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Benefits of cooperation among large-scale cohort studies and human biomonitoring projects in environmental health research: An exercise in blood lead analysis of the Environment and Child Health International Birth Cohort Group

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Abstract

A number of prospective cohort studies are ongoing worldwide to investigate the impact of foetal and neonatal exposures to chemical substances on child health. To assess multiple exposure (mixture) effects and low prevalence health outcomes it is useful to pool data from several studies and conduct mega-data-analysis. To discuss a path towards data harmonization, representatives from several large-scale birth cohort studies and a biomonitoring programme formed a collaborative group, the Environment and Child Health International Birth Cohort Group (ECHIBCG). In this study, an intra-laboratory trial was performed to harmonize existing blood lead measurements within the groups' studies. Then, decentralized analyses were conducted in individual countries' laboratories to evaluate blood lead levels (BLL) in each study. The measurements of pooled BLL samples in French, German and three Japanese laboratories resulted in an overall mean blood lead concentration of 8.66 μg l^{-1} (95% confidence interval: 8.59–8.72 μg l^{-1}) with 3.0% relative standard deviation. Except for China's samples, BLL from each study were comparable with mean concentrations below or close to 10 μg l^{-1}. The decentralized multivariate analyses revealed that all models had coefficients of determination below 0.1. Determinants of BLL were current smoking, age > 35 years and overweight or obese status. The three variables were associated with an increase in BLL in each of the five studies, most strongly in France by almost 80% and the weakest effect being in Norway with only 15%; for Japan, with the far largest sample (~18,000), the difference was 36%. This study successfully demonstrated that the laboratory analytical methods were sufficiently similar to allow direct comparison of data and showed that it is possible to harmonize the epidemiological data for joint analysis. This exercise showed the challenges in decentralized data analyses and reinforces the need for data harmonization among studies.

Keywords

Human Biomonitoring; HBM; Birth cohort; Lead; Harmonization; Pregnancy; Child; Environment

Introduction

Foetal and neonatal exposure to chemical substances may lead to adverse health effects such as developmental disorders, immune system dysfunction and hormone disruptions in later life (Barouki et al., 2012; Grandjean et al., 2008). Birth cohort studies are one of the major tools to identify these associations between the environment and children's health and, when possible, to confirm causalities. In the past decades, many birth cohort studies have been conducted to investigate the impact of a variety of chemical substances (Baldacci et al., 2018; Barbone et al., 2019; Botton et al., 2016; Boucher et al., 2009; Casas et al., 2015; Clemente et al., 2016; Dzwilewski and Schantz, 2015; Hertz-Picciotto et al., 2008; Huang et al., 2016; Iszatt et al., 2015; Perera et al., 2006; Pilsner et al., 2009; Rauh et al., 2011; Shelton et al., 2014; Trasande et al., 2009). However, those individual studies often have not yielded conclusive results as regards the association between a particular exposure and health outcomes, mainly due to insufficient statistical power. To overcome this, large-scale birth cohort studies were initiated in the late 1990s in Norway and Denmark (Magnus et al., 2016; Olsen et al., 2001). The United States (US), Japan, France, UK and South Korea

followed, the US and UK studies however, were terminated early (Branum et al., 2003; Dereumeaux et al., 2017; Kawamoto et al., 2014; Kishi et al., 2011; Lee et al., 2017; Vandentorren et al., 2009). These studies each involve 20,000–100,000 participants and represent major steps forward towards enabling the conduct of more conclusive studies into the relationships between the environment and common outcomes in children's health and development. Because of practical issues and cost of sampling and chemical analyses, however, exposure data for some specific chemicals may be available for only a subset of the cohort. In addition, for studies of rare diseases such as childhood cancers, type-1 diabetes, congenital anomalies or sudden infant death syndrome (SIDS), a single study may have insufficient statistical power. The number of 100,000 also may fall short when assessing the effect of multiple environmental factors at the same time, e.g. the collective effect of lead, mercury, cadmium, persistent organic pollutants (POPs), pesticides and other compounds of emerging concern such as perfluoroalkyl and polyfluoroalkyl substances, phthalates and parabens on children's health and development.

One way of increasing statistical power is to perform a meta-analysis of multiple study results (Huang et al., 2016). Acquiring information on associations between children's health and environmental exposures by meta-analysis of data from different birth cohort studies poses a number of challenges: studies on environmental health employ a variety of instruments, including for health and development, questionnaires, in-person or phone interviews, physical examinations, clinical tests and for environmental exposures, interviews, environmental monitoring or sampling modelling and human biomonitoring. Especially for exposure assessment, it is often hard to compare data across studies, because of non-standardized procedures used in each study. For instance, each study may employ different sampling and analytical methods for human biomonitoring. Even if they use exactly the same methods, each laboratory performs analyses differently. To overcome such problems in meta-analysis, birth cohort consortia have been formed to aim at pooled analysis or mega-analysis instead of meta-analysis. In the mega-analysis data from individual studies are pooled or combined together in a central location and analysed as one big data set, while in the meta-analysis individual decentralised analysis results are statistically compared. In short, the mega-analysis combines data and the meta-analysis gathers results from each study. Examples are the International Childhood Cancer Cohort Consortium (I4C) (Brown et al., 2007), Environmental Health Risks in European Birth Cohorts (ENRIECO) (Gehring et al., 2013) and the Birth Cohort Consortium of Asia (BiCCA) (Kishi et al., 2017). In order to pool each study's data, it is crucial to perform data or method harmonization that should involve standardisation of study procedures such as questionnaires, physical/developmental examinations, clinical tests and laboratory analyses before data collection or normalisation of existing data.

