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Systemic review of genetic and epigenetic factors underlying differential toxicity to environmental lead (Pb) exposure

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Abstract

Lead (Pb) poisoning is a major public health concern in environmental justice communities of the US and in many developing countries. There is no identified safety threshold for lead in blood, as low-level Pb exposures can lead to severe toxicity in highly susceptible individuals and late onset of diseases from early-life exposure. However, identifying “susceptibility genes” or “early exposure biomarkers” remains challenging in human populations. There is a considerable variation in susceptibility to harmful effects from Pb exposure in the general population, likely due to the complex interplay of genetic and/or epigenetic factors. This systematic review summarizes current state of knowledge on the role of genetic and epigenetic factors in determining individual susceptibility in response to environmental Pb exposure in humans and rodents. Although a number of common genetic and epigenetic factors have been identified, the reviewed studies, which link these factors to various adverse health outcomes following Pb exposure, have provided somewhat inconsistent evidence of main health effects. Acknowledging the compelling need for new approaches could guide us to better characterize individual responses, predict potential adverse outcomes, and identify accurate and usable biomarkers for Pb exposure to improve mitigation therapies to reduce future adverse health outcomes of Pb exposure.

Keywords

lead; in vivo; in vitro; epidemiology; pathways; genetics; epigenetics

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The heavy metal lead (Pb) is a ubiquitous persistent environmental and occupational toxicant affecting human populations. Despite years of intensive research, educational efforts, and remedial measures, Pb poisoning remains a major environmental health concern. Human exposure to Pb occurs through inhalation of air contaminated with Pb dust, ingestion of contaminated food and/or water, or direct contact through the skin (Olympio et al. 2009). Although Pb has been removed from paints and gasoline, it can still be found in a number of consumer products used daily such as batteries, toys, food, and water (Olympio et al. 2009). The incidence of Pb poisoning is associated with numerous factors, including socioeconomic status, rurality, race, age, and the date one's residence was built (Levin et al. 2008). Urban children in low socioeconomic status (SES) areas are at the highest risk, presumably due to the presence of Pb in older building materials and reduced access to healthy sources of nutrition (Mason et al. 2014; Tong et al. 2000). Additional sources of Pb in these areas are aging public infrastructure and mistreatment of water purification as occurred in Flint, Michigan (Masten et al. 2016).

Pb introduced into the bloodstream is excreted in urine and bile with a median biologic half-life of about 30 days (Barbosa et al. 2005), which mostly reflects acute exposure. The remaining Pb is distributed throughout soft tissues of the body, and eventually accumulates in bones with a half-life of approximately 25 to 30 years (Rădulescu and Lundgren 2019), which reflects one's cumulative exposure over time (Pawlas et al. 2012). Although Pb is not essential for biological functions, it has the capacity to disrupt biological systems by altering molecular interactions, enzyme activities, and cell signaling and function (García-Lestón et al. 2012; Sanders et al. 2009). As a cumulative toxicant, acute and chronic exposure to Pb has irreversible toxicity in several human organs and systems, such as nervous, hematopoietic, and reproductive systems, as well as in kidneys and bones (Lopes et al. 2016; Shellenberger 1984). Although early life Pb exposure may have long-term negative impacts in adult health, children are more susceptible to Pb toxicity than adults as they undergo rapid growth and development, and windows of great plasticity and vulnerability accompany these processes. Moreover, children have heavier exposures because of their behavior, diet, and metabolic and physiologic characteristics (Moya et al. 2004). In fact, they can absorb a greater percentage of Pb from the gastrointestinal tract and inadequate nutrition, iron deficiency, and calcium deficiency can further influence Pb absorption (Hon et al. 2017). The levels of Pb considered safe for children have been repeatedly lowered by regulatory agencies over the past three decades as even low levels of Pb in blood result in adverse outcomes, which currently cannot be reversed (Vorvolakos et al. 2016). According to the latest guideline from the Centers for Disease Control and Prevention (CDC), a reference level of 5 μg/dL should be used to identify children with Pb toxicity (Hon et al. 2017). This reference value is based on the 97.5 percentile of the blood Pb level in U.S. population children aged 1–5 years. Additionally, the European Food Safety Authority (EFSA) concluded that there is no safe exposure to Pb based on international studies (Authority 2012). There is a considerable variation in the severity of harmful effects of Pb exposure in both the general population and occupational workers (Kim et al. 2014). Differences in health outcome may be affected by nutritional and physiological factors, degree of exposure, and/or host factors such as age, sex, genetic differences, and

microbiome composition that can modify adsorption, distribution, metabolism and excretion (ADME), or the sensitivity to the toxic effects of Pb (Gundacker et al. 2010).

Experimental and epidemiological studies have shown gene-environment interactions and epigenetic changes to have a plausible role in variation to adverse health effects of Pb (Mitra et al. 2017). Such gene-environment interactions are still poorly understood as epidemiological studies in humans are confounded by many other factors such as co-morbidities, health and physiological status, and exposure to a wide variety of chemical mixtures over the lifetime of an individual (Harrill and McAllister 2017). Additionally, only surrogate measures of Pb exposure, that may not accurately represent body burden, are used in human studies (Barbosa et al. 2005). Challenges and limitations also exist in preclinical animal studies, the primary limitation being the use of inbred rodent strains that lack genetic diversity and thus the differential susceptibility that exists in humans. In fact, many recent studies have shown that genetic background can profoundly affect adverse outcomes of exposures to environmental contaminants (Harrill and McAllister 2017). On the other hand, analyses of animal models exposed to Pb have the potential to disclose unpredicted outcomes and, most importantly, mechanisms of toxicity relevant to human and environmental health risk assessment. Here we review available published information on Pb toxicity, genetic and epigenetic studies that underly variable Pb-induced adverse health outcomes in animal models and human cohorts.

Health effects from Pb exposure

Pb as cumulative toxicant can cause many deleterious systemic effects and yet their underlying mechanisms have not been completely unfolded. Information on Pb toxicity has been reviewed below from epidemiological studies in humans. The most extensively studied adverse health outcomes are neurological, renal, cardiovascular, hematological, reproductive, and developmental effects (Flora et al. 2012).

Research provides substantial evidence that Pb exposure alters the central nervous system with the brain being the most sensitive organ. Specifically, Pb can disrupt key molecules during neuronal migration and differentiation; interfere with synapse formation; premature differentiation of glial cells; interfere with neurotransmitter release (Mason et al. 2014). Pb effects on glutamatergic transmission can affect both development and neuronal plasticity (Sanders et al. 2009). Early-life exposure to Pb has short- and long-term consequences on cognitive function (e.g., lower IQ, lowered learning and memory, poor fine motor skills, antisocial and delinquent behaviors, and attention-deficit hyperactivity disorder (Caito and Aschner 2017). Behavioral problems, including attention-deficit hyperactivity disorder have been associated with disruption of dopaminergic functioning (Sanders et al. 2009). Moreover, recent evidence links developmental Pb poisoning with the etiology of disorders that appear much later in life, such as Alzheimer’s disease, Parkinson’s disease, and schizophrenia (Ordemann and Austin 2016). The underlying mechanism for neurotoxicity is not fully understood and is being actively explored. Oxidative stress, altered cell signaling, and neurotransmission play a major role in Pb neurotoxicity.

