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Blood lead levels ≤10 micrograms/deciliter and executive functioning across childhood development: A systematic review

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Abstract

At low levels, the effects of lead on specific neurocognitive processes, such as executive functioning, is not well understood. The aim of this systematic review is to synthesize the empirical literature examining the relationship between prenatal and postnatal low blood lead levels and executive function across childhood development. This review considers the unity and diversity model of executive functioning by assessing the domains of working memory, cognitive flexibility, inhibition, attention, and unitary executive function separately. Nineteen studies met the inclusion criteria and were synthesized in the review. The results suggest an inverse association between postnatal lead exposure and executive function processes across childhood. The inverse relationship between postnatal lead exposure and working memory and cognitive flexibility in middle childhood is most strongly represented. Additionally, a marginal inverse relationship between postnatal lead exposure and unitary executive functioning and attention in middle childhood is suggested. The evidence does not support a relationship between postnatal lead and inhibition in middle childhood. Although there is support for the inverse relationship between low level lead exposure and executive function, lack of repeated exposure and outcome measures limit firm conclusions. Furthermore, the long-term impact of lead exposure on executive function outcomes is relatively unknown given lack of studies on adolescent populations.

Keywords

Lead exposure; Executive functioning; Working memory; Cognitive flexibility; Inhibition

1. Introduction

There is no safe level of lead exposure in children (Vorvolakos et al., 2016). While legislative advances have helped decrease global blood lead levels (BLLs), in 2009 16% of children still had BLLs above 10 μg/dl (World Health Organization, 2009; World Health Organization , 2010). The true extent of childhood lead exposure is unknown as countries

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vary widely in their biomonitoring programs, though studies do suggest the greatest burden falls on low to middle income countries (Kordas et al., 2018). Additionally, despite neurological deficits being observed in children with BLLs <5μg/dl, often reports on prevalence rates focus on childhood BLLs of 5–9 μg/dl or ≥10μg/dl (Raymond and Brown , 2017). Therefore, the full spectrum of global low-level exposures is unclear.

Research examining relationships between low levels of lead exposure and neurodevelopmental outcomes in children has focused primarily on intelligence quotients (IQs) or general cognition outcomes (Lanphear et al., 2005; Liu et al., 2013; Liu and Lewis, 2014; World Health Organization, 2018). A less studied neurodevelopmental outcome is executive functioning, a collection of processes that mutually aid in goal-oriented problem solving through goal planning, monitoring, and achievement (Marcovitch and Zelazo, 2009). Executive function outcomes are critical to examine due to the relationship with poor health consequences later in life, including links with obesity, substance abuse, and risky sexual behavior in adolescence (Gowey et al., 2018; Grenard et al., 2008; Khurana et al., 2015; Pentz et al., 2015).

In infants and toddlers, hand-to-mouth activity and general oral curiosity increase the risk of lead exposure and absorption (World Health Organization, 2018). Exposure to lead in this time window has been shown to have long lasting neurodevelopmental effects (World Health Organization, 2018). In the Port Pirie longitudinal study, lifetime lead exposure, from the prenatal period to 7 years old, had inverse associations with IQ at 11–13 years old (Tong et al., 1996). Likewise, a study of participants in the Cincinnati Lead Study reported an association between high BLLs in early childhood and adult gray matter reduction in the prefrontal cortex, the area of the brain involved in executive function processes (Cecil et al., 2008). Lead exposure in prenatal and postnatal years can, therefore, influence neurodevelopment and subsequent neurocognitive outcomes across the lifespan.

During the first 5 years of life, the prefrontal cortex undergoes rapid growth, setting the stage for more mature development throughout childhood and adolescence (Diamond, 2013; Funahashi and Andreau, 2013). Therefore, executive function development can be observed in infancy and into the adolescent period. For example, from 6 to 12 months, infants exhibit increasing inhibitory control during Delayed Response tasks (Diamond and Doar, 1989). Inhibitory control continues to mature throughout adolescence and into adulthood (Diamond, 2013). Other facets involved in executive function, including cognitive flexibility, working memory, and attention, all follow similar developmental trajectories by emerging in infancy and maturing throughout late childhood into adolescence and adulthood (Anderson, 2002; Garon et al., 2008; Reynolds and Romano, 2016). Considering executive function processes are more mature in adolescence, it is possible the effects of lead exposure on this neurocognitive outcome may not be evident until later in development. This review, therefore, sought to include studies with participants from birth to adolescence to acknowledge the critical period of neurodevelopment and to attempt to capture the full scope of executive function development.

There are inconsistent methodologies that complicate the search of the executive function literature. For example, when examining executive function, many studies will either

examine one domain of executive function, consider executive function as a unitary construct, or use both approaches. Additionally, other terms are often used inter-changeably with executive function, such as “cognitive functioning” or “executive control”. Despite complexities, there are multiple executive function models that exist in the literature that help to synthesize the concept. One of the most accepted conceptual models is the unity and diversity model, which outlines executive function as a single construct that includes multiple domains such as working memory (i.e. *updating* memory to adapt to new tasks), cognitive flexibility (i.e. *shifting* from one task to another), and inhibition (i.e. suppressing an impulse for a more favorable behavior) (Miyake et al., 2000). Researchers have also suggested that selective attention plays a part within inhibition (Diamond, 2013). Evidence for this model is demonstrated across childhood development (Best and Miller, 2010; Friedman and Miyake, 2017; Lehto et al., 2003). This review conceptualized executive function inclusively by considering working memory, inhibition, cognitive flexibility, attention, and unitary executive function when synthesizing the literature.

The aims of this review were twofold: (1) To synthesize the empirical research on the relationship between low prenatal and postnatal blood lead levels and executive function outcomes across childhood development; and (2) To identify methodological and analytical limitations of current studies to make recommendations for future research.

2. Methods

2.1. Data sources

We followed Cochrane's Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist (Moher et al., 2009). We searched the databases PubMed, Embase, PsycINFO, Scopus, and Google Scholar in May of 2019 in consultation with a research librarian. Executive function outcomes included the domains working memory, cognitive flexibility, inhibition, attention, and unitary executive function. Search terms included ‘lead exposure’ and ‘executive functioning’ (Appendix A). From these, we created synonym strings which included database-controlled vocabulary terms when available (i.e. MeSH, mainsubject terms).

2.2. Literature screening

After the search, studies were systematically screened by the two reviewers by title and abstract and then by full text against the inclusion and exclusion criteria. To be included in the review, studies had to: (1) Be a longitudinal or cross-sectional study examining lead exposure measured through blood prenatally (umbilical cord blood lead levels[UCLLs]) or postnatally (BLLs) with a combined sample mean of ≤10 μg/dl; (2) Assess executive function by one of the four domains or unitary executive function; (3) Include participants from birth up to 20 years old; and (4) Be reported in English as a peer reviewed publication or dissertation. There were no limitations on years or geographic locations. We excluded studies assessing the combined effect of lead and another predictor (i.e. mercury etc.) to synthesize only the direct effect of lead on executive functioning outcomes. Finally, studies published as editorials or opinion pieces were excluded (Appendix B).

2.3. Data extraction

Data extracted included research design, sample characteristics, UCLL/BLL sample mean and standard deviation levels, executive function domain and assessment tools, and major findings. Within each executive function domain, studies were separated into three groups based on the age range of participants. Infants and preschoolers, from birth up to 5 years, were assessed together to acknowledge the robust neurodevelopment occurring in the prenatal and early postnatal period (Black et al., 2017). Middle childhood, ages 5–10 years old, were grouped to represent middle childhood outcomes. Participants over 10 years old were assessed together representing the adolescent period, a time when executive function processes are maturing (World Health Organization, 2019). The research quality was evaluated using the National Institute of Health's (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (National Institutes of Health, 2018).

3. Results

3.1. Search and selection results

The initial search, including the search string strategy and English limitation, resulted in 2262 papers. Duplicates were removed for a yield of 1616 papers. The search and selection process resulted in 19 papers for final inclusion (Fig. 1 PRISMA). The reasons for exclusion were multifaceted. Most often the study sample mean lead levels were>10μg/dl. In the full text review stage, only one study was excluded for assessing lead with another metal and no studies were excluded for assessing only maternal BLLs. Of the 19 included papers, 2 reported on the same cohort at different time periods (Bellinger et al., 1991; Stiles and Bellinger, 1993). Participant enrollment ages ranged from birth to 16 years and included participants in 7 different countries. Outcome assessment ages ranged from 30 months to 16 years. Table 1 includes descriptions of the included studies and Table 2 provides quality grading results.

3.2. Lead exposure methods

Lead exposure was measured at multiple different periods across development, most often postnatally through BLLs. Only two studies, which assessed the same cohort, measured prenatal and postnatal lead exposure via UCLLs and BLLs (Bellinger et al., 1991; Stiles and Bellinger, 1993). Of the included studies, 10 had samples with mean BLLs ≥5 μg/dl. Three studies, two of which represent the same cohort, collected lead exposure data repeatedly across development (Bellinger et al., 1991; Canfield et al., 2004; Stiles and Bellinger, 1993).