Our consortium, the Environment and Child Health International Birth Cohort Group (ECHIBCG) (Etzel et al., 2014), has been exercising the harmonization of study methods and aims at harmonizing data including infant health outcomes, biomarkers, environmental measurements, socioeconomic and migration status. Recently, we have focused on exposure measurements by identifying chemicals of common interest; comparing each study's questionnaire and laboratory methodologies; and conducting inter-laboratory procedural

tests. In order to make data comparable, retrospective harmonization is as important as prospective harmonization because in most cases data are already collected.

The major aims of this research were to perform ad hoc data harmonization for blood lead measurements, and to evaluate common factors associated with blood lead levels (BLL). Based on a comparison of each study's procedures, results of a round-robin practice and findings of a joint data analysis, we present lessons learned with respect to cooperation of birth cohort and environmental health studies.

Materials and methods

Participating studies and organisations

In late 2011, the Japan Ministry of the Environment (JMOE) invited investigators associated with some large-scale 21st century birth cohort studies to discuss about how to better design the assessment of disease outcomes, biomarkers and environmental exposures. Investigators from various large-scale cohort studies discussed the benefit of data pooling among the studies and need for study harmonization (Ishitsuka et al., 2017). The JMOE suggested that it would be useful to establish working groups to define a list of core elements for inclusion in the harmonization. Such core elements could include disease outcome definitions, biomarkers and exposure measurements. A working group was therefore proposed to discuss and exchange information about ongoing and forthcoming large-scale birth cohort studies and national bio-/environmental monitoring projects. Experts from new large-scale studies of environmental influences on children's health and development that were being planned or conducted in France, Germany, Japan, Shanghai (China) and the US constituted the Environment and Child Health International Birth Cohort Group (ECHIBCG) in 2011 (Etzel et al., 2014). Later, Denmark and Norway joined and the International Agency for Research on Cancer (IARC) became the secretariat of the group. The current ECHIBCG is jointly coordinated by Japan and Germany and consists of the Danish Birth Cohort Study (DNBC) (Olsen et al., 2001), the Etude Longitudinale Française depuis l'Enfance (Elfe) (Dereumeaux et al., 2017; Vandentorren et al., 2009), the Japan Environment and Children's Study (JECS) (Kawamoto et al., 2014; Nakayama et al., 2019), the Norwegian Mother and Child Study (MoBa) (Magnus et al., 2016), the Shanghai Birth Cohort Study (SBC) (Zhang et al., 2019) and experts from the German Environment Ministry, the German Environment Agency and (until September 2018) the US Environmental Protection Agency (the information of the member studies is summarised in the Supplementary Information and Table S1). Elfe, the Environmental Specimen Bank (ESB) from Germany (Kolossa-Gehring et al., 2012), JECS, SBC and MoBa provided data for this exercise (detailed information on sample selection and procedures followed is given in the Supplementary information).

Round-robin test procedures

The group undertook an inter-laboratory comparison (round-robin) project in 2014 for blood lead analysis. Participating laboratories were three from Japan, and one each from France and Germany. The group first examined each country's custom regulations for the transportation of frozen blood samples. Second, water samples were sent from Japan on dry ice and with temperature loggers to France and Germany to evaluate the transportation

process. The group used JECS in-house reference material (JECS RM) for whole blood round-robin tests among France, Germany and Japan. JECS RM was made from a pooled whole blood legally obtain from the Japan Red Cross. Aliquots of RM were undergone elemental analysis, including lead, mercury and cadmium, to confirm homogeneity and then frozen. The elemental analysis was also conducted after several cycles of freeze and thaw to verify the robustness of the RM (data not shown). Four vials of the JECS RM (2-ml polypropylene cryo-vials with 2-D barcode on the bottom) were shipped to each designated laboratory or facility in France, Germany and Japan. The vials were placed in a secondary container (polypropylene) that was packed in a plastic bag. The sample containers were then set in a Styrofoam box that contained a few kg of dry ice. A temperature logger was placed on top of the samples. Upon receipt, the participating laboratories visually observed the sample condition and filled out a shipment evaluation sheet. Each laboratory sent the completed evaluation sheet and the temperature logger back to the JECS Programme Office where the information was examined and compiled.

The JECS RM was kept in its original vials and stored frozen at or below negative 20°C until use. Freezers were temperature controlled and monitored with limited temperature fluctuation. Before use, a frozen sample was allowed to thaw at room temperature. The sample was mixed by gently rocking or mildly swirling (not shaking) the vial to remix any water that may have separated on freezing. Each laboratory analysed all 4 vials in at least 3 replicates for lead using its own methods. The laboratories were provided with an electronic reporting format, in which they reported the results of the analysis including concentrations, method summary description and method performance characteristics. The laboratory analytical procedures involved in this trial are shown in Table 1.

Blood lead measurements and covariate data acquisition

BLL were determined in mothers' whole blood during pregnancy in Japan and Norway, in whole blood in Germany (female ESB participants, non-pregnant women), and in cord blood in China and France. All measurements were above detection limits. Detection limits varied across studies, with the lowest limit in Norway (0.08 μg l^{-1}) and the highest limit in France (0.6 μg l^{-1}). The timing of the blood collection also varied across studies; for Norway it was 2002–08, Germany 2010–16, France 2011, Japan 2011–14 and China 2014–15. No calibrations were made for whole blood vs. cord blood or for the time period, as it was not possible to quantify the possible impact due to lack of comparison data. All BLL were harmonized to the unit of μg l^{-1}.