Adverse renal effects of Pb have been reported in numerous epidemiological studies. Despite the nephropathy caused by Pb exposure, the mechanisms by which Pb enters target cells in the kidneys are not well understood. Early-life exposure to low-levels of Pb has been shown to cause glomerular hypertrophy, which may result in renal insufficiency later in life. Furthermore, acute Pb exposure affects renal tubules determining defects in solute and amino acid transport culminating in Fanconi syndrome, whereas chronic Pb exposure results in progressive nephritis (Mitra et al. 2017). Pb-induced kidney injury has been reported to be associated with increased oxidative stress, leading to alterations of the mitochondrial permeability transition pore (MPTP) which can initiate apoptosis in kidney cells. Additionally, Pb can impair calcium distribution in renal cells leading to activation of signaling pathways that trigger apoptosis (Orr and Bridges 2017). Overall, the Pb role in kidney function is very inconsistent suggesting that individuals might have different responses to Pb poisoning. Effects on blood pressure are the most studied cardiovascular outcome. Epidemiological studies suggest a link between childhood Pb exposure and development of hypertension (Mitra et al. 2017). However, Pb exposure, as a causal factor of hypertension is still controversial (Mitra et al. 2017). High concentrations of Pb are toxic to both heart and vascular smooth muscle (Prozialeck et al. 2008) increasing the risk for mortality (Lanphear et al. 2018). Furthermore, nephrotoxicity Pb-induced can indirectly affect the cardiovascular system by modulating renin and angiotensin production.

Pb toxicity to the hematopoietic system has been confirmed in numerous studies. Exposure to Pb can result in hemolytic or Frank anemia as a consequence of the decrease in hemoglobin synthesis and in erythrocytes lifespan. In fact, Pb severely affects the heme biosynthesis by down-regulating three vital enzymes: delta-aminolevulinic acid dehydratase (ALAD), aminolevulinic acid synthetase (ALAS) and ferrochelatase. Anemia is usually observed in chronic Pb poisoning in adults and in case of iron deficiency, especially kids and women (Mitra et al. 2017). An increase in oxidative stress can damage or destabilize red blood cell (RBC) membranes.

Exposure to Pb has been reported to alter immune functions. Epidemiological and experimental studies suggest that Pb can influence levels of immunoglobulins, alter the number of lymphocytes, peripheral blood mononuclear cells (PBMCs) and macrophages, and depression neutrophil functions (Fenga et al. 2017; Mishra et al. 2003). In particular, Pb can affect both cellular and humoral immune response by altering Th cell function and increasing susceptibility to the development of autoimmunity and hypersensitivity (Mishra 2009). Pb can also deregulate cytokines production and tryptophan degradation which could produce depression of immune responses and contribute to the development of several immunological pathologies in individuals occupationally exposed (García-Lestón et al. 2012).

Reproductive studies in humans suggest Pb as a contributing factor to infertility in both men and women (Kumar 2018). Health effects on male reproductive system have been largely investigated in comparison to the female system. Specifically, it has been reported damage to sperm and potential alterations in serum levels of reproductive hormones (Naha et al. 2005; Taha et al. 2013). On the other hand, epidemiological studies conducted in women show an increased risk for miscarriages (Vigeh et al. 2010), prematurity, and earlier age

at onset of menopause (Eum et al. 2014; Irgens et al. 1998). However, results on female reproductive effects from Pb are inconsistent. Similarly, Pb exposure has been associated with developmental outcomes such as decreased birth size and child growth (Berkowitz et al. 2006; Zhu et al. 2010) and yet results are also conflicting.

In addition, adverse health outcomes from Pb exposure to other organ systems have been reported as well. Pb can be considered an endocrine disruptor compound as it can interfere with the endocrine system. Early-life Pb exposure has been associated with low levels of vitamin D (Chang et al. 2014), delayed puberty and early menopause (Eum et al. 2014). Associations have also been reported between Pb exposure and decreased lung function, increased bronchial hyperreactivity, and increased risk of respiratory diseases (Taylor et al. 2019).

Although the skeleton is the major reservoir of lead in the body, its effect on it has not been widely studied. Early-life Pb exposure impacts skeletal development through unknown mechanisms which may affect bone growth and remodeling. From *in vitro* data and clinical observations, it appears that Pb may influence cartilage differentiation at two stages: chondrogenesis enhancement and arrest of transition to bone (Puzas et al. 2004). Given the effect, lead could be an unrecognized factor in osteoporosis as it accelerates bone maturation but determining a reduction in bone mass (Puzas et al. 2004). However, human studies are limited.

In severe cases of Pb poisoning, children or adults may experience severe abdominal pain, nausea, vomiting and constipation, as the gastrointestinal tract is responsible for Pb intake and uptake (Fenga et al. 2017).

Genetic susceptibility to Pb poisoning

The results of the strength-of-evidence of association between genetic factors and Pb susceptibility, including health outcomes are summarized in Figure 1. Generally, factors influencing susceptibility to Pb toxicity include variants and polymorphisms in genes involved in Pb ADME (Onalaja and Claudio 2000).

Epidemiological studies

Three genes have been widely reported to be involved in Pb metabolism: δ-aminolevulinic acid dehydratase (*ALAD*), the vitamin D receptor (*VDR*), and the hemochromatosis (*HFE*). Polymorphisms in *ALAD*, whose genotype frequencies vary by geography and ethnic origin, have been implicated in susceptibility to Pb toxicity (Onalaja and Claudio 2000). ALAD is the second enzyme in the heme synthesis pathway and the primary binding protein in erythrocytes (Zheng et al. 2011). Human ALAD, encoded by a single gene on chromosome (Chr) 9q34, has eight variants that have been described. The most studied polymorphism is a G → C transversion at position 177 in the coding region of *ALAD* (rs1800435), substituting a neutral asparagine (Asn) for a positively charged lysine (Lys) at amino acid 59, which results in three distinct phenotypic variants (ALAD1-1, ALAD1-2, and ALAD2-2) (Battistuzzi et al. 1981; Wetmur et al. 1991). The *ALAD1* (59Asn) gene product is more electronegative than that of *ALAD2* (59Lys) suggesting that ALAD1-2/2–2 may

bind Pb more tightly than ALAD1-1. Consistent with this prediction, *ALAD2* carriers seem to retain more Pb in blood than *ALAD1* homozygotes, while there is no difference at low exposure (Scinicariello et al. 2007). Occasionally, *ALAD2* has also been reported to be associated with higher concentration of Pb in urine. Furthermore, *ALAD* polymorphisms can influence urinary excretion of δ-aminolevulinic acid (U-ALA) in children with ALA being one of the contributors to Pb-induced neurotoxicity (Tasmin et al. 2015). Furthermore, exposure to Pb negatively impacted achieved growth in children carrying *ALAD1-2* and *ALAD2-2* genotypes (Kerr et al. 2019). Other *ALAD* polymorphisms have been investigated as well, however their role in Pb accumulation is not clear due to study limitations (Mani et al. 2019). Since Pb exerts toxic effects on numerous organ systems, *ALAD* genotype might affect inter-individual variation in susceptibility to these toxic effects through differential sequestering of Pb by ALAD, making it less bioavailable for pathogenetic process. Although it has been shown that the *ALAD* genotype alters the toxicokinetics of Pb, the association between adverse health outcomes of Pb and *ALAD* genotype is not well established.

