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ABSTRACT

Lead is a ubiquitous toxic metal. This review summarizes the toxicokinetics and toxicology of lead, the methods to measure blood lead (BL) and summarizes recently published studies, and ends with an appraisal of recent regulations to protect exposed workers. Lead exposure runs *via* inhalation of lead-contaminated particulate and *via* gastrointestinal uptake. To assess BL, inductively coupled plasma mass spectrometry and electrothermal atomic absorption spectrometry are commonly applied. BL in the general population declined drastically, approaching pre-industrial levels, at least in developed nations. Using cardiovascular, renal end neurological endpoints, SPHERL, a longitudinal study in a lead-exposed workers demonstrated that current regulations effectively protect against detrimental effects. FLEMENGHO, a Flemish population study, showed how BL declined over the past 20 years and reported on the association of renal and left ventricular function with BL. A re-analysis of NHANES data representative of American adults accounted for the drastic BL fall over time (1999–2020) and produced for cardiovascular mortality estimates of the BL-attributable risk fraction and the number of avoidable deaths that were respectively >3 and >7 times smaller than in earlier analyses, which ignored the BL decline. The worldwide GBD studies published in 2012 and 2021 were inconsistent in considering the BL-associated cardiovascular endpoints and the null-effect BL level that decreased from 2.5 to 0.016 mg/dl. In conclusion, there is large progress in reducing occupational and environmental lead exposure, but designing and reinforcing stricter regulations should rank high on the agenda of policy makers, in particular in low- and middle-income countries.

Key words: blood pressure, environmental medicine, health risks, lead exposure, renal function

INTRODUCTION

Among toxic metals threatening human health, lead is by far the prime contaminant in this class. Historically, sources of lead exposure comprised pyrolytic zinc ore refinement, indoor and outdoor paints, fuels to which lead was added as antiknock agent, conduits distributing drinking water, and the usage of lead as corrosive-resistant building material. Drafting and

reinforcing regulations banning lead in most applications took until the end of the previous century in the developed world, but legislation or its enforcement lag behind in middle- and low-income countries [1]. Lead is still being widely used in manufacturing lead-acid batteries and ammunition. In Western countries, coarse and fine particulate containing lead deposited over the previous centuries remains a prime source of exposure (Figure 1) [2], whereas in other countries the gastrointestinal route is an exposure vector due to the environmental contamination of food or water [2, 3]. In developed nations, because of the tightening legislation regulating lead exposure, the mean blood lead concentration in adults drawn from the general population currently decreased to approximately 1.5 μg/dl, which is close to the estimated blood lead concentration in pre-industrial humans (2 μg/dl), only exposed to natural sources, as estimated by the Global Burden of Disease (GBD) Consortium [4].

There is currently no consensus whether or not low-level lead exposure raises blood pressure (BP) or induces kidney dysfunction. This review builds on 40 years of research on the health effect of lead exposure, starting with a pilot project in a small Belgian town [5], continuing with multiple cross-sectional [6–8] and longitudinal [9–11] analyses of a random population sample recruited in a defined area in Northern Belgium including municipalities with a high historical exposure to heavy metals due to the emissions of pyrolytic zinc smelters and neighboring municipalities with low exposure, studies in youth [12], systematic literature reviews [13, 14], studies in London civil servants [15], analyses focusing on adults representative of the population in the United States [16, 17], and culminating in a longitudinal study of newly hired workers without know previous lead exposure employed in battery recycling plants in the United States [18–22]. The latter study was previously extensively reviewed in *Polish Heart Journal* [23], but for completeness will again be shorty summarized in the section of this review dealing with the potential adverse health effects of lead exposure. From this 40-year research perspective, the aims of the present review were to summarize the toxicokinetics and toxicology of lead in humans, the methods for measuring the lead body burden, the health risks associated with the contemporary low exposure levels as observed in developed countries, and the regulations to mitigate the health-related effects of environmental and occupational exposure.

LEAD TOXICOKINETICS IN HUMANS

Depending on urbanization, dietary habits, socio-economic position, employment in lead recycling plants or leisure time activities that involve soldering, exposure occurs *via* the respiratory or gastrointestinal route. Respirable fine particulate is the main vector of exposure of the general population [24]. Once the finest dust particles reach the lung alveoli, they readily pass the air-blood barrier and are subsequently system-wide distributed *via* the blood stream. Occupational exposure entails coarser aerosols that deposit in the upper airways and then translocate to the gastro-intestinal tract by mucociliary clearance, where gastrointestinal uptake kinetics prevail (5%–10% uptake). The lead in air to blood lead (BL) slope is around 2 for ambient and 0.05 for occupational exposure [24].

Lead is a cumulative toxicant, 90%–95% of which is stored in bone, from where it is recirculated with a half-life of 20–25 years [25, 26]. BL, for 99% carried by red blood cells, reflects recent exposure over the past 1–2 months and the amount of lead released and recirculated from bone stores [25]. Both bone [26, 27] and blood [6, 26, 27] lead increase with advancing age. Bone lead is associated with blood lead [26, 27] and explains around 20% of its variance, depending on seasonality [26] and hormonal and other endogenous and environmental stimuli influencing the balance between bone formation and resorption [27]. Recirculation of lead from bone explains why there is a lag time for BL to decline when environmental [9] or occupational [25] lead exposure decreases.

PATHOPHYSIOLOGY

The prime pathophysiological mechanism relating adverse health outcomes to lead exposure is by causing hypertension and hypertension-related cardiovascular and renal complications. However, in a meta-analysis of summary statistics extracted from 31 studies and involving 58 518 participants, BL doubling was only associated with a marginally higher systolic/diastolic blood pressure (BP): 1.0/0.6 mm Hg (95% confidence interval [CI], 0.5–1.4/0.4–0.8 mm Hg). All studies pooled in this meta-analysis were published before stringent laws regulating lead exposure came into effect (2001).