Possible explanatory factors of maternal BLL as identified in a stepwise process were acquired from questionnaires developed by each study and had to be harmonized across studies. A literature search was performed first looking for factors being identified in at least one published study as influencing BLL and that had been assessed in at least the majority of our studies. Selected explanatory factors at the time of sampling were maternal smoking (current, former, not active but passive smoking in household, and never smoking including no current passive smoking); maternal age (categorized into < 25 years, 25–34 years, 35+ years); maternal body mass index (BMI) [categorized into < 18.5, 18.5–25, and 25+ kg/m^2 (combining overweight and obese, as the latter group included too few subjects)];

consumption of coffee, tea, tap water, or bottled water (all in categories less than once, 1–2 times, 3+times per week); alcohol drinking [current when pregnancy was known, former (stopped before pregnancy or as soon as known), never]; chocolate consumption (categorized into less than once, 1–2 times, 3+ times per week) and whether renovation work at home took place during pregnancy. In Germany, variables referring to pregnancy referred to the sampling period, as the sampled population was non-pregnant women. Maternal education was kept in the final model for adjustment in the original categories, usually from low to high in several steps, as studies came from different parts of the world and the attempts to harmonise were not meaningful. Other harmonised variables not kept in the final analytical model were sex of offspring, pre-term or term pregnancy, or parity (first vs. later born child) (those pregnancy-related variables are not relevant in Germany as the study population was not pregnant women), as well as consumption of bread, dairy products, seafood, or vegetables, and year of construction of the house where the woman lived. Slight compromises had to be made in variables related to food consumption, as dietary questions were not identical. In China, Japan and Norway the item “tea” consisted of only green tea while in France and Germany it included different types of tea. In Japan, coffee consumption was specified as only from beans and green tea as only from leaves. In France, units of coffee and tea consumption were measured in less than once, once, or 2+ times per week.

Statistical analysis

Because all of the studies had to follow their own countries/regions’ data protection rules/ legislation, most of the studies were not able to share the data with others. Thus, we employed de-centralized data analysis using different statistical packages. The first step was a descriptive analysis, obtaining univariate statistics by study, e.g. means, medians and percentiles. For visualisation, we created a boxplot-like figure in which the 10^{th} and 90^{th} percentiles were used as whiskers, the 1^{st} (25^{th} percentile) and 3^{rd} quartile (75^{th} percentile) as the box range, the median (50^{th} percentile) as box separator, and the 99^{th} percentile as external extra asterisk, rather than the common boxplot definition, to avoid distraction by outliers because we aimed at a visual comparison of the majority of measured values across studies. After identifying common factors influencing BLL, studies analysed their own data and selected factors having influence on the BLL, irrespective of the magnitude. From this list, a first stage linear model was developed including all factors on the combined list. From this run, all variables that did not result in at least a 20% change in BLL in at least one of the studies were removed. This final model was applied independently to each study to obtain the coefficients of the individual explanatory factors and their uncertainty, as well as the unadjusted and adjusted R^2 of the model, indicating the percentage variation in BLL explained by the model (final selection of variables described in the previous section). The 20% change criterion for choosing variables was preferred over the p-value due to the highly varying sample sizes across studies; while for Japan even tiny changes became statistically significant, this was only the case for major changes in China, for instance. Finally, we applied to the data the coefficients for smoking, maternal age and BMI, which were the relevant explanatory factors with highest comparability across studies, to compare predictions of how much BLL increase on average with exposure to current smoking, high maternal age, and high BMI in the individual studies. Instructions for analyses were developed at the IARC together with the study principal investigators, to make sure the

approach was identical; afterwards analyses were carried out de-centrally, as mentioned above. All studies had ethics approval at the national level.

Results

Inter-laboratory comparison

Germany used the inductively-coupled plasma mass spectrometry with dynamic reaction cell technology (ICP-DRC-MS) method, while the rest of laboratories used the inductivity coupled plasma mass spectrometry (ICP-MS), with slightly different sample pre-treatment procedures. The result of the round-robin trial is illustrated in Figure 1. French and German laboratories reported mean lead concentrations of 8.71 and 8.27 μg l^{-1} with relative standard deviations (RSDs) of 2.9% and 2.5%, respectively. Three Japanese laboratories showed mean concentrations of 8.76, 8.83 and 8.75 μg l^{-1} with RSDs of 1.1%, 0.8% and 0.8%, respectively. Overall mean concentration was 8.66 μg l^{-1} (95% confidence interval: 8.59–8.72 μg l^{-1}) with 3.0% RSD.

Current blood lead levels

Each study using its own method reported lead concentrations in whole blood samples. Numbers of available samples differed greatly by study, with 17,998 samples from Japan, 2,982 from Norway, 1,842 from Germany, 1,670 from France, and 423 from China. Distributions of BLL by study are displayed in Figure 2. With the exception of China, median values were close to or lower than 10 μg l^{-1} and 90th percentiles close to or lower than 20 μg l^{-1}. None of the 99th percentiles exceeded 50 μg l^{-1}. Maximum levels were 212 μg l^{-1} in Norway, 107 μg l^{-1} in France, 103 μg l^{-1} in Germany, 80.5μg l^{-1} in China, and 74.5 μg l^{-1} in Japan.