Through an entirely different pathway, another much less studied genetic variant also impacts blood Pb burden and brain ALA. The solute carrier family 15 member 2 gene (*SLC15A2*), also known as *PEPT2*, protects the brain from excess peptide-bound amino acids and potentially limits Pb-induced neurotoxicity (Hu et al. 2007). Two *PEPT2* single nucleotide polymorphisms, *PEPT2-1* and *PEPT2-2*, predominate. At lowest levels of Pb exposure, males but not females homozygous for *PEPT2-2* have significantly increased blood Pb level (Sobin et al. 2011).

Variants of the vitamin D receptor gene (*VDR*), involved in intestinal Ca^{2+} absorption and storage in the bone, have been suggested to play a role in modifying Pb absorption since it can mimic calcium at the calcium binding site of transporters. VDR plays a major role in maintaining calcium and phosphate homeostasis, regulating bone metabolism, and anti-proliferative, pro-apoptotic, and immunosuppressive activities. *VDR*, located on human Chr. 12, is regulated by the active form of vitamin D3 (1,25-dihydroxyvitamin D3). Many polymorphisms have been identified in *VDR*, mostly defined by restriction fragment length polymorphisms (RFLPs). Previous studies showed that the *Bsm* I RFLP polymorphism in intron 8 is associated with uptake of Pb (Schwartz et al. 2000; Weaver et al. 2005). There are indications that carriers of the *Bsm* I *VDR* allele are predisposed to significantly higher Pb concentrations in blood, bones, and urine compared with non-carriers of the *Bsm* I allele. Moreover, the *Fok* 1 *VDR* RFLP may modify the relationship of Pb exposure and blood Pb levels during the first two years of life, when children are most susceptible to Pb ingestion and absorption. The *Fok* 1 *VDR* allele is associated with posture disturbance as well as hearing impairment in children exposed to very low Pb levels (Pawlas et al. 2014; Pawlas et al. 2015). Little information is available about the association between blood Pb levels and other polymorphisms defined by *Apa* I and *Taq* I RFLPs of *VDR*. Overall, modification of both *ALAD* and *VDR* genes have shown to have an impact on cognition in children exposed to Pb (Pawlas et al. 2012). However, the role of *VDR* polymorphisms in Pb uptake from bone tissues remains unclear.

There is strong evidence that excessive Pb uptake affects iron metabolism and may be an important cause of iron deficiency. Thus, iron metabolism genes are potential players in Pb

absorption and storage. The hemochromatosis gene (*HFE*) is responsible for accumulation of iron in humans, variants in which can lead to severe liver failure, heart disease, or diabetes (Fleming et al. 2005). Two common missense mutations (H63D and C282Y) result in HFE deficiency, leading to upregulation of transferrin receptors and divalent metal transporters (DMTs) followed by increased iron uptake in the gut and also perhaps Pb (Hollerer et al. 2017). Pregnant mothers with H63D variants have higher Pb levels in placental tissue, umbilical cord, and blood compared to the homozygote typical (HH) (Kayaalti et al. 2015a). A strong association between Pb exposure and amyotrophic lateral sclerosis (ALS) has been reported among *HFE* C282Y variant carriers (Eum et al. 2015). However, the mechanistic basis for the relationship of increased Pb absorption and HFE deficiency has not been proven. Furthermore, there is no strong evidence for the influence of *HFE* variants on Pb body burden. In addition, several association studies revealed the influence of transferrin (*TF*) mutations, a monomeric glycoprotein that facilitates the transport of iron, in modifying the impact of cumulative Pb exposure on factors such childhood neurocognition, placental transfer, and homocysteine levels (Karwowski et al. 2014; Roy et al. 2013). Apart from *HFE* and *TF*, divalent metal transporter 1 (*DMT1*) has been implicated as a modulator of Pb toxicity in one study. A single nucleotide polymorphism (IVS4þ44C/A) in *DMT1* was associated with higher blood Pb levels in 486 unrelated and healthy individuals in a Turkish population (Kayaaltı et al. 2015b). However, the study only suggested a potential link between the genetic variant and increased disease risk. Since these polymorphisms could potentially determine several phenotypic outcomes from Pb exposure due to its crosstalk with iron, additional studies are warranted.

Several polymorphisms in the glutathione-S-transferase genes *GST* (*GSTM1*, *GSTT1*, and *GSTP1*), key players in metal-induced oxidative stress defenses, can contribute to phenotypic variation in enzymatic production and activity, and thus also may play a role in susceptibility to Pb toxicity. *GSTP1* Ile105Val and *GSTM1* null genotypes have been associated with modified Pb-induced cognitive function (Eum et al. 2015). Moreover, *GST* polymorphisms like *GSTT1* have been linked to increased blood pressure in Pb-exposed Korean male workers and inflammatory responses associated with Pb toxicity (Bozina et al. 2009; Lee et al. 2012).

Interaction with proteins is an important mechanism of Pb toxicity, especially interactions with high-affinity metal-binding proteins that have a high content of sulfhydryl groups. Metallothioneins (MTs) are cysteine-rich low molecular weight proteins with numerous functions including metal detoxification. Four major isoforms have been identified in mammals (MT1-MT4) (Raudenska et al. 2014). An inverse association between the *MT2a* variant (rs10636) and blood Pb levels has been reported (Fernandes et al. 2016; Gundacker et al. 2009; Whitfield et al. 2007). However, these studies report high variation in outcomes making the results ambiguous.

Several studies have associated cognitive impairment and/or Alzheimer's disease (AD) in adults with low-level Pb exposure (Basha et al. 2005; Weisskopf et al. 2004). However, few studies have evaluated the role of genetic susceptibility on the cognitive effects of environmental Pb exposures. Apolipoprotein E (*APOE*) epsilon-4 allele (e4) is a known genetic risk marker for cognitive function impairment and AD (Liu et al. 2013). In fact,

individuals with *APOE e4* show age-related reduction in hippocampal volume (Lind et al. 2006), decreased antioxidant capacity (Miyata and Smith 1996), and altered use of nutrients (Reiman et al. 2004). Therefore, *APOE e4* carriers may be more susceptible to Pb-induced neuroinflammation and impaired adult hippocampal neurogenesis contributing to these cognitive deficits (Engstrom et al. 2017; Prada et al. 2016).

The endothelial nitric oxide synthase gene (*NOS3*) is also of interest with respect to Pb. It has a common polymorphism *NOS3* Glu298Asp in exon 7 that involves a G → T conversion at nucleotide position 298, which is associated with Pb susceptibility to cardiovascular disease (Vaziri and Ding 2001; Vaziri et al. 2001; Weaver et al. 2003).