3.3. Executive functioning assessment methods

Executive function outcomes were assessed via 26 different instruments across domains. These were a mix of objective tasks, such as computerized child completed tasks, and subjective tasks, such as teacher and parent ratings of child behavior. Only three studies assessed executive function outcomes more than once across development (Bellinger et al., 1991; Canfield et al., 2003; Stiles and Bellinger, 1993). Some studies assessed more than one domain of executive function and are thus discussed multiple times. In both Table 1 and the discussion below, the results are separated first by executive function domain and further

by participant ages to directly compare similar developmental ages and executive function outcomes. The results discussed in the text were reported after controlling for covariates unless otherwise indicated. Table 1 provides further information on each study's included covariates.

3.4. Lead exposure and working memory

3.4.1. Middle childhood (ages 5–10 years)—Four studies, three longitudinal and one cross-sectional, assessed the relationship between UCLLs/BLLs and working memory in middle childhood. Overall, a significant inverse relationship between lead levels and working memory was suggested. In 7.5 year old children, there was an inverse cross-sectional association between BLLs and two measures of working memory within a working memory index (Chiodo et al., 2004). Of the longitudinal studies, there were multiple associations between lifetime average BLLs and errors on the Spatial Working Memory task (SWM) and the Spatial Span Task (SST) in 5.5 year old children, with some relationships remaining after controlling for child IQ in the model (Canfield et al., 2004). The remaining studies assessed the same cohort at different time periods. At 57 months, UCLLs and BLLs were not associated with scores on the Memory Index of the McCarthy scales (Bellinger et al., 1991). However, at 10 years, there were multiple marginal inverse associations between 24-month BLLs and abilities on the Story Recall (SR) and the Digit Span tasks (Stiles and Bellinger, 1993).

3.4.2. Adolescent (ages>10 years)—Two cross-sectional studies suggested the inverse relationship between BLLs and working memory in adolescence, assessing participants between 10 and 12 years. There were inverse correlations between BLLs and scores on the Memory Subscale from the McCarthy Scales (WMICS) and the WISC-Working Memory Index (Shamsudin and Majid, 2017; Shamsudin et al., 2017).

3.5. Lead exposure and cognitive flexibility

3.5.1. Middle childhood (ages 5–10 years)—An inverse relationship between BLLs and cognitive flexibility in middle childhood was suggested by four studies. BLLs at 57 months had a positive relationship with errors on the Wisconsin Card Sorting Task (WCST) at 10 years old as well as a cross-sectional relationship at 10 years (Stiles and Bellinger, 1993). There was an inverse cross-sectional relationship between BLLs and scores on a Verbal Fluency (VF) task and multiple measures on the WCST in children 7.5 years old (Chiodo et al., 2004). When examining a dose response relationship, children with higher BLLs (5-10μg/dl) achieved significantly fewer categories on the WCST than children with lower BLLs (1–2μg/dl) (Surkan et al., 2007). Finally, there were significant inverse associations between lifetime average BLLs and multiple measures on the Intradimensional-Extradimensional Shift (IED) task at 5.5 years old, with many significant associations becoming marginal after controlling for child IQ (Canfield et al., 2004).

3.6. Lead exposure and inhibition

3.6.1. Middle childhood (ages 5–10 years)—Two studies suggested a non-significant cross-sectional relationship between BLLs and inhibition in children ages 6–10 years using the Stroop Color-Word Interference Test (SWCT) (Surkan et al., 2007). There

was, however, a significant inverse association between BLLs and color-word scores on the SCWT for males (Kim et al., 2010).

3.7. Lead exposure and attention

3.7.1. Middle childhood (ages 5–10 years)—Seven studies, one longitudinal and six cross-sectional, reported an overall marginal inverse relationship between BLLs and measures of attention in middle childhood. BLLs at 30 months were not significantly related to attention at 8 years old measured via a behavioral assessment tool, the Test of Everyday Attention for Children (TEA-Ch) (Chandramouli et al., 2009). A principal components analysis (PCA) combining the TEA-Ch tool with a parent reported attention assessment tool, Conners' Parent Rating Scale – Revised Long Form (CPRS-R:L), reported BLLs as a significant predictor of attention in 5 year old children, though only when the interaction between ‘lead’ and ‘males’ was added to the analysis (McCabe, 2009). Four cross-sectional studies assessed the relationship between BLLs and the same computerized measurement tool, the Continuous Performance Test (CPT), in children ages 7–10 years. While the studies all reported significant associations, those associations varied. One study found significant positive associations between BLLs and CPT percent omission errors (inattention) and longer response times, but no association between BLLs and commission errors (impulsivity) (Chiodo et al., 2007). Another conversely reported a significant positive association between BLLs and commission errors (impulsivity), but not omission errors (inattention) (Hong et al., 2015). Yet another reported a significant positive association between BLLs and number of omission errors (inattention) both with and without adjustment for sex (males) (Kim et al., 2010). A final study reported a significant inverse association between BLLs and the number correct on the CPT (sustained attention), however, no significant association between BLLs and scores on the Talland Digit Cancellation (TCD) task, which measures focused attention (Chiodo et al., 2004). Finally, there were no significant associations between BLLs and measures on the Complex Reaction-meter Drenovac (CRD), which assesses attention in relation to speed and accuracy of psychomotor reactions to light and sound (Prpíc-Majíc et al., 2000).

3.8. Lead exposure and unitary executive functioning

3.8.1. Infant/preschool (ages<5 years)—Two studies suggested the marginal inverse relationship between BLLs and infant/preschool unitary executive function. There were significant inverse relationships between 48-month BLLs and multiple measures of unitary executive functioning measured repeatedly at 48 and 54 months, though many of these relationships attenuated when controlling for child IQ (Canfield et al., 2003). The remaining cross-sectional study utilized PCA techniques creating three factors, Focus/Execute, Shift, and Sustain, and reported no association between lifetime peak BLLs and any factor (McDiarmid, 2003).

3.8.2. Middle childhood (ages 5–10 years)—Five studies, one longitudinal and four cross-sectional, suggested the marginal inverse relationship between BLLs and unitary executive functioning in middle childhood. At 5.5 years, lifetime lead exposure had significant relationships with outcomes on the Stockings of Cambridge task, a version of the Tower of London task which assess cognitive flexibility, spatial reasoning, and working

memory abilities (Canfield et al., 2004). There were significant inverse associations between BLLs and the pattern comparison task of the Neurobehavioral Evaluation System (NES1 & 2) in 5–6 year old children (Altmann et al., 1997). In 6 year old children, there was a significant relationship between BLLs and poorer ability to inhibit in the Behavior Rating Inventory of Executive Functions (BRIEF) (Barg et al., 2018). The remaining studies found no significant relationships between BLLs and scores on the Trail Making Task (TMT) and the Children's Color Trails Test (CCTT) (Kim et al., 2010; Surkan et al., 2007).

3.8.3. Adolescence (ages>10 years)—Two cross-sectional studies suggested the marginal inverse relationship between lead exposure and unitary executive functioning in adolescence via the Swedish Performance Evaluation System (SPES), an executive function battery. At 11.6 years old, there were marginal associations between BLLs and subtest scores including a positive association with simple reaction time (attention) and inverse association with digit span (memory) tests (Min et al., 2007). There were also significant differences in symbol digit scores between a low and high lead group only when adjusting for sex, suggesting females responded more slowly than males as BLLs increased (Kim et al., 2012).

4. Discussion

To our knowledge, this is the first systematic review to synthesize the literature on the relationship between low prenatal and postnatal lead exposure and executive function across childhood development. Generally, studies included in this review suggest a long-lasting, inverse relationship between low postnatal lead exposure, measured via BLLs, and executive function in middle childhood throughout early adolescence. Specifically, BLLs are observed to be significantly inversely related to two domains of executive function in middle childhood including working memory and cognitive flexibility (Canfield et al., 2004; Chiodo et al., 2004; Stiles and Bellinger, 1993; Surkan et al., 2007). There is only marginal evidence to suggest a relationship between BLLs and attention and unitary executive functioning in middle childhood. Finally, the relationship between BLLs and inhibition is not suggested, though the lack of available evidence in this domain limits conclusions.

