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Lead and Attention-Deficit/Hyperactivity Disorder: A Meta-Analysis

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The University of Southern Mississippi

LEAD AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER:

A META-ANALYSIS

by

James K. Goodlad, III

A Thesis
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of The University of Southern Mississippi
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ABSTRACT

LEAD AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER:

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Attention-Deficit/Hyperactivity Disorder (ADHD) is thought to have a significant neurological component, and several brain structures have been implicated. Environmental variables like lead have been shown to affect brain structures, which in turn impacts cognitive development and behavior. Some studies have begun to associate environmental variables like lead with the inattentive and hyperactive-impulsive symptoms of ADHD. This meta-analysis examined the association between different components of ADHD (including attention problems and hyperactivity/impulsivity) and level of lead exposure in children and adolescents. Articles focusing on the association between lead and inattention or hyperactivity-impulsivity symptoms were gathered from the online databases PsycINFO and Medline. These articles were then coded for content, including the methods used to assess lead exposure, the type of ADHD symptoms examined, the methods used to assess ADHD, gender of participants, average age of participants, year of publication, and sample size. These variables were analyzed using meta-analytic procedures. It was predicted that a medium sized association exists between lead burden and the ADHD symptom sets of inattention and hyperactivity-impulsivity. Furthermore, it was predicted that the method of lead burden assessment, particularly the use of hair samples (as opposed to the use of blood, bone, or teeth samples) would moderate the association by causing the effect to appear larger than that

of the other methods of assessment. It was also predicted that the year of publication would moderate the association between lead burden and components of ADHD, as mean lead burden has decreased over the last few decades. The meta-analysis of 29 studies with a total N of 12,322 subjects and published between 1974 and 2010 revealed that a moderate association ($r = .19$) exists between lead burden and inattention as well as lead burden and hyperactivity-impulsivity. Neither method of lead burden assessment nor year of publication moderated the lead and inattention or lead and hyperactivity-impulsivity association. Sample size moderated the association between lead and total ADHD ratings, but this effect vanished following the removal of three outliers. Although this meta-analysis contained several limitations, it provided important information regarding the etiology, treatment, and prevention of ADHD and can be used to guide future research of the lead-ADHD symptomatology association.

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CHAPTER I

INTRODUCTION

Lead poisoning is associated with many cognitive and behavioral deficits in children (Byers & Lord, 1943). It is well known that in large quantities lead is toxic. The Centers for Disease Control (CDC) has reported that lead poisoning is “one of the most common and preventable pediatric health problems” (CDC, 1991, para 1). According to Canfield, Kreher, Cornwell, and Henderson, Jr. (2003), exposure to high levels of lead left untreated can result in very dramatic and observable consequences, including coma, convulsions, and death. Exposure to lead can also be harmful at relatively low levels by affecting cognition and behavior. Even low lead exposure can result in slower nerve conduction velocity, poorer performance on various tests of intelligence and cognitive ability, slower reaction time, poorer processing of auditory information, decreased growth, and poorer posture. Lead exposure is particularly harmful to young children whose brains and central nervous systems are still developing (Canfield et al., 2003). ADHD is a pervasive pattern of developmentally inappropriate inattention, hyperactivity, and impulsive behavior that typically begins before age seven and occurs in approximately 3-7% of US children (APA, 2000). A number of studies have examined the relation between lead burden and ADHD (e.g., Canfield et al., 2003; Minder, Das-Smaal, Brand, & Orlebeke, 1994; Nigg et al., 2008; Ris, Dietrich, Succop, Berger, & Bornschein, 2003). However, these findings have yet to be synthesized into a meta-analysis, and the current study will fill this gap in the literature.