A population-based study suggested that genetic polymorphisms within the dopamine receptor D2 gene (*DRD2*) *TAQ IA* increases susceptibility to intelligence deficits in Indian children due to Pb exposure (Roy et al. 2011). Conversely, another population study found no evidence of an interaction between the *DRD2 TAQ IA* polymorphism and Pb exposure on cognition in Mexican children (Kordas et al. 2011). The discrepancy could be due to the differences in the degree of Pb exposure and cognitive domains analyzed, as well as the genetic constitution of the exposed populations.

N-Methyl-D-aspartate receptors (NMDARs) mediate neuronal maturation and excitatory neurotransmission in mammalian brain, which affects learning and memory (Endele et al. 2010; Gavazzo et al. 2008; Omelchenko et al. 1997; Toscano and Guilarte 2005). Polymorphisms in its subunit genes *GRIN2A* and *GRIN2B* have been reported to contribute to Pb-induced toxicity. A population-based study showed that GRIN2A decreased more than 30% after Pb exposure and its SNP rs2650429 is associated with Pb-induced neurotoxicity (Wu et al. 2017). Additionally, genetic variants of *GRIN2A* (rs727605 and rs1070503) and *GRIN2B* (rs7301328 and rs1806201) have been associated with multiple adverse cognitive phenotypes in children (Rooney et al. 2018).

Two SNPs (rs10503970 and rs9642758) were identified on Chr 8 in a genomic region of Unc-5 netrin receptor D gene (*UNC5D*) in humans that have a potential impact on neurodevelopmental outcomes in response to prenatal Pb-exposure (Wang et al. 2017). UNC5D controls neuronal cell survival, cell-cell adhesion, cell guidance (*e.g.*, axon attraction or repulsion), and migration. It also acts as a dependence receptor required for apoptosis induction when not associated with netrin (Takemoto et al. 2011).

Experimental studies: in vivo

So far, only few reports have examined the role of genetic factors in Pb toxicity in rodent populations and have been published. Studies in animal models have shown an association between Pb-induced neurotoxicity and *Grin2a*, which encodes for an important subunit of the N-methyl-D-aspartate receptor (NMDAR) as mentioned previously. Pb exposure can alter GRIN2A concentrations in the brain overall and specifically in the hippocampus of rats and, consequently, can cause synaptic morphological and functional changes in hippocampal CA1 pyramidal neurons (Tüzmen et al. 2015), resulting in behavioral changes (Neal et al. 2011; Wang et al. 2016).

Additionally, adverse effects from Pb are mitigated by MTs whose synthesis has been shown to be Pb-induced in rat liver and kidney (Jurczuk et al. 2006; Stacchiotti et al. 2009). MT null mice and cells are more sensitive to Pb toxicity than wildtype equivalents (Qu et al. 2002).

Epigenetic susceptibility to Pb poisoning

The results of the strength-of-evidence of association between epigenetic factors and Pb susceptibility, including health outcomes are summarized in Figure 2.

Epidemiological studies

Studies of Pb exposure in occupational cohorts have identified DNA promoter methylation changes, where individuals have hypomethylation in long interspersed nuclear elements-1 (LINE-1) (Li et al. 2013) and hypermethylation of *ALAD* (Li et al. 2011) and *CDKN2A* (Kovatsi et al. 2010), that are associated with increased risk of toxicity from Pb exposure. LINE-1 is a repetitive DNA retrotransposon containing numerous CpG islands and its methylation helps maintain genomic stability and integrity (Li and Zhang 2014). LINE-1 methylation represents a biomarker of past Pb exposure in elderly men as it inversely correlates with bone Pb accumulation (Wright et al. 2010). Besides inhibiting ALAD enzyme activity, Pb can increase the level of *ALAD* methylation and thus decrease *ALAD* transcription (Li et al. 2011). Together these changes have been suggested as risk factors of ASD (Keil and Lein 2016). Interestingly, the dual role of the *ALAD* gene in Pb toxicity may suggest a link between epigenetic regulation and genetic polymorphisms contributing to Pb susceptibility. The tumor suppressor gene *CDKN2A*, overexpressed during neurodegeneration, is hypermethylated in individuals with high blood Pb levels, whereas individuals with lower blood Pb levels show only partial methylation (Kovatsi et al. 2010). Additionally, Pb-exposed workers have higher CpG island methylation associated with increased DNA damage making them susceptible to tumorigenesis (Yu et al. 2018). Alteration of DNA methylation within the promoter region of the collagen type 1 alpha-2 (*COL1A2*) gene, an important component of the connective tissues linked to preterm birth in humans, has been associated with blood Pb level in women undergoing *in vitro* fertilization (Hanna et al. 2012).

Lastly, Pb-induced changes in methylation have also been recently reported as transgenerational, with data indicating that a mother's blood Pb levels and methylation status can directly impact that of her children and potentially grandchildren (Sen et al. 2015b). Moreover, exposure to Pb during pregnancy can alter methylation patterns of DNA repair and antioxidant genes in newborns, which could be a risk factor for developing diseases later in life (Montes-Castro et al. 2019). For instance, Pb has been associated with decreased methylation of the glycoprotein VI platelet (*GP6*) gene (Engström et al. 2015), a key factor in platelet aggregation and thrombus formation, and with hypermethylation at the *MEG3* (Nye et al. 2016) regulatory region indicating a link between Pb and onset of cardiometabolic diseases later in life. Another study reported sex-specific changes in DNA methylation from blood of children exposed to Pb in early-life (Sen et al. 2015a). In addition, children that were exposed to Pb *in utero* exhibited irregular methylation

patterns in imprinted genes, which may determine increased risk of childhood obesity and cardiometabolic disease in adulthood (Goodrich et al. 2015; Nye et al. 2016).

Pb toxicity has also been reported to be associated with miRNAs/lncRNAs dysregulation. In particular, exportin-5 (*XPO5*) polymorphism rs2257082 is strongly associated with the susceptibility to Pb poisoning. XPO5 is a key element of the miRNA biogenesis pathway as it is required for the transport of small RNAs and double-stranded RNA-binding proteins from the nucleus to cytoplasm in a Ran-GTP dependent process. Workers harboring the C allele tend to have higher blood Pb levels (Zhang et al. 2016). However, specific molecular mechanisms for how this SNP modifies susceptibility to Pb is not known.

The reported studies show that environmentally relevant Pb exposure in humans, some resulting in even lower blood Pb levels than what recommended from CDC guidelines, can elicit changes in the epigenome that could translate into onset of diseases. However, adverse health effects from such changes can only be suggested since data from most of the human cohort studies lack phenotypic data addressing the overall health status.

Experimental studies: in vitro and in vivo

Studies performed in human cell lines and experimental animals provide evidence that prenatal Pb exposure is inversely associated with genomic DNA methylation in cord blood, suggesting that Pb can alter the fetal epigenome in humans, leading to long-term reprogramming of the DNA methylation profile and increased disease risk (Pilsner et al. 2009). Specifically, Pb exposure in human neural progenitor cells alters DNA methylation status of genes involved in neuronal growth (Senut et al. 2014). Additionally, Pb exposure in human neuroblastoma cultures disrupts IGF1 stimulated methionine synthase activity, an enzyme that regulates DNA methylation (Waly et al. 2004). In these studies, cell line exposure to Pb can be considered relevant to humans since Pb concentrations of 120–1200 nM correspond to blood Pb levels of 1–10 μg/dL. In addition, several *in vivo* studies described below used a wide range of Pb concentrations through different routes of exposures to better recapitulate human exposure and its link to disease onset.