4.1. Timing of lead exposure assessment

The findings of this review reflect the detrimental effects of lead exposure specifically in the postnatal period. The timing of lead exposure assessment is important to consider, as exposure at distinct times throughout development could have different effects on executive function outcomes. It is generally considered that foundational neurodevelopment occurs prenatally and early postnatally in the first 5 years of life (Black et al., 2017;). This aligns with a high-risk period, when children are most susceptible to lead exposure due to high oral curiosity and risk of ingesting lead particles (World Health Organization, 2018). In this review, prenatal exposure was assessed exclusively through infant UCLLs. While maternal BLLs and infant UCLLs have been shown to correlate, there are many factors that influence the transfer of lead from maternal blood to the fetus. These factors remain unclear and could include maternal variables such as hemoglobin levels and high blood pressure (Harville et al., 2005; Ladele et al., 2019). For that reason, and in an effort to synthesize homogeneous

BLL measurements, we decided to only include measurements of lead that came directly from the child. Therefore, studies assessing lead exposure through maternal BLLs were excluded. This, however, left only two studies that assessed the relationship between prenatal lead exposure and executive function outcomes. These studies assessed the same cohort and reported non-significant relationships between UCLLs and executive function outcomes. BLLs at 24 and 57 months in this cohort, however, were related to measures of working memory and cognitive flexibility at 10 years (Stiles and Bellinger, 1993). Due to the lack of studies assessing prenatal lead exposure, conclusions cannot be drawn on the relationship between prenatal lead and executive functioning outcomes across development.

Overall, the included studies lacked repeated lead exposure assessment. Only three studies, inclusive of two unique samples, assessed lead exposure more than once across development (Bellinger et al., 1991; Canfield et al., 2004; Stiles and Bellinger, 1993). Considering the half-life of blood lead is 1–2 months, a one-time assessment of lead cannot be used to quantify sustained exposure (Center for Disease Control and Prevention, 2017). Therefore, it cannot be determined if these results reflect the influence of short- or long-term lead exposure. The results could suggest that postnatal lead exposure only influences certain domains of executive function, namely cognitive flexibility and working memory. Indeed, there seem to be only marginal to non-significant relationships between BLLs and outcomes in the attentional, unitary executive function, and inhibitory domains (Chandramouli et al., 2009; Kim et al., 2010; Prpíc-Majíc et al., 2000; Surkan et al., 2007). It is important to consider that the previous lead exposure of the children in most of the included studies is unknown. Inconsistencies could, therefore, be due to the inability of these studies to assess the impact of previous lead exposure on executive functioning outcomes. Further longitudinal study, including UCLL assessment with repeated measurement of BLLs across development, is needed to assess the consequences of sustained lead exposure.

4.2. Dose and sex stratification

Six studies in this review assessed for a dose response relationship between lead exposure and executive functioning outcomes. Most studies reported that children with higher BLLs had worse executive functioning abilities compared to those with lower BLLs (Kim et al., 2012; Kim et al., 2010; Surkan et al., 2007). Researchers have hypothesized, however, that lead exposure could have a supralinear relationship with neurocognitive outcomes, with lower levels of lead inducing worse neurocognitive outcomes than higher levels (Lanphear et al., 2000; Téllez-Rojo et al., 2006). In fact, one study did report that children with lower BLLs performed worse on cognitive shift factors than children with higher BLLs (McDiarmid, 2003). Further research in this area would help determine if certain domains of executive function are more susceptible at lower levels of lead exposure compared to higher, and at what level that is.

Four studies assessed the relationship between lead exposure and executive functioning stratified by sex. The results were relatively inconsistent, reporting no constant differences between male and female performance on executive function tasks. For example, two studies reported marginal and significant relationships between BLLs and executive functioning measures only for males (Kim et al., 2010; McCabe, 2009). However, another study reported

significant relationships between BLLs and executive functioning outcomes for the whole sample and a significant difference for females, suggesting the effect of lead on female's executive functioning abilities was worse than males (Barg et al., 2018). Another study reported a significant relationship between BLLs and executive functioning only when comparing the low (< 2.76 μg/dl) to high lead dose female group (Kim et al., 2012). Researchers hypothesize that there are differing developmental trajectories of executive functioning for males versus females, though the mechanisms behind these difference, if they exist, are unknown (Wierenga et al., 2019). If there are indeed different sex-based developmental trajectories, the results reported here could be influenced by the timing of executive functioning assessment. It would be worthwhile to assess executive functioning outcomes in later adolescence to see if sex differences exist once these neurocognitive processes are more mature.

4.3. Executive functioning assessment

The lack of infant/preschool executive function assessment could be due to the difficulty in measuring these domains in younger children. Some researchers expressed difficulty finding executive function tools with age appropriate tasks. For example, in one study many young children, ages 48–54 months, were unable to complete a portion of the SST because they were incapable of identifying the shapes used in the task (Canfield et al., 2003). Children's confusion over task directions could, therefore, have impacted task accuracy and completion, thus influencing the results of this review. In infancy especially, many tools lack specificity when measuring executive function. For example, several studies examining the relationship between lead exposure and neurocognition in infancy assessed neurocognition via the Bayley Scales of Infant Development Mental Developmental Index, a general cognition tool (Al-Saleh et al., 2009; Bellinger et al., 1986; Bellinger et al., 1987; Bellinger et al., 1984; Huang et al., 2012; Liu et al., 2014; Polanska et al., 2018; Téllez-Rojo et al., 2006). Though scores have been shown to relate to later executive function outcomes, the total score represents overall cognition and, therefore, lacks specificity when measuring executive function (Anderson et al., 2010; Lowe et al., 2012; Wu et al., 2017). While other validated tools to assess executive function in infants/preschoolers exist, such as the A not B task or Delayed Response task, they were not used by the included studies (Diamond and Doar, 1989; Sun et al., 2009). Using age-appropriate, validated executive function tests is necessary to determine the true relationship between lead exposure and executive function abilities. Future studies assessing neurocognition of infants/preschoolers should consider assessing executive functioning in addition to general cognition.

Executive function processes are thought to mature throughout the adolescent period, suggesting that the true impact of lead on executive function may not be visible until later childhood into adolescence (Best and Miller, 2010). The longest cohort study in this review lends support to this hypothesis. BLLs had no relationship with executive function in early childhood but went on to have marginal/significant inverse associations with working memory and cognitive flexibility at 10 years old (Bellinger et al., 1991; Stiles and Bellinger, 1993). Studies reported a significant cross-sectional relationship between BLLs and various domains of executive function in early adolescence, suggesting lead exposure may influence adolescent executive functioning outcomes (Kim et al., 2012; Min et al., 2007; Shamsudin

and Majid, 2017; Shamsudin et al., 2017). Importantly, most studies in this review conducted executive function assessment primarily in middle childhood thereby assessing executive function before maturity. The results of this review could, therefore, be influenced by the limited age ranges at which executive function was assessed by the included studies. Future longitudinal study, from birth through adolescence with repeated measures of executive function outcomes, is needed to assess whether the negative impact of lead exposure on executive function continues into adolescence, when these processes mature.

4.4. Other influences on neurocognition

The relationship between lead exposure and executive function is influenced by several other neurocognitive, psychosocial, and biological factors. Although many studies included multiple demographic covariates (i.e. SES, parental education, etc.), some substantial potential covariates were left out. For example, while there is evidence that IQ and executive function are distinct constructs, working memory is highly correlated with IQ (Friedman et al., 2006). Only seven studies controlled for child IQ in this review (Barg et al., 2018; Canfield et al., 2004; Canfield et al., 2003; Chandramouli et al., 2009; Hong et al., 2015; McDiarmid, 2003; Surkan et al., 2007). While only three of these seven studies reported attenuated relationships when child IQ was added to the analyses, it is likely that other significant outcomes reported in this review would be attenuated when accounting for child IQ (Canfield et al., 2004; Canfield et al., 2003; Chandramouli et al., 2009). Additionally, there is a known association between iron deficiency/hemoglobin levels and lead absorption as well as overall neurocognition warranting inclusion as a covariate when assessing the relationship between lead exposure and executive function (Jáuregui-Lobera, 2014; Kwong et al., 2004). Only one study adjusted for serum iron levels in their analysis, suggesting the reported results of the other 18 studies in this review may limited due to this omission (Barg et al., 2018).

There are likely other factors that influence associations between lead exposure and executive function outcomes and future study is needed to understand the many variables involved in this relationship. Notably, lead exposure does not occur in isolation, but coexists with a multitude of early childhood risk factors (Cory-Slechta, 2005). For example, three of the included studies controlled for measures of family/environmental stress, both of which are risk factors of neurologic impairment (Chandramouli et al., 2009; Chiodo et al., 2004; McEwen, 2006; Stiles and Bellinger, 1993). As both lead and environmental stress have been shown to result in similar neurocognitive deficits, future research should also examine how lead exposure and environmental stress interact to influence neurocognitive outcomes. Researchers should consider the multiple neurocognitive, psychosocial, and biological covariates and modifiers that potentially influence the relationship in their future study.

4.5. Strengths and limitations

To our knowledge, this is the first review to synthesize the literature on the relationship between low prenatal/postnatal lead levels (≤10 μg/dl) and executive function across childhood development. Other strengths include the systematic search strategy and breadth of search terms used. The review was guided by the executive function unity and diversity model to better search and synthesize the results. The review also included only blood lead

measurements, as compared to dentine or bone lead measurements, which made the results and effect sizes from the included studies more directly comparable.