History of Lead Assessment in Children

The dangers of lead consumption have been known for centuries (Needleman, 2009), but one of the earliest known cases of lead poisoning in children was described by Tanquerel des Planches (1848), who noticed that children who played with and put lead-painted toys in their mouths often went on to develop lead colic, characterized by severe abdominal pains (Rosner, Markowitz, & Lanphear, 2005). Another series of landmark cases of youth lead poisoning was described by J. Lockhart Gibson at Brisbane Children's Hospital in 1892. Gibson attributed the cause of severe cognitive and behavioral impairments observed in children to the white lead-based paint used throughout the city of Brisbane (Needleman, 2009) as well as house dust contaminated with lead as paints broke down. Gibson treated lead poisoning in children with the use of muscle relaxers and iodine but also noted the "removal of cases from their homes to the hospital is more important than anything" (Gibson, 1904). At the time, it was believed that both children and adults who were treated for lead poisoning could fully recover without the danger of any permanent damage, but Byers and Lord (1943) were the first to describe the delayed effects of lead poisoning in children. Byers noticed that out of 20 children who had been "successfully" treated for lead poisoning, including some treated by him personally, 19 demonstrated significant problems with cognition, learning, and behavior later in life.

The children in Byers and Lord's (1943) classic study were all treated for lead poisoning in their infancy. Despite reportedly being "normal" before their lead poisoning, following recovery, Byers and Lord reported that all the children showed intellectual and emotional difficulties. The average IQ of the group was 90, and IQs ranged from 67 to

109; only 1 of the 20 children in the study ever succeeded in school and apparently did so only with great difficulty. Byers and Lord also reported that many children demonstrated sensorimotor deficits following their treatment for lead. Younger children showed difficulties manipulating blocks and fitting forms into holes on a form board. Older children showed difficulties reproducing various shapes. As the children entered school, they experienced difficulties learning to write, read, or work with numbers. Interestingly, Byers and Lord reported that some children developed normal verbal abilities despite other deficits. One child was described by his teacher as “smart enough but does not learn,” while another child was described as “bright but restless and does not concentrate,” (Byers & Lord, 1943, p. 481).

Many of the children showed different behavioral problems after their treatment for lead. Byers and Lord (1943) classified the behavioral problems as “forced reaction to stimuli in the environment” (p. 482). The behaviors were attributed to damage in the cortical areas of the brain responsible for normal inhibitory function. Byers and Lord (1943) described these behaviors as unreliable impulsive behaviors, cruel impulsive behaviors, and short attention spans. Irritability and temper tantrums, crying, distractibility, and cruelty to animals and people were also common. Byers and Lord (1943) also noted that some children seemed to exhibit behavioral problems out of frustration from their academic failures. Byers and Lord were among the first to study the delayed cognitive and behavioral effects of lead that we associate with ADHD today.

How Children Are Exposed to Lead

Children can be exposed to lead in a number of ways. Perhaps the most well-known means of exposure is through the ingestion of lead-based paint chips, as in the early case

described by Gibson (1904; 1917). Most of the cases described by Byers and Lord (1943) also involved the chewing of cribs or furniture painted with lead-based paints during infancy. Perhaps an equally important (and dangerous) means of exposure occurs through the inhalation of airborne lead particles. The size of individual lead particles is usually reported in micrometers (μm). According to Stretsky and Lynch (2001), once inhaled, approximately 70% of all lead particles smaller than 1 μm are absorbed directly into the bloodstream. Larger particles might be trapped in mucus and then swallowed to be eventually absorbed. Airborne lead can come from a variety of sources. Children might inhale lead particles from paint chips containing lead, from contact with gasoline or gasoline fumes, as well as “smelters, battery plants, and other industrial facilities that process lead,” (Stretsky & Lynch, 2001, p. 580). Concentration of lead in another substance is reported as micrograms of lead per deciliter of another substance ($\mu\text{g}/\text{dL}$).

Out of concern for the negative effects of lead burden, the Environmental Protection Agency (EPA) ordered the removal of lead from common consumer products, chiefly paints and gasoline. Lead was ordered reduced from gasoline in 1976, and removed from domestic interior paints in 1978 (Ris et al., 2003). Following this reduction of lead content in consumer products, mean blood levels in children have decreased from 15 $\mu\text{g}/\text{dL}$ to 2 $\mu\text{g}/\text{dL}$ (Needleman, 2009). Unfortunately, lead exposure remains a common problem for developing children and the problem has not been completely solved by the removal of lead from paints and gasoline. Lead exposure still remains a significant problem, particularly in inner cities where old, cheap, and poorly constructed homes still contain high levels of lead in building materials, and poorer residents may not

be able to afford renovation of the house or a move to a new residence built with lead-free materials (Needleman, 2009).