A multivariable-adjusted analysis of the 2003-2010 data from the National Health and Nutrition Examination Survey (NHANES) showed ethnic inconsistency in the

associations of BP with BL, which probably reflected unmeasured confounding and which excluded that environmental lead exposure is a major cause of hypertension in American adults [16]. The 12 725 participants included 21.1% Blacks, 20.5% Hispanics, and 58.4% Whites. Blacks compared to non-Blacks had higher systolic/diastolic BP (126.5/71.9 vs. 123.9/69.6 mm Hg) and higher hypertension prevalence (44.7% vs. 36.8%). BL was lower in Whites than in non-Whites (1.46 vs. 1.57 μg/dl). BL doubling was associated with higher systolic/diastolic BP (0.76/0.43 mm Hg; CI, 0.38–1.13/0.18–0.68 mm Hg), but not with the odds of hypertension (0.95; 0.90–1.01) [16]. Furthermore, a systematic review of five cross-sectional studies demonstrated that systolic BP (0.26 mm Hg; CI, 0.02–0.50 mm Hg) and the hypertension risk (odds ratio, 1.04; CI, 1.01–1.07) were associated with lead levels in bone (+10 mg/g) [28]. However, according to the same researchers, the evidence relating cardiovascular complications to BL was suggestive at best and insufficient to infer causality [29].

Other mechanisms potentially underpinning the association of cardiovascular disease with lead exposure are speculative and do not carry the weight of the evidence in humans, not the least because experimental studies in cell or animal models are difficult to extrapolate [30]. Of the multiple mechanisms proposed to play a role are oxidative stress and inflammation, for instance leading to neurotoxicity, endothelial dysfunction or defective DNA repair [31, 32]. Lead can substitute or compete with essential divalent cations, preferentially Ca^{2+} [31, 32], thereby interfering with signal transmission in the central and peripheral nervous system and the electromechanical coupling in muscles. Finally, individual susceptibility to lead toxicity also depends on several single nucleotide polymorphisms, epigenetic modifications and interference with regulatory RNA molecules [32].

In addition, the kidneys play an important role in the urinary clearance of lead. Lead accumulates in the kidney, resulting at high exposure levels in renal function decline and nephropathy. However, the underlying mechanisms are not well understood and might involve glomerular hypertrophy, infiltration of the renal tissue leukocytes, inflammation, interstitial fibrosis and tubular atrophy [33]. Several studies of populations [34–37] or workers [38] in Europe [6, 35], the United States [36–38] and Taiwan [39], reported an

inverse association between the glomerular filtration rate (eGFR) estimated from serum creatinine and BL or an increased risk of chronic kidney disease in relation to BL.

MEASUREMENT OF BLOOD LEAD

As suggested by World Health Organization [40], the most commonly used laboratory methods for assessing BL are inductively coupled plasma mass spectrometry (ICP-MS) and electrothermal atomic absorption spectrometry (ETAAS). Flame atomic absorption spectrometry (FAAS) can also be used, but FAAS cannot be applied to reliably assess BL in people whose BL is less than 5 μg/dl. Other methods are not frequently used in clinical practice, such as inductively coupled plasma optical emission spectrometry [40].

The Study for the Promotion of Health in Recycling Lead (SPHERL) [41] provides a methodology for the quality control of the BL measurement. SPHERL involved newly hired workers without known previous lead exposure employed at battery manufacturing and lead recycling plants in the United States. At all factories, the medical facilities where blood samples were obtained were located at sites separate from the production lines. The study nurses obtained venous blood samples after participants had fasted for 8 hours. The materials used for blood collection, including test tubes, needles and caps, were certified as being lead free (Becton, Dickinson and Company, Franklin Lakes, NJ, US). The nurses thoroughly cleansed the brachial venipuncture site and kept the tubes for the measurement of BL closed. BL was determined by ICP-MS at a single laboratory certified for this analysis in compliance with the provisions of the OSHA Lead Standard, 29CFR 1910.1025 (Occupational Safety and Health Administration). This laboratory participated in the US CDC Blood Lead Proficiency Testing Program. Prior to analysis, specimens were digested in nitric acid and spiked with an iridium internal standard. The limit of detection was 0.5 μg/dl. The deviation from known lead standards analyzed along with the samples in each test run was less than 10% [20, 41].

HEALTH RISKS

The health risks associated with lead exposure were reviewed in workers enrolled in SPHERL [22], in adults representative for the population in the United States enrolled in

successive cycles of the NHANES [42, 43], in randomly recruited people in the Flemish Study on Environment, Genes and Health Outcomes (FLEMENGHO) [44], and in publications of the GBD publications [45–48]. To our knowledge, SPHERL is the first prospective study that accounted for interindividual variability between people in their vulnerability to the toxic effects of human lead exposure by assessing the participants' health status before and after lead exposure [41] and will therefore be reviewed in greater detail than the other studies.

Environment and Health Study

The goal of the project *"Milieu en Gezondheid"* (Environment and Health) was to explore the feasibility of monitoring exposure to cumulative environmental pollutants by examining youth instead adults [12]. The rational was that at young age cumulative toxins in blood and urine reflect recent exposure, whereas at more advanced age measured levels are predominantly determined by the accrual of the contaminant over the years lived, so that they are no longer indicative of recent exposure. Of the 200 17-year olds, 100 resided near a waste incinerator and a lead processing plant and 100 in a rural area with low exposure levels [12]. Cystatin C in serum and b_2-microglobulin in urine were measured as biomarkers of glomerular and renal tubular function, respectively. BL was higher in the exposed youth (4.2 vs. 3.5 mg/dl; $P = 0.04$). With adjustments applied for sex, smoking, mean atmospheric ozone concentration, and mean daily temperature in the week before blood samples, the association sizes for a doubling of BL were +3.6% (95% CI, +1.5 to +5.7%; $P < 0.0001$) for cystatin-C and +16.0% (+2.7 to +31.0%; $P = 0.02$) for b_2-microglobulin in urine.