In addition to strengths, this review should be evaluated in recognition of certain limitations. This review did not include studies that assessed the combined impact of lead and another neurotoxicant or neurocognitive risk factor. While studying the combined impact of neurocognitive risk factors should be a focus for future study, this review sought to synthesize the direct impact of lead exposure on executive functioning. Additionally, this review did not include maternal BLLs as a prenatal lead exposure measurement, which could have omitted studies examining the relationship between maternal BLLs and executive function outcomes. Finally, this review was mostly qualitative in nature and did not examine magnitude of association between lead exposure and various executive function outcomes. This was done because of the wide variety of executive function assessment tools used by the included studies, making direct comparison difficult.

4.6. Implications for future research and practice

Future research is needed to fill methodological gaps in the area of lead exposure and executive function research. Overall, further longitudinal study is necessary, ideally beginning with prenatal lead exposure assessments and continuing with repeated lead exposure and executive function assessment throughout development into adolescence. This will allow for the assessment of not only executive function outcomes over time as they mature, but also the impact of sustained lead exposure to determine if there is a specific developmental period in which lead exposure is most detrimental to executive function. Researchers examining the longitudinal relationships between lead and neurocognition should consider assessing executive functioning outcomes in addition to general cognition to provide a more holistic view of lead's influence on neurocognition. Future studies should additionally consider the multiple variables that interplay with executive function development and control for these variables to better study the direct relationship between lead exposure and executive function. Additionally, robust inclusion of confounding variables will also increase researchers' confidence that the effect of lead is causal. Finally, the results of this review suggest that low levels of lead exposure significantly impact executive function processes in middle childhood. Providers working with children should be aware of this relationship and be proactive in assessing children's lead status and determining sources of exposure to prevent neurocognitive deficits, as even extremely low levels of lead are shown to impair executive function outcomes.

5. Conclusion

The majority of evidence suggests the inverse relationship between low postnatal lead exposure and executive function. The most evidence exists for the inverse relationship between BLLs and working memory and cognitive flexibility in middle childhood. The relationship between BLLs and unitary executive functioning and attention is marginally supported. The relationship between BLLs and inhibition, however, was not supported, though lack of available studies limits conclusions. Few studies were available assessing lead exposure repeatedly over time, limiting conclusions on the impact of sustained

exposure. Additionally, change in executive function abilities overtime in relation to lead exposure cannot be determined due to lack of longitudinal study with repeated measures. The results of this review are limited by the focus on middle childhood populations. Though executive function is more fully developed in adolescence, only four studies assessed executive function in this time period, limiting conclusions on how lead exposure influences executive functioning across development into adolescence. In summary, the results of this review suggest an inverse relationship between low postnatal lead exposure and executive function in middle childhood, though further research is needed to determine the full extent of this relationship across childhood development.

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Appendix

Appendix A.

Search strings by database

Database	Search string
PubMed	(Pb OR “blood lead” OR “lead exposure” OR “Lead”[Mesh]) AND (“Executive Function”[Mesh] OR “Attention”[Mesh] OR “Cognition” [Mesh] OR “executive function” OR “cognitive development” OR “cognitive flexibility” OR “attentional control” OR “inhibition control” OR “working memory” OR app“neuropsychological tests”)
Embase	(‘lead blood level’/exp. OR ‘lead exposure’ OR ‘blood lead’) AND (‘executive function’/exp. OR ‘executive function’ OR ‘attention’/exp. OR ‘working memory’ OR ‘cognition’/exp. OR ‘cognitive development’ OR ‘cognitive flexibility’ OR ‘inhibition control’ OR ‘attentional control’)
PsycINFO	(mainsubject.Exact(“lead”) OR “lead exposure” OR “blood lead”) AND (mainsubject.Exact(“executive function” OR “cognition” OR “attention”) OR “executive function” OR “working memory” OR “inhibition control” OR “cognitive development” OR “cognitive flexibility” OR “attentional control” OR “neuropsychological tests”
Scopus	TITLE-ABS-KEY ((“*blood lead*” OR “*lead exposure*”) AND (“*executive function*” OR “*working memory*” OR “*cognitive development*” OR “*cognitive flexibility*” OR “*attentional control*” OR “*inhibition control*” OR “*neuropsychological tests*”))
Google Scholar	(“blood lead”) AND (“executive function” OR “working memory” OR “cognitive development” OR “cognitive flexibility” OR “attentional control” OR “inhibition control” OR “neuropsychological tests”)

Appendix B.

Inclusion and exclusion criteria

	Inclusion	Exclusion
Population	Infants-Adolescents ages 0–20 years old. No geographic restrictions.	Participants older than 20 years old.
Exposure: blood lead levels	Sample mean blood lead levels ≤10 micrograms/dl Cord blood or postnatal lead levels.	Sample mean blood lead levels >10 micrograms/dl Dentin or bone lead levels. Maternal blood lead levels only.
Outcome: executive function	Assessments of the domains either 1. Cognitive flexibility (shifting) 2. Working memory (updating) 3. Inhibition control (inhibition)	Assessments of ‘general’ cognition or IQ. Disorder diagnosis (i.e. ADHD, autism, etc.)

	Inclusion	Exclusion
	4. Attention 5. Unitary executive functioning. Direct child studies or teacher/parent reports. Individual subtests of general cognition tools.	Assessments of motor, sensory, or auditory abilities.
Study design	Longitudinal/long-term/Cross-sectional design. Studies assessing the association between lead exposure and executive functioning. No intervention. Correlational/observational design.	Studies assessing the combined impact of lead exposure and another predictor (ex. mercury) on executive functioning. Studies including an intervention. Animal studies.
Language	Studies written in English.	Any other language.
Publication	Published paper, dissertations/thesis to reduce publication	Editorials, poster presentations, opinion pieces.

References

Al-Saleh I, Nester M, Mashhour A, Moncari L, Shinwari N, Mohamed GED, Rabah A, 2009. Prenatal and postnatal lead exposure and early cognitive development: longitudinal study in Saudi Arabia. J. Environ. Pathol. Toxicol. Oncol 28 (4), 283–302. 10.1615/JEnvironPatholToxicolOncol.v28.i4.40. [PubMed: 20102326]

Altmann L, Sveinsson K, Kramer U, Winneke G, Wiegand H, 1997. Assessment of neurophysiologic and neurobehavioral effects of environmental pollutants in 5- and 6-year-old children. Environ. Res. 73 (1–2), 125–131. 10.1006/enrs.1997.3697. [PubMed: 9311538]

Anderson P, 2002. Assessment and development of executive function (EF) during childhood. Child Neuropsychology 8 (2), 71. 10.1076/chin.8.2.71.8724. [PubMed: 12638061]

Anderson P, De Luca CR, Hutchinson E, Roberts G, Doyle LW, Group, t.V.I.C., 2010. Underestimation of developmental delay by the new Bayley-III Scale. JAMA Pediatr. 164 (4), 352–356. 10.1001/archpediatrics.2010.20.

Barg G, Daleiro M, Queirolo EI, Ravenscroft J, Manay N, Peregalli F, Kordas K, 2018. Association of low lead levels with behavioral problems and executive function deficits in schoolers from Montevideo, Uruguay. Int. J. Environ. Res. Public Health 15 (12). 10.3390/ijerph15122735.

Bellinger D, Needleman H, Leviton A, Waternaux C, Rabinowitz M, Nichols M, 1984. Early sensory-motor development and prenatal exposure to lead. Neurobehavioral Toxicology & Teratology 6 (5), 387–402. [PubMed: 6514103]

Bellinger D, Leviton A, Needleman HL, 1986. Low-level lead exposure and infant development in the first year. Neurobehav. Toxicol. Teratol 8 (2), 151–161. [PubMed: 2423895]

Bellinger D, Leviton A, Waternaux C, 1987. Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development. N. Engl. J. Med 316 (17), 1037–1043. 10.1056/NEJM198704233161701. [PubMed: 3561456]

Bellinger D, Sloman J, Leviton A, Rabinowitz M, Needleman HL, Waternaux C, 1991. Low-level lead exposure and children's cognitive function in the preschool years. Pediatrics 87 (2), 219–227. [PubMed: 1987535]

Best JR, Miller PH, 2010. A developmental perspective on executive function. Child Dev. 81 (6), 1641–1660. 10.1111/j.1467-8624.2010.01499.x. [PubMed: 21077853]

Black MM, Walker SP, Fernald LCH, Andersen CT, DiGirolamo AM, Lu C, … Grantham-McGregor S, 2017. Early childhood development coming of age: Science through the life course. The Lancet 389 (10064), 77–90. 10.1016/S0140-6736(16)31389-7.