Over time, the measure of average safe blood lead levels has changed several times as more research became available. Initially set at less than 80 $\mu\text{g}/\text{dL}$, it was lowered to 60 $\mu\text{g}/\text{dL}$ (Ris et al., 2004) and 40 $\mu\text{g}/\text{dL}$ (Kirkconnell & Hicks, 1980). Most recently, the CDC (1991) reported that blood lead levels less than 10 $\mu\text{m}/\text{dL}$ were considered safe levels, though negative cognitive effects and poorer cognitive performance have been observed in children with blood lead levels between 10 $\mu\text{m}/\text{dL}$ and 5 $\mu\text{m}/\text{dL}$ (Lanphear et al., 2000). Currently, the average blood lead level in US children is approximately 1-2 $\mu\text{g}/\text{dL}$ (CDC, 2005).

Assessment of Lead Burden

There are several methods that are commonly used to assess an individual's level of lead burden. One of the most well-known methods of lead assessment is through the analysis of the subject's blood. Estimates of lead burden taken from blood samples are preferable for a number of reasons. They are easily compared across studies (Smith, 1984), and normal versus abnormal blood lead levels are relatively standardized (Lansdown et al., 1974). Blood lead levels are an excellent estimate of recent lead exposure, but because the half-life of lead in blood is between 27 and 30 days (Minder et al., 1994; Needleman, 2009), they are not very reliable in estimating long-term lead burden. Blood samples may be more invasive than other samples (e.g., hair), especially in children. Most problematic, blood lead levels may not accurately reflect previous lead burden, especially previous burden during periods of "developmental vulnerability" (Smith, 1984, p. 27).

Another way to estimate total lead burden is through the analysis of lead concentrations in teeth. The amount of lead in teeth generally represents a more long-term exposure to lead, unlike blood lead levels; the half-life of lead in teeth is about 30 years (Needleman, 2009). Teeth can be relatively easy to obtain, particularly when the population of interest is at an age where the shedding of deciduous teeth is a normal and frequent occurrence (Needleman et al., 1972). However, there is the potential for variance in lead levels in teeth within the same mouth. Smith and colleagues (1983) recommend that when dentine lead levels are assessed, care should be taken to analyze the same type of tooth (e.g., molars) for each participant. Smith (1984) reported that of the studies that have used dentine lead levels, several different analysis methods have been used. Furthermore, there may be variance in lead levels within different parts of the same tooth (Minder et al., 1994).

Lead can also be assessed through the analysis of hair. In this method, hair samples are generally taken from the nape of the subject's neck and as close to the scalp as possible to maximize the accuracy of the assessment (Marlowe et al., 1985). Many researchers (e.g., Marlowe et al., 1985; Minder et al., 1994) prefer this method because it is noninvasive and extremely easy to acquire multiple samples from the same subject. Hair assessment can be used for subjects of any age unlike dentine samples (Smith, 1984). Lead in hair is not affected by short-term changes and variations in lead exposure. Instead, it represents a relatively stable exposure to the metal that has been built up over time (Marlowe & Errera, 1982). Unfortunately, lead levels in hair, unlike blood or teeth, can be directly influenced by the environment through washing procedures. Even the

color and structure of the hair can influence the amount of lead stored in hair (Minder et al., 1994).

Lead and Intelligence, Aggression, and Conduct Problems

Lead has been determined to have a significant detrimental impact on IQ. After Byers and Lord's (1943) original studies, the trend in lead research focused not on aggression, but on cognitive ability. Intelligence scores (IQ scores) are often used to estimate global cognitive ability, and IQ has been demonstrated to be a reliable and valid predictor of academic, employment, and economic successes (Canfield et al., 2003). Results from IQ tests can also offer insight into how lead affects specific cognitive abilities, such as visual-spatial processing, sustained attention, or reaction times. The relation between lead exposure and intelligence is thought to be causal (Lanphear et al., 2005; Surkan et al., 2007).