DNA methylation is maintained by DNA methyltranferases (DNMTs) including DNMT1 and DNMT3a and 3b, and involves the recruitment of methyl-CpG binding protein 2 (MECP2) and other proteins (Bestor 2000). DNMT1 is responsible for maintaining methylation patterns following DNA replication whereas DNMT3a and 3b are required for *de novo* methylation and are essential for the establishment of DNA methylation patterns during development (Okano et al. 1999). MECP2 is an important epigenetic regulator as it acts as a transcriptional repressor by recruiting histone deacetylases and other factors to silence target genes (Im et al. 2010). Another study reported a significant decrease in DNMT1 levels across the lifespan of mice developmentally exposed to Pb and altered expression of MECP2, which could contribute to cognitive deficits observed in early-life exposure to Pb (Stansfield et al. 2012).

DNA promoter methylome analysis from a cortical neuron-specific population of cells of male adult mice exposed to Pb *in utero* showed methylation changes, albeit small, in regions connected to neurodevelopment and cognitive functions (Dou et al. 2019). Another study

reported hypomethylation of cadherin 7, type 2 (*Chd7*), a gene essential for neural crest migration and patterning, and its potential link to autism spectrum disorders (ASD) (Hill et al. 2015).

Early-life Pb exposure in rodents was associated with altered expression of genes coding for amyloid-beta precursor protein (*App*) and beta-site *APP*-cleaving enzyme 1 (*Bace1*) later in life, dysregulating biological pathways important to late-onset AD pathogenesis (Kim et al. 2014). Amyloid β (Aβ) plays a crucial role in the pathogenesis of neurodegeneration and its increase can generate ROS and modulate epigenetic patterns of cytosines interfering with repair and oxidation potential of adjacent oxidized guanines (Zawia et al. 2009). This observation is consistent with the role of *APOE e4* in AD and Pb susceptibility due to its role in the process of Aβ deposition contributing to the formation of aggregates or clearance alteration (Dodart et al. 2002). It is possible that the individuals carrying the *APOE e4* variant and exposed to Pb in early life could be even more susceptible to the AD onset.

Epigenetic outcomes from Pb exposure can also happen at the histone level (Schneider et al. 2016). Developmental exposure to Pb can induce aberrant histone modifications in the hippocampi of rats resulting in attention-deficit/hyperactivity disorder (ADHD) (Luo et al. 2014). In addition, mice exposed to Pb during post-natal day (PND) 1–20 showed both decreased levels of specific epigenetic marks such as H3K9Ac and H3K4me2, which are associated with gene activation, and increased levels of H3K27me3 indicative of gene repression (Eid et al. 2016).

The analysis of rats' hippocampi chronically exposed to Pb revealed changes in the expression of miRNAs (*Mir204*, *Mir211*, *Mir448*, *Mir449a*, *Mir34b*, and *Mir34c*) associated with neuronal injury and neurodegeneration (An et al. 2014). The SNP rs 7958904 in the lncRNA *HOTAIR*, involved in oxidative stress, has been linked to Pb susceptibility in workers with high blood Pb levels (Chen et al. 2018). Another study reported an increased expression of the lncRNA lncRpa and the circRNA circRar1, which directly regulate *Mir671* expression to promote neuronal apoptosis in the hippocampus and cerebral cortex of a mouse model of Pb-induced neurotoxicity (Nan et al. 2017). Moreover, early postnatal exposure to Pb alters the expression of miRNAs that target epigenetic mediators and neurotoxic AD-related proteins (Masoud et al. 2016). Undoubtedly, Pb can affect ncRNA expression, but further studies are needed to unveil molecular mechanisms and consequences of such change following exposure.

Discussion

The severity of a toxic effect depends on dose, duration, and windows of exposure (*i.e.* pre- and post-natal development) (Sexton and Hattis 2007). However, humans show great variability in response to environmental exposures even under similar exposure settings (Dornbos and LaPres 2018). The high variability in clinical consequences of Pb exposure may be explained, in part, by the genetic background and the epigenetic changes that can alter susceptibility to Pb. The mechanisms by which Pb, interacting with genetics, trigger epigenetic changes remain to be clarified, and the causal relationship between such alterations and potential aberrant phenotypes needs to be further investigated. Therefore,

it is crucial to understand how genetics and epigenetics influence the wide range of possible outcomes from Pb exposure within populations. This review presents the status of current knowledge on associations between adverse outcomes from Pb exposure and specific genetic and epigenetic factors involved in individual susceptibility to Pb toxicity (Figure 3). At least three polymorphic genes are well-established susceptibility markers in humans: *ALAD*, *VDR*, and *HFE*. Moreover, many other genes reviewed here also modulate Pb absorption and toxicokinetics, but their role remains to be explored as their impact on health effects of Pb are still unclear (Mani et al. 2019). Unlike genotoxic factors, which lead to permanent changes of genes, epigenetic changes are reversible and responsive to different environmental factors including lifestyle, diet, and other exposures (Crews et al. 2014; Foley et al. 2009). Epigenetic modifications occurring early in life have the potential to alter later life events. In fact, disturbances in critical developmental windows can lead to increased risk of adult chronic diseases, including neurodevelopmental disorders that can manifest in childhood, adulthood, or even transgenerationally (Perera and Herbstman 2011). Epigenetic modifications are mediated through a series of interconnected pathways that include DNA methylation, histone modifications, and ncRNAs (Handy et al. 2011). All three epigenetic mechanisms are critical players in the development of a healthy brain. Although it is no coincidence that the previously mentioned Pb-induced epigenetic changes have been primarily associated with neurotoxicity (Senut et al. 2012), it is likely they have roles in other adverse health outcomes in other organ systems as well.

Most of the literature reviewed here relies on epidemiological studies which can address the exposure-response relationship and susceptibility to Pb, but they have been challenging due to the variety of clinical symptoms, uncontrolled environments, the use of safety measurements in occupational environments, difficulty in relating phenotypic effect to dose, uncontrolled genetic backgrounds, and modifying effects of other chemicals. Furthermore, most human exposure studies are underpowered, lacking sufficient information on timing and duration of exposure, and require additional validation in multiple independent sample sets or functional analyses to further elucidate the gene-phenotype relationship. The heterogenous results of these studies is likely due to the difficulty of characterizing gene-environment interactions.

On the other hand, we retrieved very few studies utilizing *in vitro* and/or *in vivo* models particularly regarding the genetic susceptibility to Pb-induced adverse health outcomes.

Although animal models cannot completely mimic real-world exposures, results from animal studies can still provide valuable information to the body of evidence linking genetic and epigenetic factors with susceptibility to Pb toxicity. Animal studies can also shed light on biological mechanisms critical for determining adverse responses from Pb exposure. Understanding these processes as they relate to Pb susceptibility may help identify prevention and/or treatment strategies.