Canfield RL, Gendle MH, Cory-Slechta DA, 2004. Impaired neuropsychological functioning in lead-exposed children. Dev. Neuropsychol 26 (1), 513–540. 10.1207/s15326942dn2601_8. [PubMed: 15276907]

Canfield RL, Kreher DA, Cornwell C, Henderson CR Jr., 2003. Low-level lead exposure, executive functioning, and learning in early childhood. Child Neuropsychology 9 (1), 35–53. 10.1076/chin.9.1.35.14496. [PubMed: 12815521]

Cecil KM, Brubaker CJ, Adler CM, Dietrich KN, Altaye M, Egelhoff JC, Lanphear BP, 2008. Decreased brain volume in adults with childhood lead exposure. PLoS Med. 5 (5), e112. 10.1371/journal.pmed.0050112. [PubMed: 18507499]

Center for Disease Control and Prevention, 2017. Biomonitoring summary. Retrieved from. https://www.cdc.gov/biomonitoring/Lead_BiomonitoringSummary.html.

Chandramouli K, Steer CD, Ellis M, Emond AM, 2009. Effects of early childhood lead exposure on academic performance and behaviour of school age children. Arch. Dis. Child 94 (11), 844–848. 10.1136/adc.2008.149955. [PubMed: 19770197]

Chiodo LM, Jacobson SW, Jacobson JL, 2004. Neurodevelopmental effects of postnatal lead exposure at very low levels. Neurotoxicol. Teratol 26 (3), 359–371. 10.1016/j.ntt.2004.01.010. [PubMed: 15113598]

Chiodo LM, Covington C, Sokol RJ, Hannigan JH, Jannise J, Ager J, … Delaney-Black V, 2007. Blood lead levels and specific attention effects in young children. Neurotoxicology and Teratology 29 (5), 538–546. 10.1016/j.ntt.2007.04.001. [PubMed: 17553667]

Cory-Slechta DA, 2005. Studying toxicants as single chemicals: does this strategy adequately identify neurotoxic risk? NeuroToxicology 26 (4), 491–510. 10.1016/j.neuro.2004.12.007. [PubMed: 16112317]

Diamond A, 2013. Executive functions. Annu. Rev. Psychol 64, 135–168. 10.1146/annurev-psych-113011-143750. [PubMed: 23020641]

Diamond A, Doar B, 1989. The performance of human infants on a measure of frontal cortex function, the delayed response task. Dev. Psychobiol 22 (3), 271–294. 10.1002/dev.420220307. [PubMed: 2707496]

Friedman NP, Miyake A, 2017. Unity and diversity of executive functions: individual differences as a window on cognitive structure. Cortex 86, 186–204. 10.1016/j.cortex.2016.04.023. [PubMed: 27251123]

Friedman NP, Miyake A, Corley RP, Young SE, DeFries JC, Hewitt JK, 2006. Not all executive functions are related to intelligence. Psychol. Sci 17 (2), 172–179. [PubMed: 16466426]

Funahashi S, Andreau JM, 2013. Prefrontal cortex and neural mechanisms of executive function. Journal of Physiology-Paris 107 (6), 471–482. 10.1016/j.jphysparis.2013.05.001.

Garon N, Bryson SE, Smith IM, 2008. Executive function in preschoolers: a review using an integrative framework. Psychol. Bull 134 (1), 31–60. 10.1037/0033-2909.134.1.31. [PubMed: 18193994]

Gowey MA, Lim CS, Dutton GR, Silverstein JH, Dumont-Driscoll MC, Janicke DM, 2018. Executive function and dysregulated eating behaviors in pediatric obesity. J. Pediatr. Psychol 43 (8), 834–845. 10.1093/jpepsy/jsx091. [PubMed: 28595362]

Grenard JL, Ames SL, Wiers RW, Thush C, Sussman S, Stacy AW, 2008. Working memory capacity moderates the predictive effects of drug-related associations on substance use. Psychol. Addict. Behav 22 (3), 426–432. 10.1037/0893-164X.22.3.426. [PubMed: 18778136]

Harville EW, Hertz-Picciotto I, Schramm M, Watt-Morse M, Chantala K, Osterloh J, … Rogan W, 2005. Factors influencing the difference between maternal and cord blood lead. Occup Environ Med 62 (4), 263–269. 10.1136/oem.2003.012492. [PubMed: 15778260]

Hong SB, Im MH, Kim JW, Park EJ, Shin MS, Kim BN, … Cho SC, 2015. Environmental lead exposure and attention defcit/hyperactivity disorder symptom domains in a community sample of South Korean school-age children. Environmental Health Perspectives 123 (3), 271–276. 10.1289/ehp.1307420. [PubMed: 25280233]

Huang PC, Su PH, Chen HY, Huang HB, Tsai JL, Huang HI, Wang SL, 2012. Childhood blood lead levels and intellectual development after ban of leaded gasoline in Taiwan: a 9-year prospective study. Environ. Int 40 (1), 88–96. 10.1016/j.envint.2011.10.011. [PubMed: 22280932]

Jáuregui-Lobera I, 2014. Iron deficiency and cognitive functions. Neuropsychiatr. Dis. Treat 10, 2087–2095. 10.2147/NDT.S72491. [PubMed: 25419131]

Khurana A, Romer D, Betancourt LM, Brodsky NL, Giannetta JM, Hurt H, 2015. Stronger working memory reduces sexual risk taking in adolescents, even after controlling for parental influences. Child Dev. 86 (4), 1125–1141. 10.1111/cdev.12383. [PubMed: 26081926]

Kim Y, Cho SC, Kim BN, Hong YC, Shin MS, Yoo HJ, … Bhang SY, 2010. Association between blood lead levels (< 5 mug/dL) and inattention-hyperactivity and neurocognitive profiles in school-aged Korean children. Sci Total Environ 408 (23), 5737–5743. 10.1016/j.scitotenv.2010.07.070. [PubMed: 20825975]

Kim DS, Ahn S, Yu S, Lee EH, 2012. The association between lead concentration in the blood and neurobehavioral performance of children. Toxicol. Environ. Heal. Sci 4 (2), 87–91. 10.1007/s13530-012-0121-x.

Kordas K, Ravenscroft J, Cao Y, McLean EV, 2018. Lead exposure in low and middle-income countries: perspectives and lessons on patterns, injustices, economics, and politics. Int. J. Environ. Res. Public Health 15 (11), 2351. 10.3390/ijerph15112351.

Kwong WT, Friello P, Semba RD, 2004. Interactions between iron deficiency and lead poisoning: epidemiology and pathogenesis. Sci. Total Environ 330 (1), 21–37. 10.1016/j.scitotenv.2004.03.017. [PubMed: 15325155]

Ladele JI, Fajolu IB, Ezeaka VC, 2019. Determination of lead levels in maternal and umbilical cord blood at birth at the Lagos University Teaching Hospital, Lagos. PLoS One 14 (2), e0211535. 10.1371/journal.pone.0211535. [PubMed: 30730916]

Lanphear BP, Dietrich K, Auinger P, Cox C, 2000. Cognitive deficits associated with blood lead concentrations<10 <g/dL in US children and adolescents. Public Health Rep. 115 (6), 521–529. 10.1093/phr/115.6.521. [PubMed: 11354334]

Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger DC, … Roberts R, 2005. Low-level environmental lead exposure and children's intellectual function: An international pooled analysis. Environmental Health Perspectives 113 (7), 894–899. 10.1289/ehp.7688. [PubMed: 16002379]

Lehto JE, Juujärvi P, Kooistra L, Pulkkinen L, 2003. Dimensions of executive functioning: evidence from children. Br. J. Dev. Psychol 21 (1), 59–80. 10.1348/026151003321164627.

Liu J, Chen Y, Gao D, Jing J, Hu Q, 2014. Prenatal and postnatal lead exposure and cognitive development of infants followed over the first three years of life: a prospective birth study in the Pearl River Delta region, China. NeuroToxicology 44, 326–334. 10.1016/j.neuro.2014.07.001. [PubMed: 25124739]

Liu J, Lewis G, 2014. Environmental toxicity and poor cognitive outcomes in children and adults. Journal of Environmental Health 76 (6), 130–138. [PubMed: 24645424]

Liu J, Li L, Wang Y, Yan C, Liu X, 2013. Impact of low blood lead concentrations on IQ and school perfomrance in Chinese children. PloS 8 (5), e65230. 10.1371/journal.pone.0065230.

Lowe JR, Erickson SJ, Schrader R, Duncan AF, 2012. Comparison of the Bayley II Mental Developmental Index and the Bayley III Cognitive Scale: are we measuring the same thing? Acta paediatrica (Oslo, Norway : 1992) 101 (2), e55–e58. 10.1111/j.1651-2227.2011.02517.x.

Marcovitch S, Zelazo PD, 2009. A hierarchical competing systems model of the emergence and early development of executive function. Dev. Sci 12 (1), 1–18. 10.1111/j.1467-7687.2008.00754.x. [PubMed: 19120405]

McCabe ME, 2009. Lead Exposure, Attentional Outcomes, and Socioenvironmental Influences. (AAI3327182), PsycINFO Database.