FLEMENGHO

Recruitment for the FLEMENGHO started in 1985 [44]. From August 1985 until November 1990, a random sample of the households living in a geographically defined area of Northern Belgium was investigated with the goal to recruit an equal number of participants in each of six subgroups by sex and age (20–39, 40–59, and ≥60 years). All household members with a minimum age of 20 years were invited to take part, provided that the quota of their sex-age group had not yet been satisfied. From June 1996 until January 2004 recruitment of families

continued, using the former participants (1985–1990) as index persons and also including teenagers [49]. The participants were repeatedly followed-up. In all study phases, the same standardized methods were applied to measure clinical and biochemical variables, to administer questionnaires, and to ascertain the incidence of fatal and nonfatal outcomes.

In an article published in 1992 [6], mean BL was 7.5 μg/dl in 1016 women and 11.4 μg/dl in 965 men. In sex-stratified analyses, a 10-fold higher BL was associated with a 13 and 10 ml/min lower creatinine clearance in women and men, respectively. However, given that approximately 70% of lead excretion occurs *via* the urine [50, 51], observational studies with a cross-sectional design, such as the early FLEMENGH article [6] and other reports [35–39] cannot ascertain the directionality of the association between eGFR and BL, reduced eGFR being associated with less urinary lead excretion and higher BL, or conversely higher BL being associated with a decline in eGFR. Several other FLEMENGHO reports published around the same time could not demonstrate any association of BL with BP or the prevalence or hypertension or cardiovascular disease [7, 8]. However, in a prospective FLEMENGHO analysis of 728 individuals [9], BP was measured by auscultation at baseline (1985–1989) and at follow-up (1991–1995) and by 24-hour ambulatory BP monitoring at follow-up. Over 5.2 years, BL dropped by 32% from the baseline level of 8.7 μg/dl (range: 1.7–72.5 μg/dl). Changes in the auscultatory BP were unrelated to BL at baseline and the BL changes over follow-up. Along similar lines, the 24-hour ambulatory BP was not related to BL at baseline or follow-up.

In 179 FLEMENGHO participants [10], BL and the 24-h urinary cadmium excretion (UVCD) at baseline (1985–2000) averaged urinary 4.14 mg/dl and 0.68 mg, respectively. Systolic and diastolic left ventricular (LV) function was assessed 11.9 years (median) later (2005–2010) by Doppler imaging of the transmitral blood flow and the mitral annular movement and speckle tracking. In multivariable-adjusted linear regression, LV systolic function decreased with BL. For a doubling of exposure, estimates were –0.392% for global longitudinal strain (P = 0.034), –0.618% and –0.113 s^{-1} for regional longitudinal strain (P = 0.028) and strain rate (P = 0.008), and –0.056 s^{-1} for regional radial strain rate (P = 0.050). Regional longitudinal strain rate (–0.066 s^{-1}; P = 0.009) and regional radial strain (–2.848%; P = 0.015) also decreased with UVCD. Models including both exposure indexes did not

allow differentiating whether LV dysfunction was predominately related to BL or UVCD. Diastolic LV function was not associated with BL or UVCD ($P \geq 0.159$). Although effect sizes were small, these FLEMENGHO results suggested that environmental exposure to lead, cadmium, or both might be a forerunner of heart failure, particularly in susceptible patients with comorbidities [10].

In view of the potential role of fine particulate as transmission vector in lead exposure, air pollutants were also investigated in a further FLEMENGHO study [11]. In 671 participants (51.7% women; mean age, 50.4 years), the annual exposures to black carbon, $PM_{2.5}$, PM_{10} and NO_2 averaged 1.19, 13.0, 17.7, and 16.8 mg/m^3 (Figure 2). Systolic left ventricular function was worse ($P \leq 0.027$) with higher black carbon, $PM_{2.5}$, PM_{10} and NO_2, and mitral E and a' peak velocities were lower ($P \leq 0.021$) with higher black carbon, $PM_{2.5}$ and PM_{10}. Moreover, systemic inflammation was identified as a possible mediator of associations with black carbon [11].

NHANES

Analysis of the NHANES III data (1988–1994) [43] illustrates how metrics covering the adverse health effects of lead exposure in the general population are dependent on assumptions [14]. The hazard ratio (HR) relating mortality over 19.3 years of follow-up to a baseline BL increment from the 10th–90th percentile (1.0–6.7 μg/dl) was 1.37 (95% CI, 1.17–1.60). The BL-associated population-attributable risk fraction (PAF) was 18.0% and the number of attributable deaths 412 000 per year. This NHANES III analysis inflated estimates by the range for which association sizes were computed and completely ignored the drastic fall in BL among US adults [43]. Surprisingly given the pathophysiology of lead-associated hypertension, the findings were not affected by adjustment for BP or hypertension [43].

A recently published analysis of the 2-year NHANES examination cycles from 1999 until 2020, including 34 806 individuals, accounted for the drastic fall in BL and included a mediation analysis considering the direct pathway relating BL to mortality and the indirect pathways running *via* BP or socioeconomic status (SES) [42]. In time-stratified analyses, BL decreased from 1.76 μg/dl in 1999–2004 to 0.93 μg/dl in 2017–2020, while the proportion of

individuals with BL <1 mg/dl increased from 19.2% to 63.0%. Total mortality was unrelated to BL (HR for a 4-fold BL increment: 1.05 [95% CI, 0.93–1.17]). The HR for cardiovascular death was 1.44 (95% CI, 1.01–2.07) in the 1999–2000 cycle, but lost significance thereafter. BL was directly related to cardiovascular mortality, whereas the indirect BL pathway *via* BP was not significant. Low SES was directly related to BL and cardiovascular mortality, but the indirect SES pathway *via* BL lost significance in 2007–2010. From 1999–2004 to 2017–2020, the PAF for cardiovascular mortality decreased from 7.8% (0.17%–14.4%) to 2.5% (0.05%–4.7%) and number of attributable deaths from 53 878 to 7539 deaths [42]. The findings of this study may be applicable to developed regions such as the European Union, where repeated BL measurement in the same population showed a declining trend over 20 years (Figure 3). However, their generalizability to low-or middle-income countries in Africa or South-East Asia may be limited.