In conclusion, the examination of the available literature on associations between genetic and epigenetic factors and human health outcomes from Pb exposure indicate that both factors can influence an individual’s response to Pb and likely the variation in the types of responses. Moreover, the discrepancy of some reports reveals gaps in knowledge within

the field which would benefit from utilizing new approaches to validate, perhaps by utilizing more *in vitro* and *in vivo* models, and help find additional genetic factors or modifiers contributing to Pb susceptibility. Such knowledge could allow the identification of biomarkers for early diagnosis, disease susceptibility, and design of novel therapeutic or mitigation strategies to prevent long-lasting, Pb-induced effects.

Methods

This study used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to report the results (Figure 4).

Search Strategy

Five databases were searched: Medline (Ovid), Global Health (Ovid), CINAHL (Ebsco), Cab Abstracts (Ovid), and Embase (Ovid) with the concepts of Pb, genetic susceptibility, and human or rats or mice. The search was developed by a medical librarian (M.J.F.) with expertise in systematic reviews. The search strings used to identify studies of interest are reported in Table 1. Results retrieved from the searches were uploaded to Covidence, which identifies duplicates and manages the screening process. Lastly, database searches were supplemented with studies identified through citation searching of included or highly relevant studies.

Study Eligibility Criteria

To be included studies needed to examine the association between general environmental, occupational, and experimental exposures to Pb, genetic and/or epigenetic factors, and health outcomes. Table 2 was developed to identify relevant to health effects of exposure to Pb detailing the Populations of interest, Exposures, Comparators, and Outcomes (PECO). Studies that reported health outcomes from Pb exposure without any link to genetic or epigenetic variation were excluded. Conference abstracts, letters, and editorials were also excluded. Articles were limited to those published between 2000 and September 2020. Only English-language primary studies were eligible.

Study Selection and Extraction

Study selection was conducted in two steps, first by title and abstract, then by full text. A standardized form was developed in Covidence to extract data from included studies. The form covered the following information: study type, risks of bias, location, population, route of exposure, window of exposure, exposure definition (*i.e.*, general environmental, occupational, experimental, relevance to humans), research type (*i.e.*, genetic or epigenetic variation), genetic variants, epigenetic variation, and health outcomes from genetic and epigenetic variants. The health outcomes were classified based upon organ dysfunction or Pb accumulation. The selection and extraction were completed by one reviewer in Covidence (D.C.) and data was exported from Covidence to Microsoft Excel and uploaded into the Texas Data Repository (https://doi.org/10.18738/T8/DTGDZB).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Available of data and material

All data generated or analyzed during this study are included in this published article.

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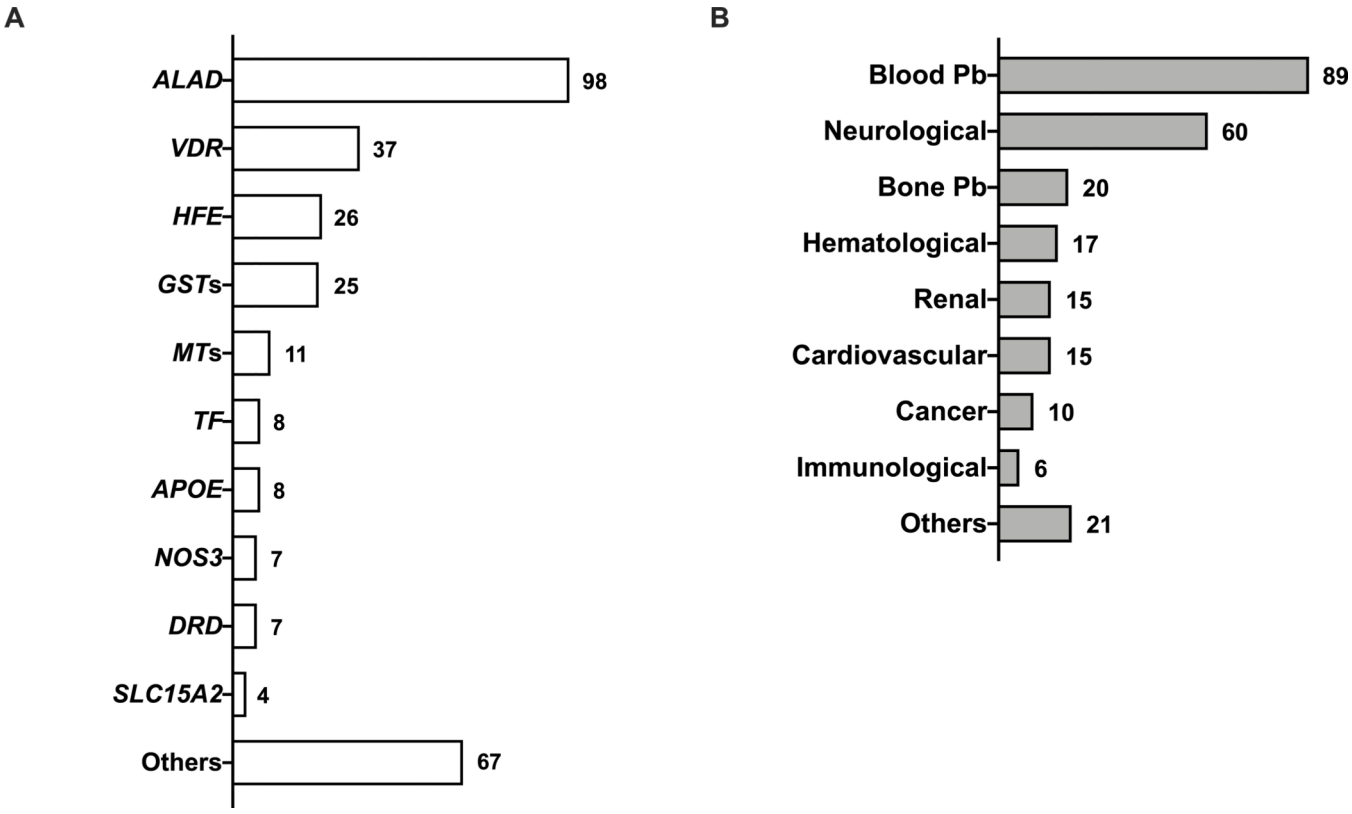

Fig. 1.

Gene polymorphisms in Pb susceptibility (A) and phenotype associations (B). Numbers indicate the number of studies for a given genetic factor and adverse health outcomes associated with them when reported.