Needleman and colleagues (1979) completed one of the most important studies of the effects of lead on intelligence in the general population. In this study, two groups of children were selected from the general population and differentiated based on dentine lead levels. Only children in the highest or lowest 10th percentile of dentine lead levels (> 24 ppm and < 6 ppm, respectively) were included in the study. Whenever possible, a second or third dentine sample was analyzed for agreement of dentine lead levels across teeth from the same participant. Needleman and colleagues found a significant difference between groups on IQ scores as measured by the Wechsler Intelligence Scale for Children Revised (WISC-R). Specifically, there was a 4 1/2 point difference between groups on Verbal IQ and Performance IQ as well as Full Scale IQ on the WISC-R. There were also significant differences on particular subtests measuring auditory and verbal

processing and reaction time (Needleman et al., 1979). This evidence supports the negative relation between lead and cognitive performance. It should be noted though that there were additional differences between the lead-burdened and control groups that could have acted as confounding variables, especially social disadvantage and potential sampling errors (Smith, 1984).

Previously, examinations of the association between lead and intelligence in children sampled very specific populations of children who lived in dense urban areas or near industrial centers where lead was smelted (Lansdown et al., 1974). Some researchers believed that due to confounding variables like socioeconomic status and a limited sample size, the results from these studies were difficult to generalize to the population as a whole. When Needleman and colleagues (1979) studied the association between lead and IQ, they sampled children from two suburbs of Boston—Chelsea and Somerville—and this study sought to demonstrate that lead exposure in children was not exclusively an “urban” problem. The results from this study and its 11-year follow-up (Needleman et al., 1990) maintained that there was an association between lead and IQ and “initiated the modern era of sophisticated research on lead effects” (Ris et al., 2004, p. 261).

Marlowe and Errera (1981) conducted a similar study to assess the relation between lead burden and cognitive abilities. However, their study was based in a rural area to extend the findings to a different population of children. Even in their rural sample from Tennessee, approximately 20% of the sample had an above-average level of lead burden. A number of similar studies followed (e.g., Smith et al., 1983; Thatcher et al., 1982; Winneke, 1979; Winneke, 1983; Yule et al., 1981), and there have also been a number of meta-analyses synthesizing the relation of lead and intelligence across studies. For

instance, Needleman and Gatsonis (1990) found average effect sizes of $r = -.15 \pm .05$ for a group using blood analysis and $r = -.08 \pm .05$ for a group using dentine analysis.

Pocock, Smith, and Baghurst (1994) reported a small effect size of about $r = -.05$ to $-.1$.

Interestingly, not all studies have found a relation between lead and IQ scores. Sachs and colleagues (1978) found no differences in IQ between a lead poisoned group and a control group. However, this study was thought to be confounded by other variables, particularly a poorly defined control group. Some researchers have argued that because the control group was described simply as having lead levels “below 40 $\mu\text{g/dL}$ ” that it may have included children who actually had a lead burden high enough to place them in the “lead” group based on what we know about blood lead levels today (Kirkconnell & Hicks, 1980). By keeping children with significant lead burden in the comparison group, it is no surprise that few differences between groups were found.

Since Byers and Lord’s (1943) original observations of children previously thought to be “cured” of lead poisoning, elevation in lead burden has been consistently linked with aggressive behavior (Marlowe, Stellern, Moon, & Errera, 1984), delinquent and antisocial behavior (Needleman, 2009; Needleman, Riess, Tobin, Biesecker, & Greenhouse, 1996), and even violent crimes, including homicide (Stretesky & Lynch, 2001). Needleman and colleagues (1996) sampled first grade boys from the general population who were more at risk for antisocial behaviors. Lead burden was measured using in vivo K X-ray fluorescence spectroscopy of the subject’s tibia, where lead is known to deposit in meaningful amounts. They found that higher-lead subjects were more likely to report higher scores on self-report items of delinquency. They were also rated higher by teachers and parents on the Child Behavior Checklist (CBCL) delinquent,

aggressive, and externalizing scales. Furthermore, they were more likely to obtain scores in the clinical level on CBCL subscales of attention, aggression, and delinquency during a four year period of observation (Needleman et al., 1996), suggesting a relation between lead exposure in children and increased instances of antisocial and delinquent behavior.