GBD Publications

The GBD study 1999–2010 proposed that from the age of 25 years onwards, there is a causal association between systolic BP and lead exposure [45]. High BP was the leading single risk factor globally, accounting for 9.4 million deaths (95% uncertainty interval [UI]: 8.6–10.1 million) and 7.0% (UI: 6.2%–7.7%) of global disability-adjusted life-years, which account for both years lived with a disability and the years of life lost [45]. For environmental lead exposure, these estimates were 0.67 million deaths (UI: 0.58–0.78 million) and 0.56% of disability-adjusted life-years lost (UI: 0.47%–0.66%) [45]. The GBD investigators listed among possible limitations of their result: (i) residual confounding; (ii) uncertainty as to the extent to which the effect sizes were generalizable; (iii) and the impossibility to account for temporal changes in the exposure to risk factors [45]. Furthermore, the issue of residual confounding requires calculating PAF for clusters of risk factors, rather than for a single risk indicator. Indeed, cardiovascular risk factors and exposures to various environmental pollutants cluster within individuals. Later GBD [46] or GBD-associated [47, 48] publications moved the focus of lead-associated adverse health outcomes from hypertension to ischemic heart disease and suggested that the pre-industrial blood lead concentration in man might have been as low as 0.016 μg/dl, based on extrapolation by linear regression of

BL on bone lead in data obtained from environmentally or occupationally exposed humans. One wonders why stroke, the complication most closely associated with the BL level was not considered as primary endpoint rather than ischemic heart disease and how blood and bone samples collected in the early 1990's and the linear extrapolation might justify the 0.016 mg/dl BL level, which with the current technology is even not measurable.

SPHERL

The Study for the Promotion of Health in Recycling Lead (SPHERL [NCT02243904]) is the first prospective study, which monitored the health effects related to occupational lead exposure in newly hired workers without known previous exposure [22]. The co-primary endpoints, for which SPHERL was powered [41], were the changes in BP and renal function. The secondary endpoints included the autonomous nervous regulation of the cardiovascular system, as captured by heart rate variability (HRV), neurocognitive function and peripheral nerve conductivity. The workers underwent follow-up visits 1 and 2 years after enrolment. Detailed flow charts describing the selection of workers analyzed for each endpoint have been published [18–22].

For BP and renal function [22], the 234 workers analyzed were on average 28.5 years old and included 91.9% men. The baseline BL concentration was 4.35 μg/dl and increased 3.2-fold over 2 years of follow-up (range: 0.92–6.45 years). The changes in BP and renal function were not significantly correlated with the follow-up-to-baseline BL ratio. The fully-adjusted changes in systolic/diastolic BP associated with a doubling of BL were –0.25/–0.12 mm Hg (CI, –0.94 to 0.44/–0.66 to 0.42 mm Hg). Heat maps (Figure 4) demonstrated that the changes in BP were mainly determined by the baseline BP (P <0.0001), while the change in BL did not reach significance in these analyses (P ≥0.47). Accordingly, in the unadjusted, adjusted and fully adjusted analyses, the HRs for incident hypertension were not significant (P ≥0.063). Similarly, the changes in eGFR derived from serum creatinine or serum cystatin C were not related to the follow-up-to-baseline BL ratio, amounting to –0.70 ml/min/1.73 m^2 (CI, -1.70 to +0.30 ml/min/1.73 m^2) and to –1.06 ml/min/1.73 m^2 (–2.16 to +0.03 ml/min/1.73 m^2), respectively. Heat maps (Figure 5) indicated that the changes in renal

function were mainly determined by the baseline eGFR ($P \leq 0.0011$), while the change in BL did not reach significance in these analyses ($P \geq 0.057$).

HRV was measured from 5-minute ECG recordings in the supine and standing positions, using the Cardiax software, V.4.14.0 (International Medical Equipment Development, Budapest, Hungary). The analyses of heart rate and HRV [19] included 195 workers (91.3% men; mean age, 27.8 years). Study participants with irregular heart rhythm or taking antihypertensive agents or neuro-active drugs (benzodiazepines, neuroleptics, anti-epileptics, sympathomimetics, amphetamines, and recreational drugs) were excluded from analysis. In analyses stratified by quartiles of blood lead changes, trends in heart rate and in HRV derived by the Fourier or autoregressive approach did not reveal a dose-response curve [19]. In multivariable-adjusted mixed models, heart rate, and HRV were unrelated to BL with no differences between baseline and follow-up. Along similar lines, the orthostatic heart rate responses were not altered by increasing lead exposure. Thus, an over 3-fold BL increment did not affect autonomous neural function, as captured by HRV [52].

Nerve conduction velocity is a common test of the function of the peripheral nervous system in lead-exposed workers [53, 54]. The study nurses used a handheld device and related software (Brevio Nerve Conduction Monitoring System, NeuMed, West Trenton, NJ, US) to stimulate the left and right median nerve at a gradually increasing voltage, until the maximum compound motor action potential of the short thumb abductor muscle was reached [52]. Peripheral nerve conduction velocity was assessed in 192 workers. From the lowest to the top quartile of the distribution of the follow-up-to-baseline blood lead concentration ratio, the percent changes in latency time were 2.91% (CI, –0.89% to 6.85%; $P = 0.14$), 0.86% (CI, –2.48% to 4.32%; $P = 0.064$), 2.14% (CI, –0.86% to 5.23%; $P = 0.057$), and 2.57% (CI, –0.93% to 6.19%; $P = 0.67$); the *P*-value for linear trend was 0.98. The percent changes in latency time associated with a doubling of blood lead from baseline to follow-up were –0.05% (CI, –0.57% to 0.46%; $P = 0.84$) unadjusted and –0.09% (CI, –0.58% to 0.40%; $P = 0.72$) fully adjusted for confounders. As a real-world experiment and using a wide range of endpoints [41], SPHERL confirmed the safety of workers in battery-recycling plants in the United States operating under OSHA regulations.

