be a greater number of clusters without data, increasing the overall uncertainty.

Data for some countries were limited to mercury biomarker concentrations measured in population subgroups suspected of having high exposures. For example, many of the studies conducted in South American countries, for example, focused on people living in areas in which artisanal and small scale gold mining (ASGM) is conducted (Gibb, O'Leary, 2014). Rather than considering the individuals sampled to be representative of the entire population, we used data from the referent groups assembled for these studies or studies of individuals who, based on geography, were not likely to be impacted directly by ASGM activities. However, population subgroups exposed to ASGM are likely to be affected disproportionately by MeHg and a failure to consider them in estimating the burden of disease within a country in which such ASGM is common would result in an underestimate. The number of individuals directly involved in ASGM is 10–15 million worldwide, including 3 million women and children, mostly in Africa, Asia, and South America (United Nations Environment Programme, 2013). The number exposed collaterally to MeHg dispersed as a result of these activities is likely to be many-fold higher.

Impairment of children's cognitive development is generally considered the most sensitive indicator of MeHg toxicity in humans, but it is possible that a greater burden of disease is associated with some other endpoint, such as cardiovascular toxicity (Roman et al., 2011).

The method for estimating burden of disease requires that endpoints be defined categorically rather than dimensionally. In the case of ID, it is assumed that no burden accrues unless Full-Scale IQ is reduced, as a result of exposure to MeHg, to a value below 70. For instance, a decrease in IQ from 90 to 89 is detrimental, but it would not be an increase in disease burden simply because it does not increase ID (IQ < 70). Studies of many chronic disease risk factors, however, show that, at a population level, burden accrues even at values below those used to diagnose clinical disease. For example, the positive relationship between blood pressure and risk of ischemic heart disease is evident even at systolic and diastolic values below 140 and 90 mmHg, respectively (Lewington et al., 2002). Similarly, it is not only when IQ is reduced to below 70 that an individual's disease burden increases. In cost-benefit analyses based on Full-Scale IQ, for example, monetary costs are assigned to each IQ point lost, regardless of whether the final IQ score is below or above 70 (e.g., Grosse et al., 2002). Our calculations therefore likely underestimate the true health burden associated with MeHg (Sly et al., 2016). In a similar vein, Salkever (2014) reports that the IQ impacts from lead exposure are understated.

For consistency with the WHO estimates of the global burden of foodborne disease, the disability weights used in this study were adopted from the WHO Global Health Estimates study (World Health Organization, 2017). Of note, the disability weights for intellectual disability in the WHO study are substantially higher than the weights used in the GBD study (Salomon et al., 2015), i.e., 0.127 vs 0.043 for mild ID, and 0.293 vs 0.100 for moderate ID. Applying the GBD weights would thus have resulted in a lower DALY estimate of around 670,000 DALYs.

We assumed that the relationship between maternal hair mercury concentration and IQ is linear over the entire range of hair mercury levels, and, furthermore, the same dose-response relationship exists in all countries. Social factors do not appear to modify this relationship

Table 3
Disability-adjusted life years (median and 95% uncertainty interval) due to MeHg-associated intellectual disability (ID) by region and subregion, 2015.

Region	Mild ID	Moderate ID	Total	Total per 100,000 population
Africa (AFR)	326,198 (55,099–2070,622)	74,171 (42,430–131,480)	400,451 (97,400–2201,318)	40 (10–222)
AFR D	170,620 (30,522–1052,252)	36,367 (21,263–63,511)	207,039 (51,846–1115,628)	44 (11–235)
AFR E	155,473 (24,287–1018,378)	37,837 (21,185–68,028)	193,298 (45,455–1086,404)	37 (9–210)
America (AMR)	188,823 (68,286–439,258)	28,740 (12,358–60,987)	218,122 (80,867–500,143)	22 (8–51)
AMR A	18,355 (6094–42,797)	7622 (2467–18,133)	26,034 (8657–60,409)	7 (2–16)
AMR B	124,195 (44,182–283,888)	16,763 (7154–35,695)	140,954 (51,496–318,140)	27 (10–61)
AMR D	44,912 (16,392–126,275)	4367 (2444–7606)	49,314 (18,865–133,611)	54 (21–146)
Eastern Mediterranean (EMR)	158,207 (51,051–735,969)	34,435 (20,698–56,634)	193,347 (71,966–792,038)	30 (11–122)
EMR B	37,545 (14,036–99,402)	6149 (3079–11,881)	43,982 (17,145–109,565)	24 (9–60)
EMR D	119,313 (33,282–640,935)	28,138 (17,040–46,695)	147,995 (50,413–686,425)	32 (11–147)
Europe (EUR)	88,394 (32,712–232,978)	20,812 (9776–41,805)	109,846 (42,771–268,188)	12 (5–29)
EUR A	46,104 (16,748–106,188)	8669 (3520–18,797)	54,829 (20,202–123,851)	12 (5–28)
EUR B	25,047 (8455–107,889)	6937 (3903–12,028)	32,227 (12,418–118,158)	14 (5–50)
EUR C	15,039 (5444–34,773)	5212 (1977–11,702)	20,294 (7453–45,821)	9 (3–19)
Southeast Asia (SEAR)	179,718 (63,467–411,747)	61,891 (21,770–142,960)	242,356 (85,478–550,758)	13 (4–29)
SEAR B	49,574 (16,573–115,413)	10,275 (3554–23,882)	59,903 (20,196–138,414)	17 (6–40)
SEAR D	130,276 (46,265–300,819)	51,638 (18,191–119,101)	182,193 (65,567–413,182)	12 (4–26)
Western Pacific (WPR)	647,277 (221,190–1487,732)	69,850 (26,832–155,553)	716,868 (248,741–1640,906)	38 (13–88)
WPR A	17,396 (6371–44,076)	2691 (1330–5242)	20,145 (7727–48,828)	12 (5–30)
WPR B	628,863 (215,311–1446,813)	67,149 (25,456–150,333)	696,417 (241,240–1592,639)	41 (14–93)
World	**1661,831 (622,979–4809,130)**	**292,703 (153,952–542,058)**	**1963,869 (780,769–5272,924)**	**27 (11–72)**

significantly (Davidson et al., 1999, 2004), though certain genetic polymorphisms might (Julvez et al., 2013). Because we lacked country-specific data on the distributions of IQ scores, we assumed that the distributions have the same mean and standard deviation in all countries.

We used the dose-effect relationship reported by Axelrad et al. (2007) to estimate incidence rates of ID, but recent evidence suggests that the slope is underestimated unless the potentially beneficial impact of seafood consumption on child development is taken into account (Oken et al., 2005, 2008; Budtz-Jorgensen et al., 2007; Strain et al., 2008; Lederman et al., 2008). Axelrad et al. (2007) did not take negative confounding into account (Choi et al., 2008) so the present analysis might underestimate the disease burden associated with MeHg-associated ID.

5. Conclusion

In conclusion, the burden of disease associated with prenatal exposure to MeHg varies considerably from one subregion to another. In absolute terms, the greatest burden is borne by countries in WPR B, while the greatest per capita burden is borne by countries in AMR D. The priority given to reducing this burden in light of other health needs can be expected to vary considerably by subregion.

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Competing interests

The authors declare they have no actual or potential competing financial interests.

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