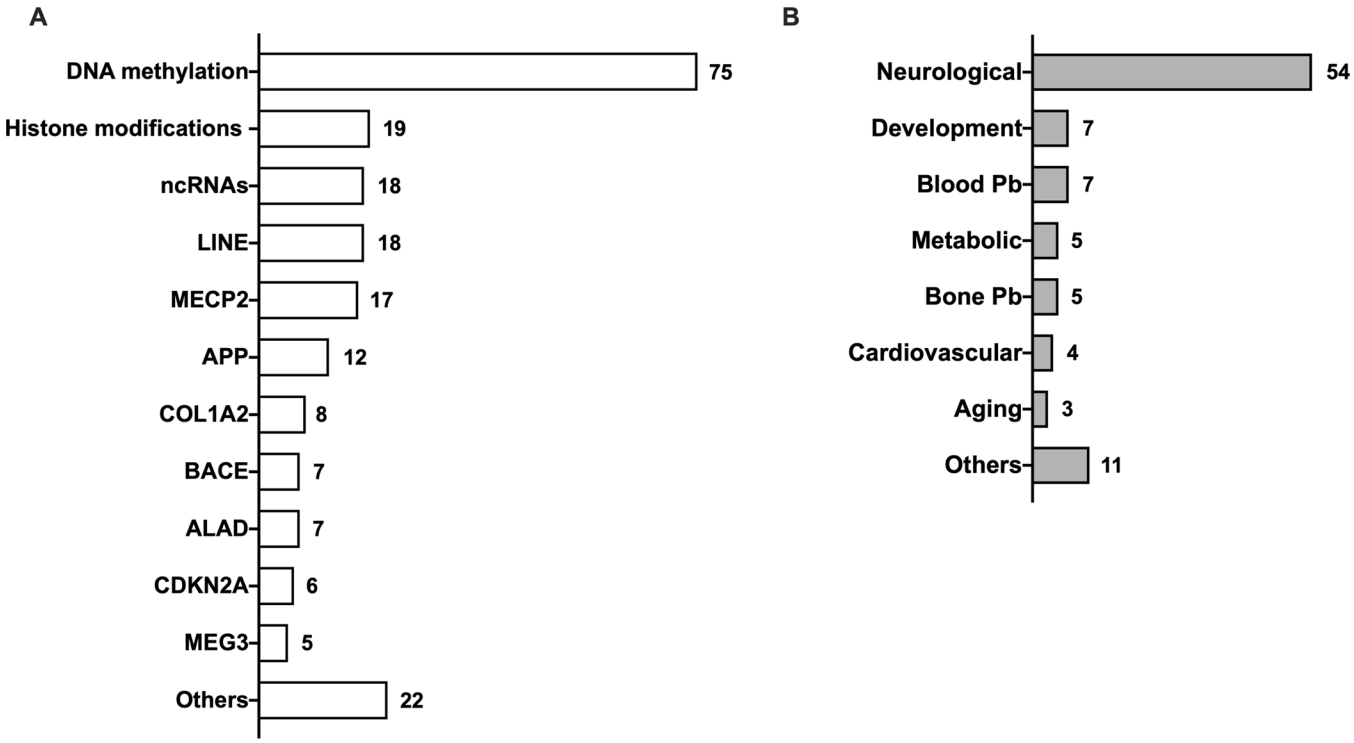

Fig. 2.

Epigenetic factors in Pb susceptibility (A) and phenotype associations (B). Numbers indicate the number of studies for a given epigenetic factor and adverse health outcomes associated with them when reported.

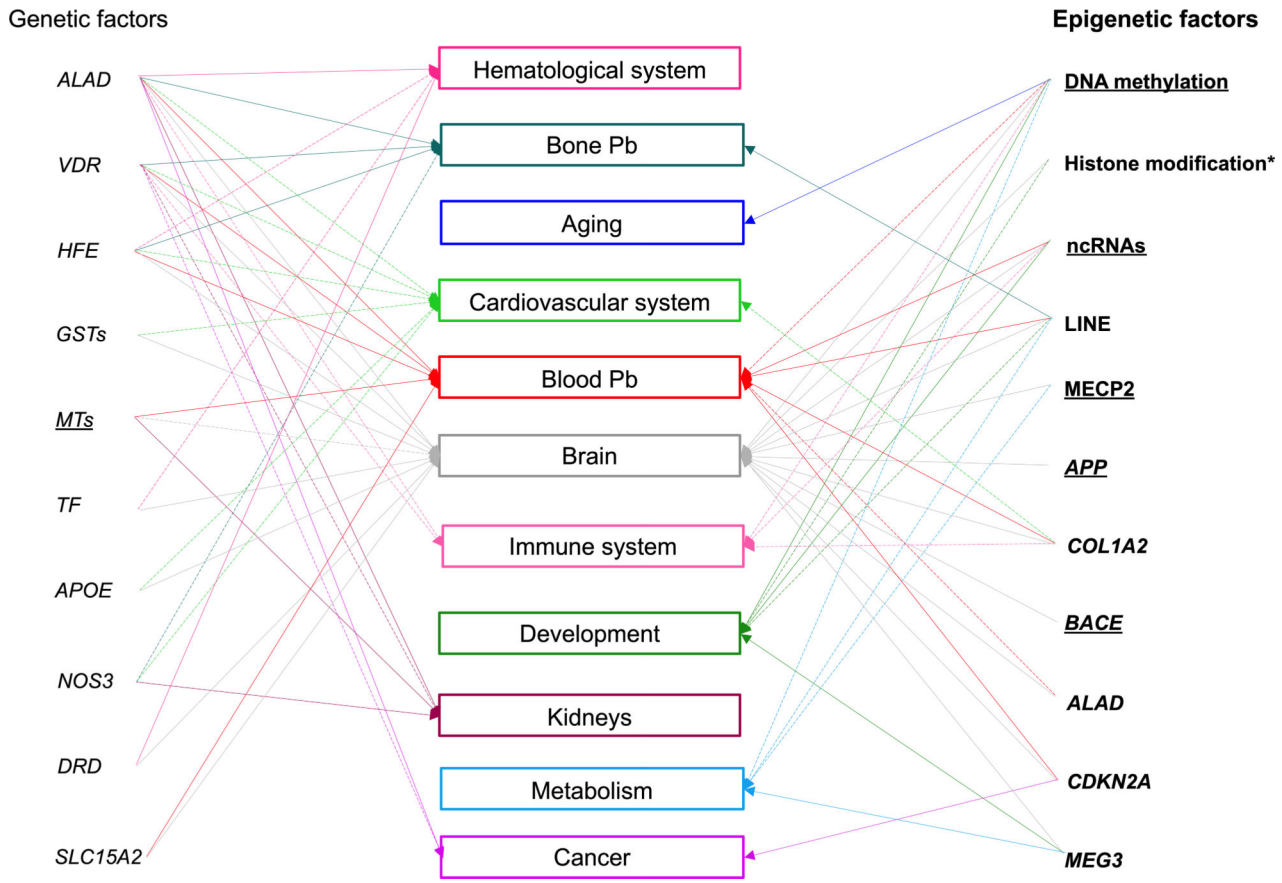

Fig. 3.

An illustrative summary of well-known or suggested associations between genetic or epigenetic factors and health adverse outcomes from Pb exposure in humans. Italic font style indicates genetic factors, bold font style illustrates epigenetic factors and rectangles identify targets/adverse health outcomes. Underlined factors have been reported in both humans and rodents, asterisks delineate factors reported solely in rodents. The solid lines connecting either genetic or epigenetic factors represent a well-established relation with adverse health outcomes from Pb exposure and dotted lines a potential relation.