REGULATIONS ADDRESSING LEAD EXPOSURE

Tightening environmental regulations led to the banning of lead containing paint (1976), the phasing out of leaded gasoline by the end of the 20th century [55], the elimination of lead as construction material, the replacement of lead pipes in drinking water distribution, the elimination of lead solder in food cans and the compulsory and systematic recycling of lead batteries and other lead waste. Accordingly, BL in American adults dropped from 13.1 μg/dl in NHANES II (1976–1980) to 2.76 μg/dl in NHANES III (1988–1994), to 1.64 μg/dl in NHANES IV (1999–2002), and to 0.93 μg/dl in the 2017–2020 NHANES cycles [16, 42].

OSHA provides regulations stipulating how lead exposure at the workplace should be contained. The compulsory measures comprise regular medical monitoring, proper workplace ventilation, and the obligatory use of personal protective equipment. Recently, EU Directive (6417/23) was adopted, amending Council Directives 98/24/EC and 2004/37/EC with regard to the occupational limits for BL and inorganic lead compounds and diisocyanates. The new Directive proposes a reduction of lead in air from 0.15 mg/m^3 to 0.03 mg/m^3 and decreases permissible BL thresholds from 70 μg/dl to 30 μg/dl until 2028 and further to 15 μg/dl thereafter. Workers whose BL is above thresholds due to past exposure must undergo regular medical surveillance, but can continue working if their BLs show a decreasing trend. To mitigate reprotoxic effects, the BL level requiring medical surveillance in female workers of childbearing age was set at 4.5 μg/dl. The Directive, for the first time in Europe, imposes limits for isocyanate functional groups of diisocyanate compounds (NCOs): 6 μg NCO/m^3 for chronic and 12 NCO/m^3 for short-term exposure. However, the Directive recognized that it may be difficult to comply with the proposed NCO limits, because of measurement feasibility and the time needed to implement risk management. Therefore, a transitional value of 10 μg NCO/m^3 with an associated short-term exposure limit of 20 μg NCO/m^3 applies until the end of 2028. A matter of concern is that in middle- and low-income countries, legislation to protect lead-exposed workers is still under revision or only loosely reinforced [1].

PERSPECTIVES

Lead is worldwide a ubiquitous metal with high toxicity affecting not only the cardiovascular system in adults, as currently reviewed, but most other organs as well. Even though lead exposure had substantially declined in developed countries, the long-term health effects of lead exposure in low- and middle-income countries still remain a matter of concern [56], because regulations are still being developed or insufficiently reinforced [57, 58]. However, the literature on the health effects of lead exposure is skewed by publication bias favoring articles supporting a relation between disease and lead exposure and by selective citation of such studies, as illustrated by a recently published review [59]. This review did not include a stated strategy to search the literature and to select publications for inclusion and in contrast to other articles [29], did not include any reference reaching conflicting interpretations. To be clear on this point, the current review, as explicitly stated in the Introduction, summarized a 40-year research track of a single consortium of investigators.

Although since the turn of the century huge progress has been made in reducing occupational and environmental lead exposure, further lowering exposure to practicable limits should rank high on the agenda of policy makers, especially in low-income countries with outdated industrial infrastructure. Along with eliminating the few remaining point sources of lead, some of which until now escaped detection, lead-exposure containing environmental policies should focus on reducing the exposure to particulate loaded with lead deposited in the previous century [2] and on educating and empowering deprived social groups, particularly in low- and middle-income countries.

From clinical point of view, the 2024 Guidelines for the Management of Elevated Blood Pressure and Hypertension [60], state that the pathogenesis of hypertension involves complex interactions between environmental and behavioral factors, genes, hormonal networks, and multiple organs systems, including the renal cardiovascular and central nervous system. The take home message for the practicing clinicians is therefore that in the pathogenic work-up of unexplained hypertension or chronic kidney disease, environmental pollutants and their exposure vectors should always be considered. If lead exposure is suspected and given that co-exposure is common, blood or urinary lead and cadmium should

be measured, but only at a certified laboratory qualified for the measurement of heavy metals.