McDiarmid MD, 2003. The Relation between Low-level Lead Exposure and Attention in Preschool Children. (AAI3065162). PsycINFO database.

McEwen BS, 2006. Protective and damaging effects of stress mediators: central role of the brain. Dialogues Clin. Neurosci 8 (4), 367–381. [PubMed: 17290796]

Min JY, Min KB, Cho SI, Kim R, Sakong J, Paek D, 2007. Neurobehavioral function in children with low blood lead concentrations. NeuroToxicology 28 (2), 421–425. 10.1016/j.neuro.2006.03.007. [PubMed: 16644013]

Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, 2000. The unity and diversity of executive functions and their contributions to complex “frontal lobe” tasks: a latent variable analysis. Cogn. Psychol 41 (1), 49–100. 10.1006/cogp.1999.0734. [PubMed: 10945922]

Moher D, Liberati A, Tetzlaff J, Altman DG, 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6 (7), e1000097. 10.1371/journal.pmed.1000097. [PubMed: 19621072]

National Institutes of Health, 2018. Study quality assessment tools. Retrieved from. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

Pentz MA, Shin H, Riggs N, Unger JB, Collison KL, Chou C-P, 2015. Parent, peer, and executive function relationships to early adolescent e-cigarette use: a substance use pathway? Addict. Behav 42, 73–78. 10.1016/j.addbeh.2014.10.040. [PubMed: 25462657]

Polanska K, Hanke W, Pawlas N, Wesolowska E, Jankowska A, Jagodic M, … Calamandrei G, 2018. Sex-dependent impact of low-level lead exposure during prenatal period on child psychomotor functions. Int J Environ Res Public Health 15 (10). 10.3390/ijerph15102263.

Prpíc-Majíc D, Bobíćc J, Šimíćc D, House DE, Otto DA, Jurasovíćc J, Pizent A, 2000. Lead absorption and psychological function in Zagreb (Croatia) school children. Neurotoxicol. Teratol 22 (3), 347–356. 10.1016/S0892-0362(99)00079-3. [PubMed: 10840178]

Raymond J, Brown MJ., 2017. Childhood blood lead levels in children aged<5 years — United States, 2009–2014. MMWR Surveill. Summ 66 (SS-3), 1–10. 10.15585/mmwr.ss6603a1external. 2017.

Reynolds G, Romano A, 2016. The development of attention systems and working memory in infancy. Front. Syst. Neurosci (15), 10. 10.3389/fnsys.2016.00015. [PubMed: 26924967]

Shamsudin SB, Majid AA, 2017. Association of blood lead levels and working memory ability of primary school children surrounding ex-copper mining area in Ranau, Sabah (Malaysia). Acta Scientifica Malaysia 1 (1), 01–03.

Shamsudin SB, Marzuki A, Jeffree MS, Lukman KA, 2017. Blood lead concentration and working memory ability on malay primary school children in urban and rural area, Malacca. Acta Scientifica Malaysia 1 (1), 04–07.

Stiles KM, Bellinger DC, 1993. Neuropsychological correlates of low-level lead exposure in school-age children: a prospective study. Neurotoxicol. Teratol 15 (1), 27–35. 10.1016/0892-0362(93)90042-M. [PubMed: 8459785]

Sun J, Mohay H, O'Callaghan M, 2009. A comparison of executive function in very preterm and term infants at 8 months corrected age. Early Hum. Dev. 85 (4), 225–230. 10.1016/j.earlhumdev.2008.10.005. [PubMed: 19006652]

Surkan PJ, Zhang A, Trachtenberg F, Daniel DB, McKinlay S, Bellinger DC, 2007. Neuropsychological function in children with blood lead levels<10μg/dL. NeuroToxicology 28 (6), 1170–1177. 10.1016/j.neuro.2007.07.007. [PubMed: 17868887]

Téllez-Rojo MM, Bellinger DC, Arroyo-Quiroz C, Lamadrid-Figueroa H, Mercado-García A, Schnaas-Arrieta L, … Hu H, 2006. Longitudinal associations between blood lead concentrations lower than 10 μg/dL and neurobehavioral development in environmentally exposed children in Mexico City. Pediatrics 118 (2), e323–e330. 10.1542/peds.2005-3123. [PubMed: 16882776]

Tong S, Baghurst P, McMichael A, Sawyer M, Mudge J, 1996. Lifetime exposure to environmental lead and children's intelligence at 11–13 years: the Port Pirie cohort study. Br. Med. J 312 (7046), 1569–1575. [PubMed: 8664666]

Vorvolakos T, Arseniou S, Samakouri M, 2016. There is no safe threshold for lead exposure: alpha literature review. Psychiatry 27 (3), 204–214.

Wierenga LM, Bos MGN, van Rossenberg F, Crone EA, 2019. Sex effects on development of brain structure and executive functions: greater variance than mean effects. J. Cogn. Neurosci 31 (5), 730–753. 10.1162/jocn_a_01375. [PubMed: 30726177]

World Health Organization, 2009. Global Health Risks: Mortality and Burden of Disease Attributable to Selected Major Health Risks. (Retrieved from Geneva, Switzerland).

World Health Organization, 2018. Lead poisoning and health: key facts. Retrieved from. https://www.who.int/en/news-room/fact-sheets/detail/lead-poisoning-and-health.

World Health Organization, 2019. Adolescent health and development. Retrieved from. http://www.searo.who.int/entity/child_adolescent/topics/adolescent_health/en/.

World Health Organization, 2010. Childhood Lead Poisoning. Retrieved from https://www.who.int/ceh/publications/leadguidance.pdf.

Wu M, Liang X, Lu S, Wang Z, 2017. Infant motor and cognitive abilities and subsequent executive function. Infant Behav Dev 49, 204–213. 10.1016/j.infbeh.2017.09.005. [PubMed: 28950223]

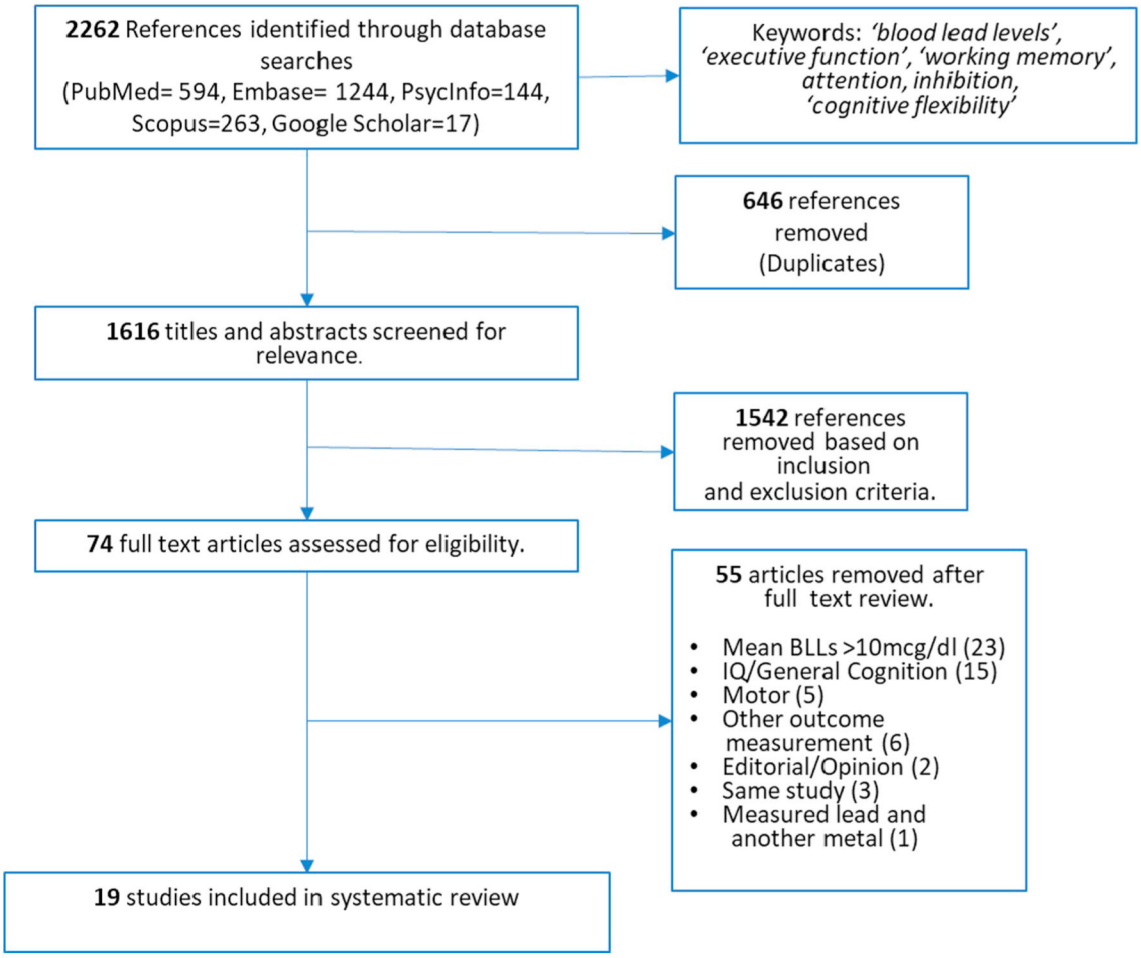

Fig. 1.
PRISMA diagram.