Determinants of blood lead levels

Each group analysed their own data to examine determinants of BLL according to the same instructions as described in the previous section. Table 2 shows the results of the final model with explanatory factors having an impact of at least a 20% change in average BLL in at least one study, and subsequently applied to all studies. Items shown in Table 2 include the number of subjects in each category, the coefficient of change and its standard error compared to the reference category, as well as the intercept of the model (reflecting the BLL by country sample with all explanatory factors in their reference category; bottom of the table) and the R^2 values. In line with Figure 2, the intercept shown in Table 2 confirms the lowest BLL in Japan and France and the highest in China and in Germany. The R^2 was below 0.1 in each study; the highest R^2 was seen in France. Current smoking was associated with increased BLL in all studies in a similar magnitude (including the very low number of subjects in China), except for Germany, where the increase was more pronounced. A positive association also was seen in all studies with increasing maternal age, whereas most studies showed an increase in overweight and obese women, with the exception of Norway. Patterns of coffee, tea or tap water consumption showed weaker associations, not always entirely consistent across studies, and even lesser so for alcohol, chocolate and renovation work at home (Table 2). Figure 3 shows the change in BLL by of women who were never active smokers and were not passive smokers, were aged <25 years, and were underweight

compared to those who were current smokers, aged 35 years or older, and were overweight or obese. The combination of those 3 variables was associated with an increase in BLL in each of the 5 studies; most strongly in France by almost 80% and the weakest effect in Norway with only 15%, for Japan, with the far largest sample, the difference was 36%.

Discussion

Round-robin trial

The United States National Institute of Standards and Technology (NIST) standard reference material (SRM) 995c (toxic elements in caprine blood), which was certified for lead at four concentration levels: a base level and three progressively elevated levels, was initially considered suitable for use in the round-robin trial. It appeared, however, that in most countries a health certificate was required to import the SRM 955c (made of goat blood). Considering that NIST was not ready to issue the certificate, the use of the SRM 955c did not seem practical. The group decided to use a JECS in-house RM made of human blood officially acquired from the Japanese Red Cross. The shipment took from 3 days and went well with the temperature kept below negative 60°C on dry ice. China found that it could not import human materials easily. Sending samples on dry ice to China was also extremely difficult and expensive. There are existing mechanisms of international laboratory accreditation such as the German Environmental Quality Assurance Scheme (G-EQUAS) and the Canadian Programme run by the Centre de Toxicologie du Quebec (CTQ). Since lead is a well-studied contaminant, all the laboratories performed very well on the blood lead analysis. Repeatability of the measurements was satisfactory with RSD of replicate analyses being < 3% for all the participating laboratories. With this precision, a common statistical practice resulted in detecting statistically significant differences ($p < 0.05$) among individual laboratories' results. However, such small differences were considered irrelevant for the anticipated data use. After pooling data from all the laboratories, the overall RSD was still 3.0%.

Determinants of blood lead levels

The major aim of this part of the study was to evaluate common factors associated with BLL, and some observed consistencies (see Table 2). Some inconsistencies across the five studies from five different countries are of interest. The R^2 was below 10% in each study, suggesting that, albeit being associated with the BLL, the explanatory factors have little predictive power to estimate individual BLL. This was common across studies, although we used a very inclusive approach of investigating potential explanatory factors. This confirms that not all relevant information that may explain variation in BLL can be captured by questionnaires. For example, on dietary-related factors, individual dietary patterns (e.g., how many vegetables one eats on average) have less influence on BLL than the food location or the processing method of the vegetables the person consumes. This is the likely reason why all dietary factors, including type of water consumption or beverages like coffee, tea or alcohol, did not emerge as strong associations. It is an important finding however, as this observation applies commonly to all countries. The main modifiable factor at the individual level to lower BLL appears to be quitting smoking, again consistent across countries. Other consistent factors are either not modifiable, like age, or not recommendable to attain for

health reasons, e.g. BLL were lower in underweight persons. Additionally, the cause-and-effect relationship is not always clear. For instance, there are partly opposite findings in the literature for the relation between BLL and BMI. Although some authors find increased BLL being related to lower BMI and obesity in children, adolescents, and adults (Cassidy-Bushrow et al., 2016; Scinicariello et al., 2013; Shao et al., 2017), there also is sex-specific evidence for the opposite (Wang et al., 2015). Additionally, the effect of chronic lead exposure, as expressed e.g. by dentin lead levels (Kim et al., 1995), might differ from the effect of short-term lead exposure, which in our data cannot be disentangled. And finally, the actual cause-and-effect relationship could possibly be both ways—either the increased food intake of obese individuals subsequently results in increased lead uptake, or alterations in metabolism or the epigenome causing obesity are the effect of lead exposure, e.g. Wang et al. (2015) conclude that oxidative stress caused by lead exposure may be one factor inducing obesity.

Coffee and tea consumption were associated with higher BLL, of somewhat differing magnitude by country, and it was not possible to disentangle whether the underlying factor was the coffee, the tea or the water in which it was prepared. A number of dietary factors (e.g. chocolate intake) were associated with BLL in France, albeit not strongly, but were not confirmed in the other countries. Interestingly, the association was reversed for chocolate intake in several countries. We did not find an association between gestational age, sex of the offspring or parity and BLL in any country.

In this study, we aimed to identify possible potential problems of decentralised data analyses. Evaluation of BLL determinants was performed in a decentralised manner. It indicated the analytical part could be harmonised using an appropriate reference material. On the other hand, it proved difficulty in decentralised analysis due to the difference in sample types (cord blood for France and China, maternal blood for Japan and Norway and non-pregnant women’s blood for Germany) and questionnaire data. Our practice showed the importance of harmonisation of study protocols for future mega-analysis of biomonitoring and cohort studies.