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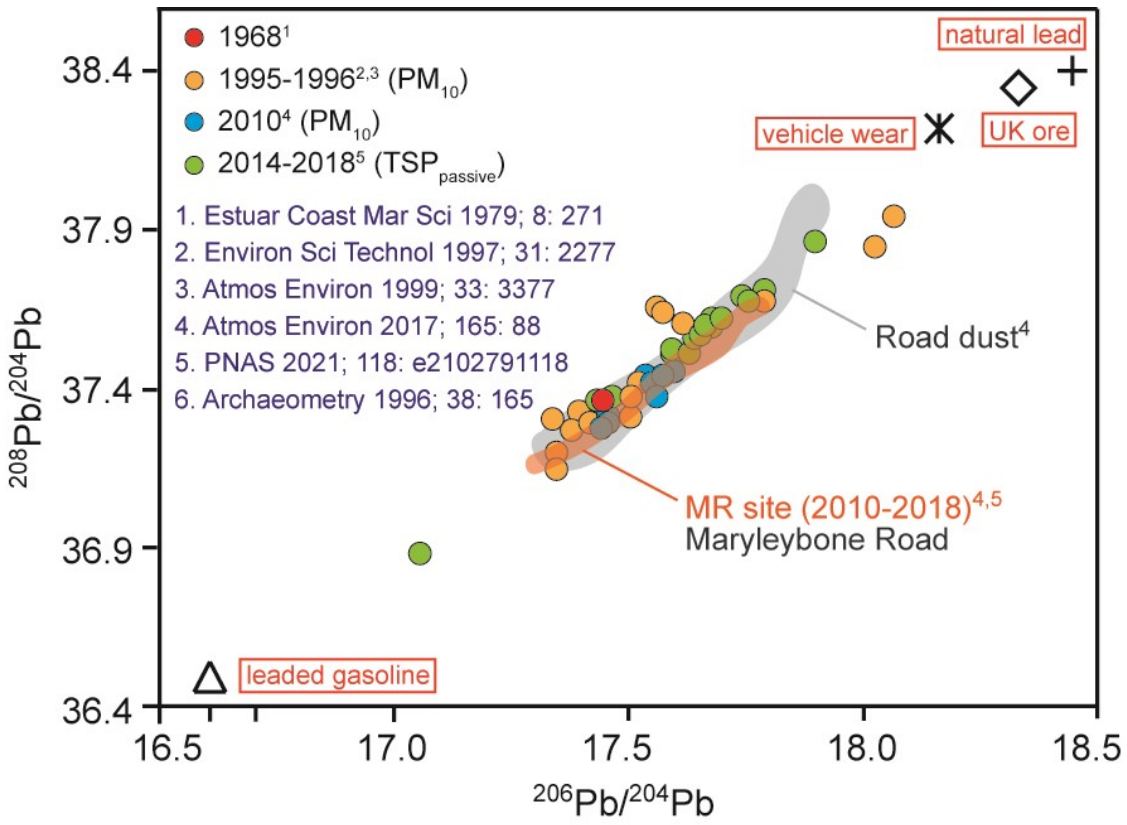

Figure 1. Contribution of 20th century lead deposition to atmospheric environment in London. Marleybone Road is a thoroughfare with very heavy traffic in central London within the City of Westminster. The isotopic ratios of lead in dust particles allow to identify the origin of the lead contamination. Reproduced from [2]

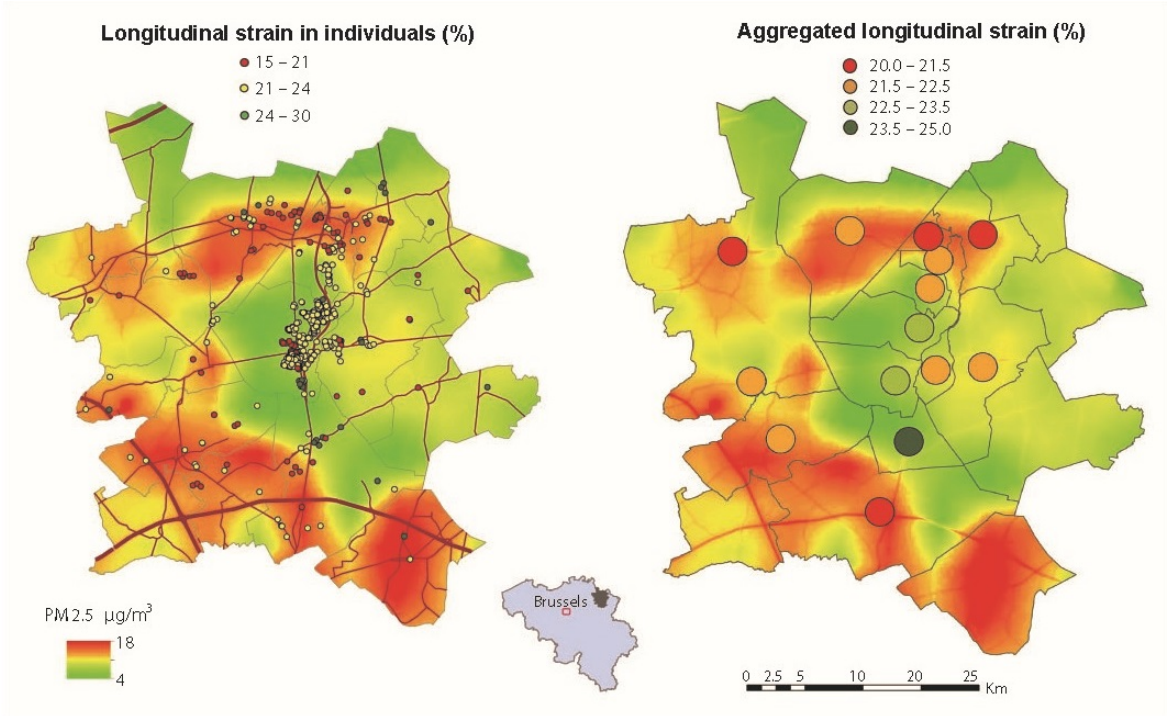

Figure 2. Geographical association of multivariable-adjusted longitudinal LV strain at the individual level or aggregated per municipality were associated with $PM_{2.5}$ air pollution contours. Grey lines indicate borders of municipalities. Red lines represent the air pollution contours of major roads. The Spearman rank correlation between longitudinal LV strain and exposure to $PM_{2.5}$ was –0.13 (P = 0.0005) and –0.90 (P <0.0001) in individual and aggregated data, respectively. Reproduced from [45]