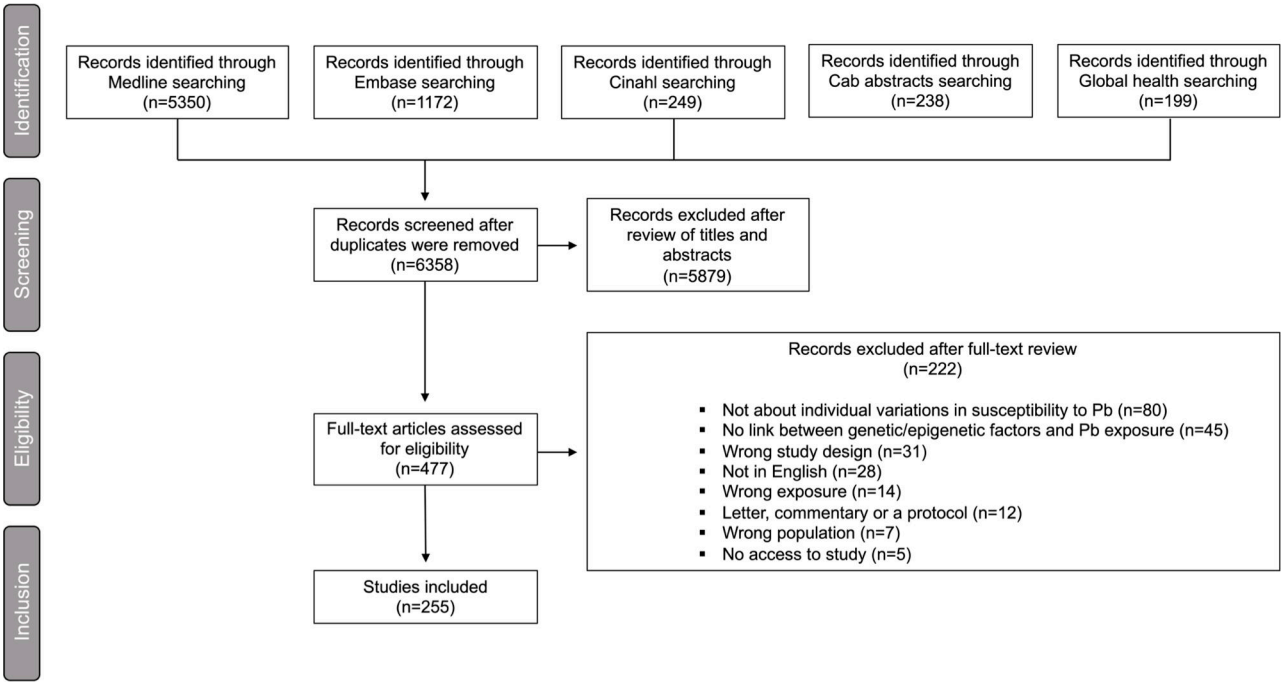

Fig. 4.

Literature search and screening results for studies reporting on the associations between genetic/epigenetic factors and susceptibility to Pb displayed as a PRISMA flow diagram (http://www.prisma-statement.org).

Table 1

Search strategy for systematic review

Databases searched	Search strings
Medline	1. exp Lead Poisoning/ 2. exp Lead/ or (lead or pb).ti,ab. 3. exp environmental exposure/ or exp food contamination/ or exp Occupational Exposure/ or exp Environmental Pollutants/ 4. (poison* or exposure* or contaminat* or toxic* or intoxic* or pollut*).ti,ab. 5. toxicity.fs. 6. 1 or (2 and (3 or 4 or 5)) 7. exp Genetic Predisposition to Disease/ or exp Genetic Variation/ or exp Disease Susceptibility/ or exp Gene-Environment Interaction/ or exp Epigenomics/ or exp genomics/ 8. (gene* adj2 (predispos* or suscept*)).ti,ab. 9. (epigen* or genomic*).ti,ab. 10. disease suscept*.ti,ab. 11. (genetic adj1 variation*).ti,ab. 12. or/7–8 13. exp animals/ not humans.sh. 14. (rats or rat or mouse or mice).ti,ab. or exp Rats/ or exp Mice/ 15. (6 and 12 and 14) or ((6 and 12) not 13)
Embase	1. exp lead poisoning/ 2. exp lead/ or (lead or pb).ti,ab,kw. 3. exp environmental exposure/ or exp food contamination/ or exp Occupational Exposure/ or exp Environmental Pollutants/ 4. (poison* or exposure* or contaminat* or toxic* or intoxic* or pollut*).ti,ab. 5. 1 or (2 and (3 or 4)) 6. exp genetic predisposition/ or exp disease predisposition/ or exp genotype environment interaction/ or exp epigenetics/ or exp genomics/ or exp genetic variability/ or exp genetic variation/ 7. (gene* adj2 (predispos* or suscept*)).ti,ab. 8. (epigen* or genomic*).ti,ab,kw. 9. disease suscept*.ti,ab. 10. (genetic adj1 variation*).ti,ab. 11. or/6–7 12. exp animals/ not humans.sh. 13. (rats or rat or mouse or mice).ti,ab. or exp mouse/ or exp rat/ 14. (5 and 11 and 13) or ((5 and 11) not 12) 15. limit 14 to yr=“2000 -Current”
Cinhal	(MH “Lead Poisoning”) OR (((MH “Lead”) or AB (lead or pb) or TI (lead or pb)) AND ((MH “Environmental Pollution+”) OR (MH “Occupational Exposure”) OR (MH “Food Contamination+”) OR (MH “Toxins+”) OR (AB (poison* or exposure* or contaminat* or toxic* or intoxic* or pollut*)) OR (TI (poison* or exposure* or contaminat* or toxic* or intoxic* or pollut*)))) AND ((MH “Epigenomics”) OR (MH “Genomics+”)) OR (AB ((disease suscept* or epigen* or genomic*) or (gene* n2 (predispos* or suscept*)) or (genetic n1 variation*))) OR (TI ((disease suscept* or epigen* or genomic*) or (gene* n2 (predispos* or suscept*)) or (genetic n1 variation*))) AND (MH “Human”) OR (AB (rats or rat or mouse or mice or human*)) OR (TI (rats or rat or mouse or mice or human*))
CAB Abstracts	1. (lead or pb).ti,ab. 2. (poison* or exposure* or contaminat* or toxic* or intoxic* or pollut*).ti,ab. 3. (disease suscept* or epigen* or genomic* or (gene* adj2 (predispos* or suscept*)) or (genetic adj1 variation*)).ti,ab. 4. (rats or rat or mouse or mice or human*).ti,ab. 5. and/1–4 6. exp genomics/ 7. exp man/ 8. exp rats/ 9. exp mice/ 10. predisposition.sh. 11. exp lead poisoning/ 12. 11 or (1 and 2) 13. 3 or 10 14. 4 or 7 or 8 or 9 15. and/12–14
Global Health	((lead or pb) and (poison* or exposure* or contaminat* or toxic* or intoxic* or pollut*)).ti,ab. AND ((disease suscept* or epigen* or genomic*) or (gene* adj2 (predispos* or suscept*)) or (genetic adj1 variation*)).ti,ab. (rats or rat or mouse or mice or human*).ti,ab.

Table 2

Population, Exposure, Comparator and Outcome (PECO) statement

PECO element	Evidence
Population	Human populations or rodent models.
Exposure	Pb exposure without any restrictions of the definition, measurement methods, length, or timing. Co-exposure studies that examined individual susceptibilities were only included if Pb effects could be extrapolated.
Comparators	Comparison group with lower exposure or no exposure.
Outcome	Dysfunction for any health outcome.