Comparison of blood lead levels in each study

Measured BLL were lowest in Japan, followed by France and Norway, somewhat higher in Germany and highest in China. This applies however to our study sub-samples and is not necessarily representative for a cross-country comparison, due to different sampling strategies of study participants and study methodologies including selection of sub-sample for lead measurement. First, the impact of whole blood vs. cord blood and sampling in slightly different time periods, as well as some analytical uncertainty as shown by the round-robin test, cannot be quantified to calibrate the measured values; in addition, differences across most countries were not very large. Per this exercise, we had to use BLL data from difference sample matrices across the studies. Even though maternal to cord blood lead concentration ratio have been found to be close to 1 (Iwai-Shimada et al., 2019), we cannot compare the results directly. This also indicates the importance of pre-harmonisation for pooled data analysis. Second, the sample from Japan is by far the largest and therefore had considerably less random variation, possibly being the most representative. Third, direct

comparison with Germany and China is not straightforward. In Germany, sampled women were not pregnant and different lifestyles, living conditions and behaviours make them less comparable to the pregnant women in the other studies. In China, the study was only carried out in Shanghai, a metropolitan area, while the other studies included fewer urban environments. Nevertheless, all studies have in common that in general measured BLL were low, with very few levels exceeding 50 μg l^{-1}.

Implication of the harmonization exercise

We demonstrated that BLL data can be harmonised by using a reference material. The data can be compared and pooled in reference to the measurement results of the reference material, even though each study employs its own analytical protocols and own laboratory and performs the analysis in different time and places. Our practice also showed the usefulness of a round-robin exercise to illustrate the performance of each study analysis. We knew that each study used laboratories having accreditations for the particular analysis or having participated in an external quality assurance programme such as the German External Quality Assessment Scheme (G-EQUAS). However, that was not sufficient to evaluate the comparability of the analysis data among the group. The round-robin results demonstrated the importance of the use of reference materials in each study in order to pool the data afterwards.

There have been efforts to pool cohort study data with environmental measurements, e.g. the Environmental Health Risks in European Birth Cohorts (ENRIECO) project (Casas et al., 2013; Gehring et al., 2013). The ENRIECO proved a possibility of pooling data from different cohort studies, while identifying some difficulties in calibrating the results from different laboratories and different measurement timings. The practice also revealed the importance of harmonizing questionnaire harmonization. The data harmonization in ECHIBCG also confirms such experiences, namely that some precision in items needs to be sacrificed for the creation of joint variables. This applies to some extent already to variables having exactly the same meaning in each study, e.g. maternal age, when assessed categorically and those categories differ across countries. It becomes an even bigger challenge for variables seemingly the same but reflecting slightly different habits in different countries; e.g. fish and seafood consumption across diverse countries such as France, Norway, Germany, China and Japan do not necessarily mean exactly the same type of fish or seafood. The likely effect of collapsing categories, broadening definitions or lumping precise definitions into broader groups is a potential dilution of associations, if they exist; in our case, the association between BLL and their possible explanatory factors. Evidently, this is inherent in the design, namely the conduct of independent national studies and their multinational pooling, and the overall gain in statistical power as well as the opportunity to identify study-specific associations outweighs the limitations from compromises made at the harmonization stage.

Conclusions

In this project of the ECHIBCG, a consortium of cohort studies, supported by Germany and Japan, compared BLL across five countries and evaluated potential explanatory factors of

increased levels. The first purpose was to demonstrate that the laboratory analytical methods were sufficiently similar to allow direct comparison of data, as well as demonstrating that it is possible to harmonize the epidemiological data for joint analysis. From this perspective, the exercise was successful and encourages further joint projects. The second purpose—comparing BLL—revealed three associations that were consistent across countries, namely, smoking, age and, to a lesser extent, BMI. Other factors appeared to be more modestly related or differed by country. This exercise showed the challenges in decentralized data analyses and reinforces the need for data harmonization among studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Blood lead levels were compared across five countries and potential determinants were evaluated.
- Intra-laboratory trial on lead analysis showed variation was small enough for joint analysis.
- Current smoking, age and BMI were the most prominent explanatory factors of blood lead levels.
- The challenges in decentralized analysis reinforce the need for data harmonization and pooling.

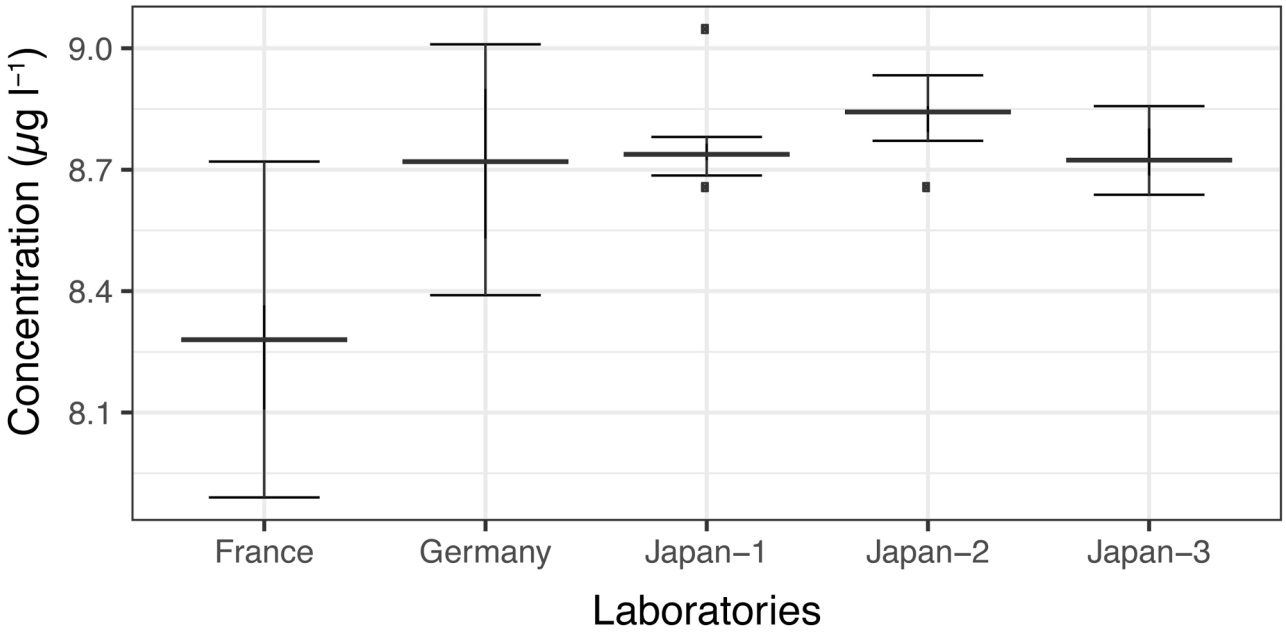

Figure 1.