Abbreviations: LV, left ventricular; PM, particulate matter

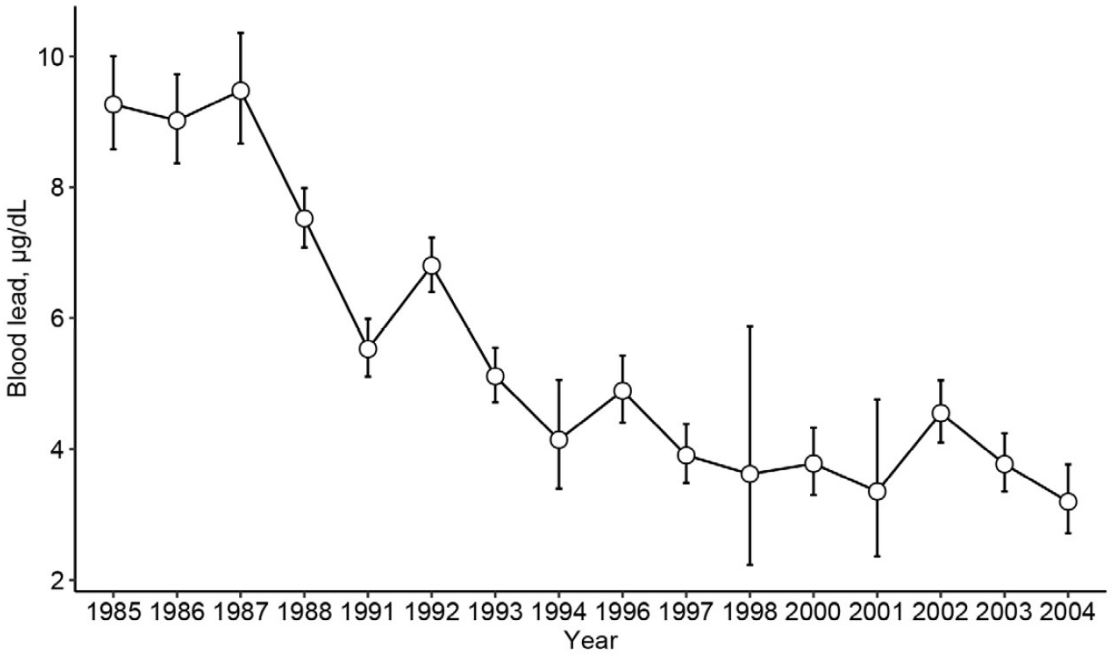

Figure 3. Secular trend of blood lead level of participants with repeated measures in FLEMENGHO Study. Shown is the geometric mean and standard error of blood lead. Reproduced from [28]

Abbreviation: FLEMENGHO, Flemish Study on Environment, Genes and Health Outcomes

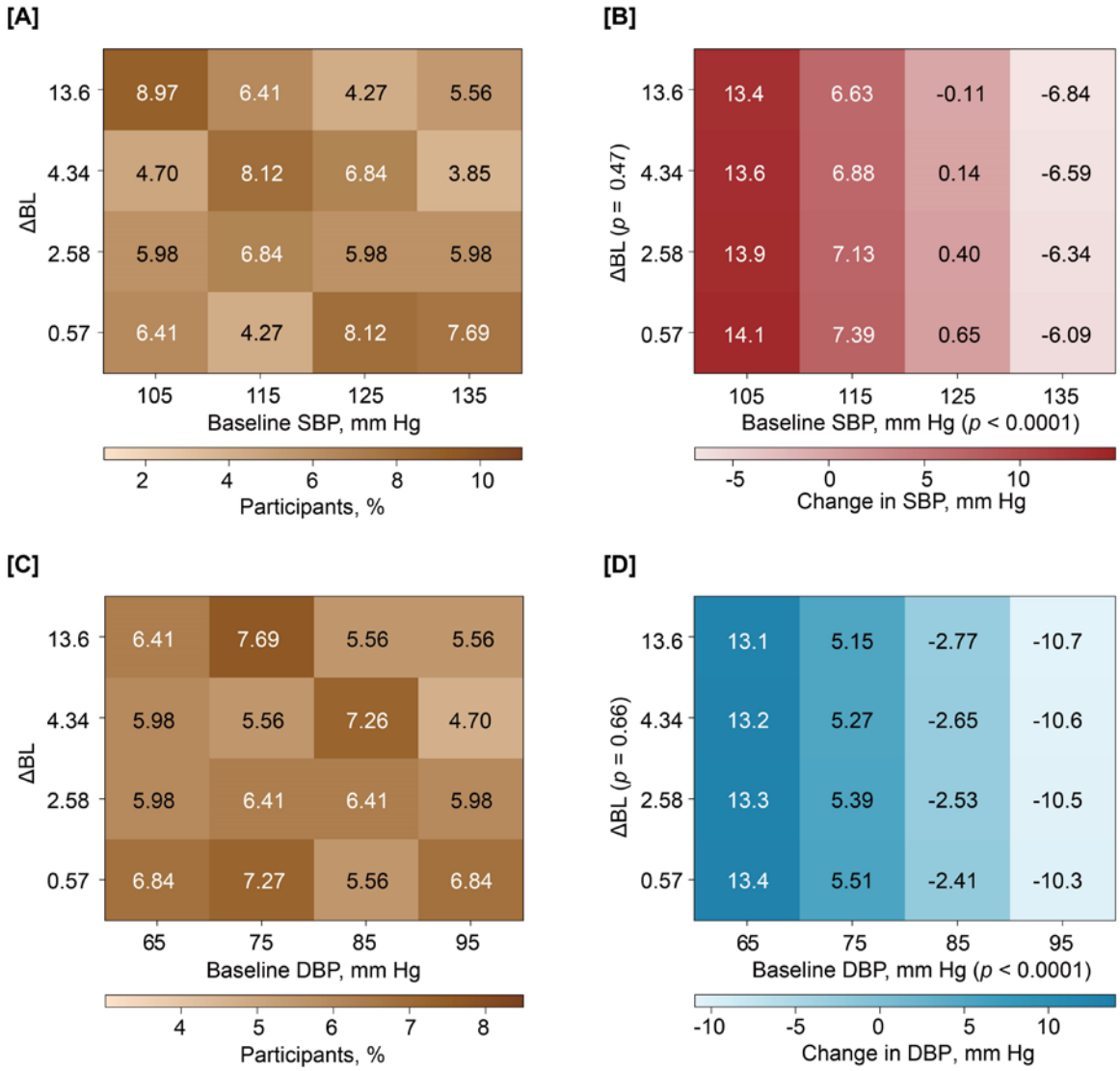

Figure 4. Heat maps relating the change in systolic and diastolic blood pressure to the blood pressure level at baseline and the change in blood lead from baseline to last follow-up. For SBP (**B**) and DBP (**D**), the associations were derived by mixed models accounted for sex, age, BP and body mass index at baseline, ethnicity (white vs other), change in body weight during follow-up, and the baseline values of and the changes during follow-up in heart rate, smoking status, total-to-HDL serum cholesterol ratio, γ-glutamyltransferase, and serum creatinine. All models were fully adjusted. The percentage of participants (**A** and **C**) contributing to the cross-classification between the baseline blood pressure (horizontal axis) and the fold change in BL (vertical axis) are given for each analysis run. Reproduced from

[29], which was published was an open-access article under the terms of the Creative Commons Attribution-NonCommercial-No Derivatives License.