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Table 1

Characteristics of included studies.

Domains	Study characteristics	Study design	Lead measurement method	Mean (SD) lead level (μg/dl)	Executive function measures	Results (All results are controlled for covariates unless otherwise noted; Significant results are bolded)
Working Memory						
Middle Childhood						
Chiodo et al., 2004	"inner city", USA *N* = 236 E = 7.5 years O = 7.5 years	Cross-sectional	BLLs	5.4 ± 3.3	Working Memory-WISC III	**Significant inverse association between BLLs and Seashore Rhythm and Digit Span scores**.[a,d,f]
Canfield et al., 2004	New York, USA *N* = 42 E = 6 months O = 5.5 years	Longitudinal	BLLs (lifetime average; semiannually 6-24 m, 36, 48, 60 m)	7.2 ± 3.6	CANTAB-SWM SSP	Significant inverse association between BLLs and 6-box problem errors in SWM task, though this relationship attenuated after including child IQ in the model. **Significant positive association between BLLs and total non-target errors and total errors on the SSP**. The relationship with total errors became marginal after including child IQ in the model.[a,b,c,d]
Bellinger et al., 1991	Boston, USA *N* = 170 E = Newborn O = 57 months	Longitudinal	UCLLS & BLLs (24 & 57 months)	7.0 ± 6.3 (24 month) 6.4 ± 4.1 (57 month)	Memory Index- MSCA	No significant association between UCLLs or BLLs at 24 and 57 months and Memory Index scores at 57 months.[a,c]
Stiles and Bellinger, 1993	Boston, USA *N* = 123–145 E = Newborn O = 10 years	Longitudinal	UCCLs & BLLs (6, 12, 18, 24, 57 months & 10 years)	<8 (Lifetime average; 90% below 13)	SR, Digit Span	**24-month BLLs were marginally negatively associated with SR delayed recall score. Digit Span was marginally negatively associated with 24-month BLLs**.[a,c,f]
Adolescent						
Shamsudin et al., 2017	Melaka, Malaysia *N* = 111 E = 10–11 years O = 10–11 years	Cross-sectional	BLLs	6.86 ± 4.63 (rural) 8.51 ± 3.61 (urban)	WMI- WISC	**Significant inverse correlation between BLLs and WMI scores among urban and rural participants**.
Shamsudin and Majid, 2017	Ranau Sabah, Malaysia *N* = 100 E = 11–12 years O = 11–12 years	Cross-sectional	BLLs	4.9 ± 0.79 (non-exposed) 5.28 ± 0.97 (exposed)	WMICS	**Significant inverse correlation between BLLs and WMICS scores**.
Cognitive Flexibility						
Middle Childhood						
Canfield et al., 2004	New York, USA *N* = 145–170 E = 6 months O = 5.5 years	Longitudinal	BLLs (lifetime average; semiannually 6–24 month, 36, 48, 60 month)	7.2 ± 3.6	CANTAB-IED	**Significant negative association between BLLs and number of stages completed and likelihood of completing an ED shift; This became marginal after adding child IQ to the model. Significant positive association between BLLs and number of trials to reach and complete a stage 7**.[a,b,c,d]

Domains	Study characteristics	Study design	Lead measurement method	Mean (SD) lead level (μg/dl)	Executive function measures	Results (All results are controlled for covariates unless otherwise noted; Significant results are bolded)
Chiodo et al., 2004	"inner city", USA *N* =48 (WCST), 235 (TL), 236 (VF) E = 7.5 years O = 7.5 years s	Cross-sectional	BLLs	5.4 ± 3.3	WCST, TL, VF	**Significant inverse association between BLLs and VF scores. Significant positive association between BLLs and WCST errors and significant negative relationship with BLLs and number of conceptual level responses on WCST. No significant association with TL scores.**[a,d,f]
Surkan et al. (2007)	New England, USA *N* = 408 E = 6–10 years O = 6–10 ye years	Cross-sectional	BLLs	2.3 ± 1.6 (No maternal IQ data) 2.2 ± 1.6 (Maternal IQ data)	WCST	**Children with BLLs of 5–10 μg/dL showed the most consistent deficits, compared to BLLs 1–2 μg/dl, achieving significantly fewer categories and making more perseverative errors on the WCST.**[a,b,c,d]
Stiles and Bellinger, 1993	Boston, USA *N* = 134 E = Newborn O = 10 years	Longitudinal	UCLLs & BLLs (6, 12, 18, 24, 57 months & 10 years)	<8 (Lifetime average; 90% below 13)	WCST	**BLLs at 57 months were significantly positively related to scores of preservation and total number of errors at 10 years. BLLs at 10 years were significantly positively associated with percent of preservation errors and marginally positively associated with number of perseverative responses and perseverative errors. BLLs at 12 months were marginally positively associated with the number of trials to reach the first category on the WCST.**[a,c,f]
Inhibition						
Middle Childhood						
Surkan et al., 2007	New England, USA N = 408 E = 6–10 years O = 6–10 years	Cross-sectional	BLLs	2.3 ± 1.6 (No maternal IQ data) 2.2 ± 1.6 (Maternal IQ data)	SCWT	No significant association between BLLs and SCWT scores.[a,b,c,d]
Kim et al., 2010	South Korea *N* = 275 E = 8–10 years O = 8–10 yea years	Cross-sectional	BLLs	1.5 ± 1.58	SCWT	**Significant inverse association between BLLs and color-word score on SCWT when adjusted for sex (males)**. No significant difference between low (2.18 μg/dl) and high (> 2.18 μg/dl) lead group.[a,d]
Attention						
Middle Childhood						
McCabe, 2009	Rochester, NY, USA *N* = 151 E = 60 months O = 60–66 months	Cross-sectional 151	BLLs	5.43 ± 3.87	CPRS-R:L, TEA-Ch	**In PCA analysis, BLLs were a significant predictor of selective attention/shifting only when a 'lead × sex' interaction term was included (males) suggesting males are more vulnerable to attentional effects of lead exposure.**[a,c,d]
Chiodo et al., 2004	"inner city", USA *N* = 225 E = 7.5 years O = 7.5 years	Cross-sectional	BLLs	5.4 ± 3.3	CPT, TDC	**Significant inverse association between BLLs and the number correct on visual CPT (sustained attention)**. No significant association between BLLs and TDC.[a,d,f]

Domains	Study characteristics	Study design	Lead measurement method	Mean (SD) lead level (μg/dl)	Executive function measures	Results (All results are controlled for covariates unless otherwise noted; Significant results are bolded)
Chiodo et al., 2007	Detroit, USA *N* = 464 E = 7 years O = 7 years	Cross-sectional	BLLs	5 ± 3.0	CPT	**Significant positive association between omission errors (%) and longer reaction times on the CPT and BLLs**. No significant association between BLLs and commission errors (impulsivity) on the CPT.[a,c]
Chandramouli et al., 2009	UK *N* = 488 E = 30 months O = 8 years	Longitudinal	BLLs	4.22 (97% of BLLs ± 2)	TEA-Ch	No significant associations between BLLs and TEACh outcomes.[b,d,f]
Kim et al., 2010	South Korea *N* = 275 E = 8–10 years O = 8–10 years (9.7 years)	Cross-sectional	BLLs	1.5 ± 1.58	CPT	**Significant positive association between BLLs and number of omission errors on the CPT. This model remained significant when adjusted for sex, suggesting males had significantly more omission errors. Significant difference between low (2.18 μg/dl) and high (> 2.18 μg/dl) lead group and omission errors**.[a,d]
Prpíc-Majíc et al., 2000	Croatia N = 275 E = 9–10 years O = 9–10 years	Cross-sectional	BLLs	7.08 ± 1.78	CRD	No significant association between BLLs and CRD.[a,d]
Hong et al. (2015)	South Korea *N* = 839 E = 8–11 years O = 8–11 years (9.05 years)	Cross-sectional	BLLs	1.8 ± 1.40	CPT	**Significant positive association between BLLs and commission errors (impulsivity) but not omission errors (inattention)** on the CPT.[a,b,d]
Unitary Executive Function *Infant/ Preschool*						
McDiarmid, 2003	Illinois, USA *N* = 39 E = 30–72 months O = 30–72 months (4.1 years)	Cross-sectional	BLLs	7.0 ± 3.4 (peak for low lead group) 2.4 ± 1.1 (peak for very low lead group)	PCA creating 3 factors (Focus/ Execute, Shift, and Sustain)	In regression analysis, peak BLLs did not account for significant variability in the three factors (Focus/ Execute, Shift, and Sustain). **There were significant differences between the low BLL (5–10 μg/dl) and very low BLLs (< 5 μg/dl) in the Shift and Sustain composite factor score where children in the low BLL group performed better on Sustain factor tasks than the very low BLL group, however, performed worse than the very low BLL group on Shift factor tasks**.[b,d]
Canfield et al., 2003	Rochester NY, USA *N* = 160 (48 months) 157 (54 months) E = 48 months O = 48&54 months	Longitudinal	BLLs (only 48 months in this analysis)	6.49 (SD not reported)	SST	Significant inverse association between BLLs and control and inhibit efficiency at 48 & 54 months, though these relationships attenuated when child IQ was added to the models. No significant association between switch and inhibit/switch efficiency and BLLs. Significant inverse relationship between BLLs and number of tasks completed and color knowledge.[a,b,c,d]
Middle Childhood						