Concentrations of lead in the whole blood reference material as determined in the round-robin exercise (μg l^{-1}).

Boxplots were depicted using 1.5 times the interquartile range as whiskers, interquartile range as the box ranges and the median as the box separators.

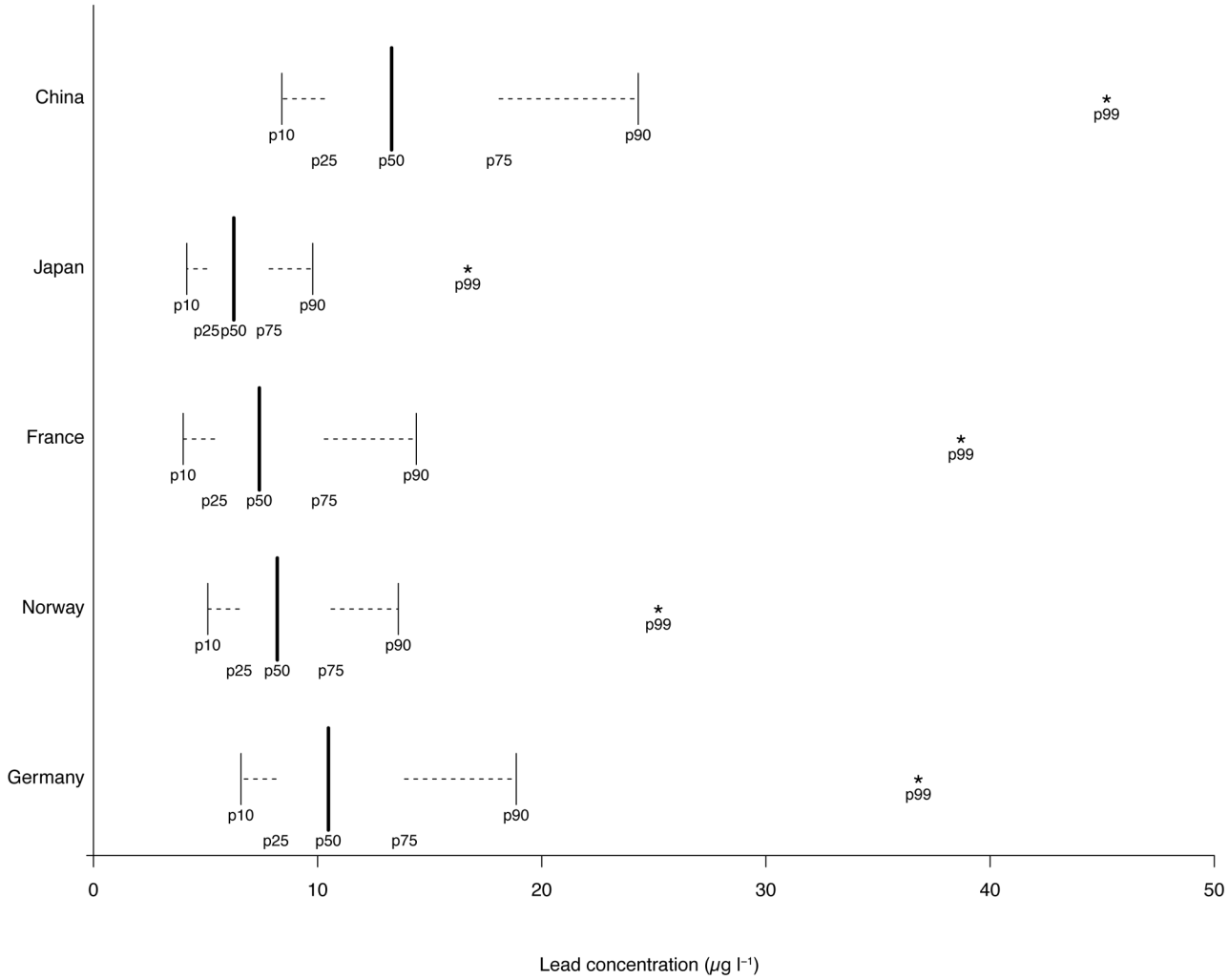

Figure 2.

Illustrative representation of summary statistics of blood lead level in each study.

Summary statistics of blood lead levels in each study are illustrated in boxplot-like shapes. P10, P25, P50, P75, P90 and P99 represents the 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th} and 99^{th} percentile, respectively.