Abbreviations: ΔBL, change in blood lead; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure

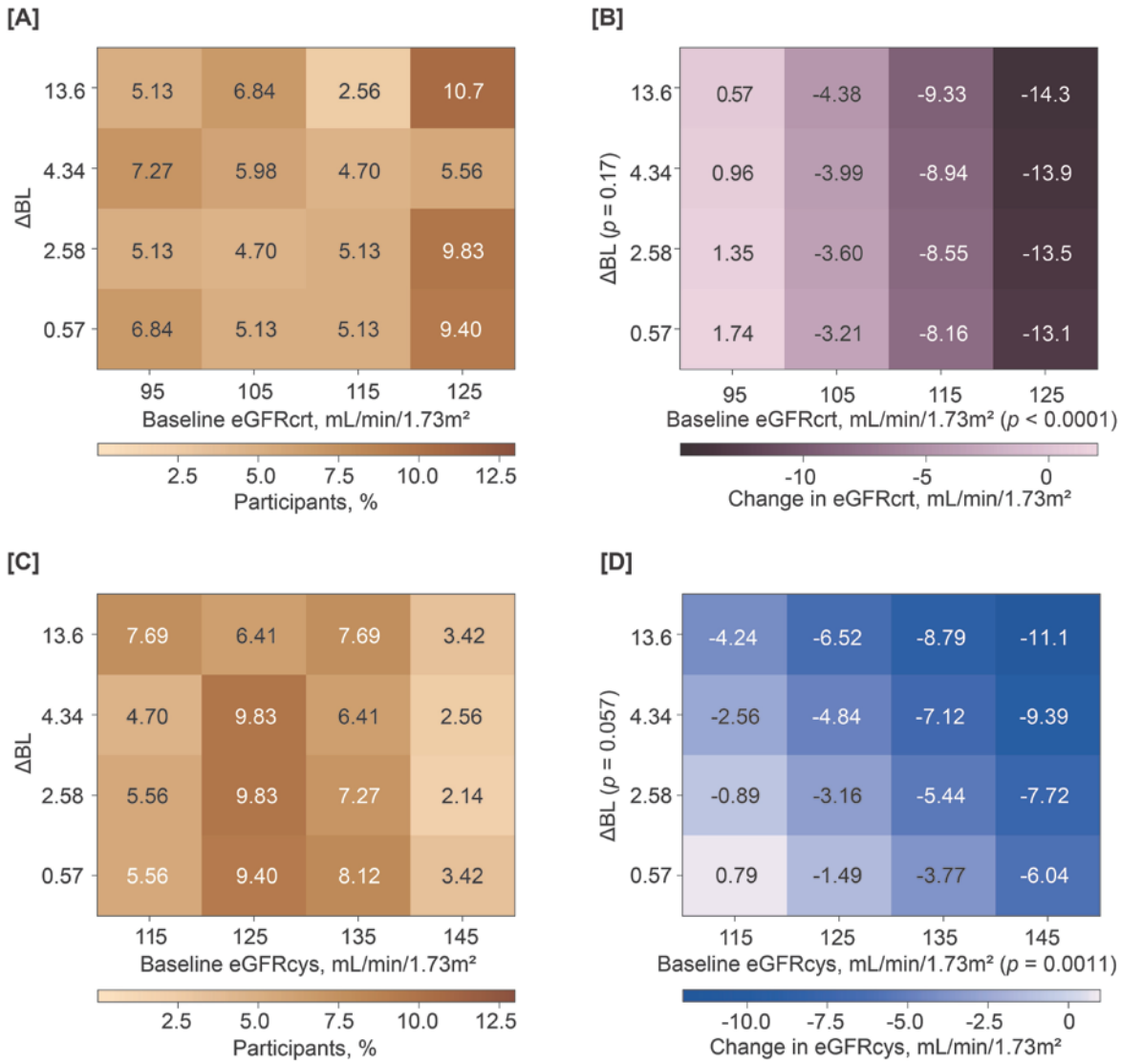

Figure 5. Heat maps relating the change in eGFRcrt and eGFRcys to the eGFR level at baseline and the change in blood lead from baseline to last follow-up. For eGFRcrt (**B**) and eGFRcys (**D**), the associations were derived by mixed models, sex, age, follow-up duration, the time of day of blood sampling (nighttime vs. daytime), the baseline renal function

measure being analyzed, baseline body mass index, change in body weight, and the baseline values of and changes during follow-up in smoking status, mean arterial pressure (diastolic BP plus one third of the difference between systolic and diastolic BP, the total-to-HDL cholesterol ratio and γ-glutamyltransferase, and changes in antihypertensive medication (yes vs. no) during follow-up. All models were fully adjusted. The percentage of participants (**A** and **C**) contributing to the cross-classification between the baseline blood pressure (horizontal axis) and the fold change in BL (vertical axis) are given for each analysis run. Reproduced from reference 29, which was published was an open-access article under the terms of the Creative Commons Attribution-NonCommercial-No Derivatives License

Abbreviations: eGFRcrt, the glomerular filtration rate estimated from serum creatinine; eGFRcys, the glomerular filtration rate estimated from serum cystatin C; other — see Figure 4