Domains	Study characteristics	Study design	Lead measurement method	Mean (SD) lead level (μg/dl)	Executive function measures	Results (All results are controlled for covariates unless otherwise noted; Significant results are bolded)
Altmann et al., 1997	East and West Germany *N* = 367 E = 5–6 years O = 5–6 years	Cross-sectional	BLLs	4.9 ± 5.2 (Duisburg) 6.9 ± 6.8 (Leipzig) 4.8 ± 4.8 (Gardelegen)	NES 1 & 2 (Pattern comparison & memory; CPT)	**Significant inverse associations only between BLLs and pattern comparison task.**[d]
Barg et al., 2018	Montevideo, Uruguay *N* = 206 E = 6 years O = 6 years	Cross-sectional	BLLs	4.2 ± 2.1	BRIEF	**Significant association between BLLs and poorer ability to inhibit (higher inhibit score on BRIEF). When stratified by sex, this relationship was only significant for females.**[a,b,d,e]
Surkan et al., 2007	New England, USA N = 408 E = 6–10 years O = 6–10 years	Cross-sectional	BLLS	2.3 ± 1.6 (No maternal IQ data) 2.2 ± 1.6 (Maternal IQ data)	TMT	No significant association between BLLs and TMT.[a,b,c,d]
Kim et al., 2010	South Korea N = 275 E = 8–10 years O = 8–10 years (9.7 years)	Cross-sectional	BLLs	1.5 ± 1.58	CCTT	No significant association between CCTT scores and BLLs in covariate model and when adjusted for sex (males). No significant difference between low (2.18 μg/dl) and high (> 2.18 μg/dl) lead group.[a,d]
Canfield et al., 2004	New York, USA N = 145–170 E = 6 months O = 5.5 years	Longitudinal	BLLs (lifetime average; semiannually 6-24 m, 36, 48, 60 m)	7.2 ± 3.6	SOC	**Significant negative association between BLLs and problems solved in minimum moves. Significant positive association between BLLs and 3-problem moves which became marginal after adding child IQ to the model. Significant positive association between BLLs and mean subsequent planning time on 2-move problems.**[a,b,c,d]
Adolescent						
Min et al., 2007	Seoul, South Korea *N* = 61 E = 7–16 years O = 7–16 years (11.6 years)	Cross-sectional	BLLs	2.83 ± 0.86 (Males) 2.88 ± 0.74 (Females)	SPES-K	**Marginal positive association between BLLs and simple reaction time and inverse association between BLLs and digit span which, respectively, reflect attention and short-term memory**. Adjusted for mother's test performance.
Kim et al., 2012	South Korea *N* = 153 E = 6th grade O = 6th grade (12–13 years)	Cross-sectional	BLLs	2.76 ± 1.01	SPES	**Only significant differences between the low (< median) and high (> median) groups was the Symbol Digit scores in girls. Girls reacted more slowly in Symbol Digit with the increase in the level of blood lead**.

Executive Function Measures: Behavior Rating Inventory of Executive Functions (BRIEF); Cambridge Neuropsychological Test Automated Battery (CANTAB); Children's Color Trails Test (CCTT); Complex Reaction-meter Drenovac (CRD); Conners' Parent Rating Scale – Revised Long Form (CPRS-R:L); Continuous Performance Test (CPT); Intradimensional-Extradimensional Shift Task (IED); McCarthy Scales of Children's Abilities (MSCA); Neurobehavioral Evaluation System (NES); Principal components analysis (PCA); Stockings of Cambridge Task (SOC); Spatial Span Task (SSP); Shape School Task (SST); Spatial Working Memory (SWM); Story Recall (SR); Stroop Color and Word Test (SCWT); Swedish Performance Evaluation System (SPES); Swedish Performance Evaluation System Korean Version (SPES-K); Talland Digit Cancellation (TDC); Test of Everyday Attention for Children (TEA-Ch); Tower of London (TL); Trail Making Task (TMT); Verbal Fluency (VF); Wechsler Intelligence Scale for Children (WISC); Wisconsin Card Sorting Test (WCST); Working Memory Index (WMI); Working Memory Index Cumulative Score (WMICS); **Lead Measurement Method**: UCLLs- indicates prenatal lead exposure BLLs- indicates postnatal lead exposure.; **Ages**: Infant/Preschool (< 5 years) –Middle Childhood (5–10 years) – Adolescent (> 10 years); **Study Characteristics**: E =enrollment age, O = outcome age.

Studies in italics appear multiple times in the table.

Adjusted for:

[a] SES.

[b] Child IQ.

[c] Caregiver IQ.

[d] Caregiver education.

[e] Hemoglobin/serum iron levels.

[f] Stress/stress approximation.

Table 2

Study quality assessment results.

Study	1. Clear research question	2. Clear population	3. Participation rate 50%	4. Similar subject recruitment	5. Sample size justification	6. Exposure before outcome	7. Sufficient timeline	8. Varying exposure levels	9. Exposure measures clearly defined	10. Exposure assessed more than once	11. Outcome measures defined and valid	12. Outcome assessors blinded	13. Loss to follow-up <20%	14. Key confounding variables included
Altmann et al. (1997)	Y	Y	CD	Y	N	N	N	Y	NR	N	Y	Y	Y	N
Barg et al. (2018)	Y	Y	N	Y	N	N	N	Y	N	N	Y	Y	Y	Y
Bellinger et al. (1991)	Y	Y	N	Y	N	Y	Y	Y	NR	Y	Y	Y	Y	Y
Canfield et al., 2003	Y	N	CD	Y	N	Y	Y	Y	NR	Y	Y	NR	Y	Y
Canfield et al. (2004)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	NR	N	Y
Chandramouli et al. (2009)	Y	Y	N	Y	Y	Y	Y	Y	NR	N	Y	Y	Y	Y
Chiodo et al. (2004)	Y	Y	Y	Y	N	N	N	Y	N	N	Y	Y	Y	Y
Chiodo et al. (2007)	Y	Y	CD	Y	N	N	N	Y	NR	N	Y	Y	Y	Y
Hong et al. (2015)	Y	Y	CD	Y	N	N	N	Y	Y	N	Y	Y	N	Y
Kim et al. (2010)	Y	Y	Y	Y	N	N	N	Y	Y	N	Y	Y	Y	Y
Kim et al. (2012)	Y	N	CD	Y	N	N	N	Y	NR	N	Y	Y	NR	N
McCabe, 2009	Y	Y	CD	Y	N	N	N	Y	Y	N	Y	Y	N	Y
McDiarmid, 2003	Y	Y	CD	Y	Y	N	N	Y	NR	N	Y	NR	Y	Y
Min et al. (2007)	Y	N	CD	Y	N	N	N	Y	Y	N	Y	Y	Y	N
Prpíc-Majíc et al., 2000	Y	Y	Y	Y	Y	N	N	Y	NR	N	N	Y	Y	Y
Shamsudin and Majid (2017)	Y	Y	CD	Y	N	N	N	N	Y	N	Y	Y	Y	N

Study	1. Clear research question	2. Clear population	3. Participation rate 50%	4. Similar subject recruitment	5. Sample size justification	6. Exposure before outcome	7. Sufficient timeline	8. Varying exposure levels	9. Exposure measures clearly defined	10. Exposure assessed more than once	11. Outcome measures defined and valid	12. Outcome assessors blinded	13. Loss to follow-up <20%	14. Key confounding variables included
Shamsudin et al. (2017)	Y	Y	CD	Y	N	N	N	N	NR	N	Y	Y	Y	N
Stiles and Bellinger, 1993	Y	Y	N	Y	N	Y	Y	Y	NR	Y	Y	Y	Y	Y
Surkan et al. (2007)	Y	Y	Y	Y	N	N	N	Y	NR	N	Y	Y	Y	Y

Y = yes; N = no; NR = not reported; CD = cannot be determined.