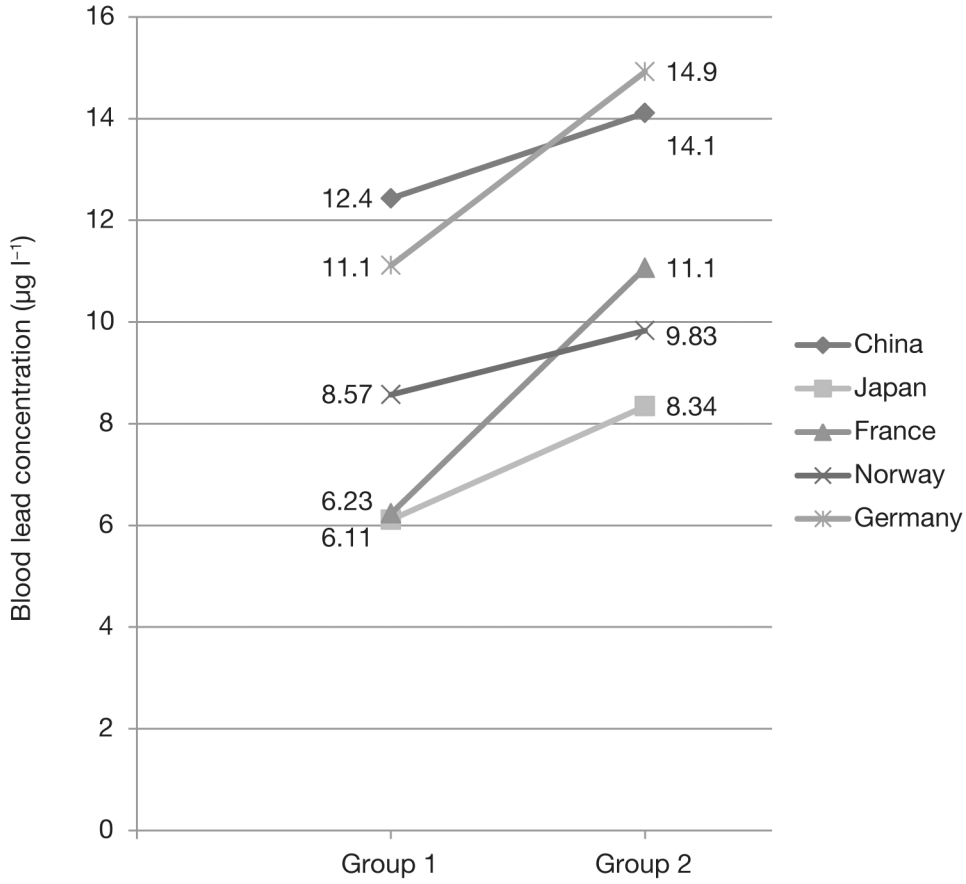

Figure 3.

Change in blood lead concentrations according to the influence of the variables age, BMI and smoking patterns for each study.

Women who never smoked and had no passive smoke exposure, were aged <25 years and were underweight (Group 1) in comparison to current smoking, age 35+ years and overweight or obese women (Group 2).

Table 1.

Summary of the analytical procedures employed in the laboratories that participated in the round-robin trial.

	France	Germany	Japan
Sample preparation	Samples (300 µl) were transferred into a 13-ml polypropylene tube and mixed with 2,700 µl dilution solution. Dilution solution was made by adding 10 ml 25% NH4OH, 250 mg EDTA dipotassium salt and 250 µl Triton X-100 into a volumetric flask and filled up to 500 ml with double distilled water.	Samples (300 µl) were transferred into a 13-ml polypropylene tube and mixed with 2,700 µl dilution solution. Dilution solution was made by adding 10 ml 25% NH4OH, 250 mg EDTA dipotassium salt and 250 µl Triton X-100 into a volumetric flask and filled up to 500 ml with double distilled water.	Samples (200 µl) were diluted (1:19) with the dilution solution and vortex mixed. Dilution solution consisted of 2% v/v butan-1-ol, 0.1% TMAH, 0.5 g l^{-1} POE and 0.5 g l^{-1} H_4EDTA
Instrumental analysis	ICP-MS (Agilent 7500) with ASX 500 auto-sampler	ICP-DRC-MS (Agilent 7500cx) with ASX 500 auto-sampler	ICP-MS (Agilent 7700 ICP-MS) with auto-sampler
Calibration and calculation	External calibration was used. The limit of quantitation was 0.15 µg l^{-1}.	External calibration was used. The limit of quantitation was 0.15 µg l^{-1}.	External calibration was used. The limit of quantitation was 0.14 µg l^{-1}.

Table 2.

Analyses of factors influencing lead concentration in blood by study, showing the numbers in categories (N), the regression coefficient (β) and its standard error (S.E.), and the intercept and unadjusted and adjusted R^2 at the bottom of the table.

		French National Birth Cohort Study (Elfe)			German Environmental Specimen Bank (ESB)			Japan Environment and Children's Study (JECS)			Norwegian Mother and Child Cohort Study (MoBa)			Shanghai Birth Cohort Study		
Sample size for the lead analysis		**1,670**			**1,842**			**17,998**			**2,982**			**423**		
Timing and type of sampling for lead		**Cord blood 2011**			**Whole blood from women aged 20–29 2010–2016**			**Maternal blood (mid–late trimester) 2011–2014**			**Maternal blood (week 18 of pregnancy) 2002–2008**			**Cord blood 2014–2015**		
Variable		**N**	**β**	**S.E.**	**N**	**β**	**S.E.**	**N**	**β**	**S.E.**	**N**	**β**	**S.E.**	**N**	**β**	**S.E.**
Smoking	Never	701	1.00	-	1081	1.00	-	7032	1.00	-	1552	1.00	-	335	1.00	-
	Passive	20	0.08	1.87	332	0.84	0.30	2894	0.17	0.07	100	0.35	0.46	74	1.43	0.88
	Former	399	−0.09	0.42	200	1.65	0.36	6729	0.34	0.05	1157	0.20	0.19	12	3.98	2.60
	Current	380	1.13	0.49	213	3.33	0.35	884	1.27	0.11	173	1.19	0.39	2	NA	NA
Maternal age[&]	<25 years	255	1.00	-	1224	1.00	-	1403	1.00	-	241	1.00	-	25	1.00	-
	25-34 years	1144	0.81	0.56	618	0.66	0.24	9149	0.21	0.08	2257	−0.003	0.32	352	0.69	1.67
	35+ years	261	1.98	0.68	0	NA	NA	4000	0.60	0.09	484	0.53	0.38	46	0.58	2.10
BMI	<18.5 kg/m^2 (underweight)	123	1.00	-	112	1.00	-	2573	1.00	-	94	1.00	-	56	1.00	-
	≥18.5 and 25 kg/m^2 (healthy)	1032	0.80	0.69	1494	0.43	0.56	11579	0.07	0.06	1913	−0.22	0.47	320	1.68	1.20
	≥25 kg/m^2 (overweight and obese)	494	1.72	0.73	228	0.48	0.61	1691	0.36	0.09	918	−0.46	0.49	47	1.10	1.75
Coffee consumption[*]	Less than 1 time per week	790	1.00	-	653	1.00	-	13116	1.00	-	1489	1.00	-	0	1.00	-
	1-2 times per week[$]	225	0.72	0.64	85	1.00	0.54	1309	0.27	0.08	410	0.60	0.26	0	NA	NA
	More than 3 times per week[$$]	482	1.52	0.41	1101	0.27	0.25	1287	0.20	0.08	1083	0.91	0.20	0	NA	NA
Tea consumption[**]	Less than 1 time per week	937	1.00	-	501	1.00	-	8822	1.00	-	2091	1.00	-	358	1.00	-
	1-2 times per week[$]	233	−0.07	0.60	160	−0.14	0.39	2335	0.07	0.07	380	0.04	0.26	0	NA	NA
	More than 3 times per week[$$]	205	1.95	0.52	1181	0.21	0.24	4686	0.31	0.05	511	1.07	0.23	65	0.32	1.16
Tap water consumption[#]	Less than 1 time per week	640	1.00	-	37	1.00	-	10380	1.00	-	87	1.00	-	101	1.00	-
	1-2 times per week[$]	80	0.56	0.83	12	0.69	1.60	1390	0.10	0.08	30	−0.20	0.96	0	NA	NA

		French National Birth Cohort Study (Elfe)			German Environmental Specimen Bank (ESB)			Japan Environment and Children's Study (JECS)			Norwegian Mother and Child Cohort Study (MoBa)			Shanghai Birth Cohort Study		
Sample size for the lead analysis		**1,670**			**1,842**			**17,998**			**2,982**			**423**		
Timing and type of sampling for lead		**Cord blood 2011**			**Whole blood from women aged 20–29 2010–2016**			**Maternal blood (mid–late trimester) 2011–2014**			**Maternal blood (week 18 of pregnancy) 2002–2008**			**Cord blood 2014–2015**		
Variable		**N**	**β**	**S.E.**	**N**	**β**	**S.E.**	**N**	**β**	**S.E.**	**N**	**β**	**S.E.**	**N**	**β**	**S.E.**
Bottle water consumption	More than 3 times per week[$$]	781	0.68	0.44	1788	0.39	0.78	4073	0.25	0.05	2829	−0.48	0.50	322	0.79	1.06
	Less than 1 time per week	344	1.00	-	NA	1.00	-	7379	1.00	-	1800	1.00	-	165	1.00	-
	1-2 times per week[$]	152	0.76	0.66	NA	NA	NA	1834	−0.13	0.08	377	−0.20	0.25	0	NA	NA
	More than 3 times per week[$$]	999	−0.89	0.48	NA	NA	NA	6630	−0.21	0.05	640	−0.26	0.21	258	2.28	1.58
Alcohol (when pregnancy was known)	Never	1269	1.00	-	NA	1.00	-	8018	1.00	-	278	1.00	-	347	1.00	-
	Former	105	0.16	0.70	NA	NA	NA	7320	0.15	0.05	2599	0.57	0.30	43	−1.04	1.38
	Current	283	−0.13	0.46	NA	NA	NA	505	0.81	0.13	79	1.91	0.61	2	NA	NA
Chocolate consumption[##]	Less than 1 time per week	212	1.00	-	196	1.00	-	2773	1.00	-	880	1.00	-	0	1.00	-
	1-2 times per week	174	0.39	0.71	173	0.20	0.43	4797	−0.12	0.05	1244	−0.19	0.20	0	NA	NA
	More than 3 times per week	1087	−0.70	0.52	1472	−0.52	0.32	8358	−0.23	0.05	794	−0.25	0.22	0	NA	NA
Works at home	No renovation of residential home[+]	887	1.00	-	NA	1.00	-	17044	1.00	-	NA	1.00	-	356	1.00	-
	Renovation of residential home[++]	616	0.33	0.35	NA	NA	NA	564	0.28	0.06	NA	NA	NA	16	−3.22	2.20
			Value			**Value**			**Value**			**Value**			**Value**	
Intercept (α)			6.23			11.11			6.11			8.57			12.43	
R^2			0.09			0.04			0.03			0.03			0.05	
R^2 (adjusted)			0.08			0.04			0.03			0.03			0.00	

NA: not applicable

[&] age (Germany)

[*] from leaf (Japan)

** green tea (China, Japan and Norway)

all types of water (Germany)

sweets including chocolate (Germany)

$ weekly (France)

$$ daily (France and China, except for coffee)

+ after becoming pregnant (Japan)

++ after becoming pregnant (Japan)