Marlowe and Errera's (1982) study of lead burden and behavioral problems sampled children living in a rural setting to further extend the lead-behavior association to a different population. In this study, lead levels were taken from hair samples of students in a rural region of Tennessee who were identified by their teacher as exhibiting conduct and behavioral problems and were compared to students in a control group who did not have behavioral problems. There were no significant differences in socioeconomic status, sex, or ethnic group distributions. Teachers rated each student in the study using the Walker Problem Behavior Identification Checklist (WPBIC). Higher lead levels based on hair analysis correlated significantly and positively with a number of the WPBIC subscales, including aggression and poor peer relations as well as distractibility and immaturity. Marlowe and Errera (1982) concluded that although more research needs to be conducted, enough evidence exists to show that even low levels of lead may influence behavioral problems.

Recently, Marcus, Fulton, and Clarke (2010) conducted a meta-analysis examining the relation between lead exposure and conduct disorder, oppositional behavior, aggression, violence, delinquency, and antisocial behavior in children. Marcus and colleagues (2010) found an average r of .19 which is considered to be a medium effect size (Cohen, 1988). They also found that studies using hair analysis yielded much larger effect sizes than studies that used blood, tooth, or bone analyses. Despite methodological

heterogeneity between the studies included in the meta-analysis, effect sizes remained remarkably consistent between all studies, excluding those that used hair analysis. This meta-analysis did not include measures of ADHD symptoms (Marcus et al., 2010).

Attention-Deficit/Hyperactivity Disorder

ADHD was originally described by George Still and Alfred Tredgold (Barkley, 1998). Still (1902) wrote about children who demonstrated a variety of behaviors, including aggression, defiance, excessive emotionality, and problems in sustained attention. Still and Tredgold believed these children demonstrated “a defect in moral control” and were primarily motivated by immediate gratification. Currently, the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR, APA, 2000) defines this collection of cognitive and behavioral deficiencies as attention-deficit/hyperactivity disorder. According to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (APA, 2000), symptoms must have an onset prior to age 7 and must be impairing across multiple settings (e.g., home and school). There are three subtypes of ADHD. A diagnosis of ADHD, Predominantly Inattentive Type (ADHD-PI) is given when an individual meets at least six criteria related to inattention but not hyperactivity/impulsivity for the last six months. A diagnosis of ADHD, Predominantly Hyperactive/Impulsive Type (ADHD-PH) is given when an individual meets at least six criteria for hyperactivity or impulsivity but not inattention for the last six months. If an individual meets both sets of criteria for at least six months, a diagnosis of ADHD, Combined Type (ADHD-C) is given (APA, 2000).

ADHD can be conceptualized as a “developmental delay in response inhibition,” (Barkley, 1997, p. 226). Those with ADHD show difficulties in the initiation of self-

regulation due to an inability to inhibit a prepotent response to a stimulus. Prepotent responses are an individual's responses to a stimulus that are usually reinforced almost immediately after they occur, or they have a strong history of being reinforced in a particular context (Mash & Barkley, 2003). In ADHD, the mechanism of behavioral inhibition does not inhibit a prepotent response to a stimulus or stop an ongoing response to a stimulus from occurring. This failure to inhibit the prepotent response prevents a period of delay that should normally occur. Normally during this period, an individual can stop and think about a stimulus (self-directed response) and then formulate a plan (goal-directed response). However, because the individual has already responded to the stimulus (a prepotent response that was not inhibited), there can be no self-directed or goal-directed responses (Barkley, 1997). Several executive functions may be susceptible to a lack of a delay period where self-directed and eventually goal-directed actions should occur, including both verbal and nonverbal working memory, internalization and self-regulation of affect, and reconstitution and internalization of play (Mash & Barkley, 2003). If a prepotent behavior is inhibited or delayed, there is no interference, and these four executive functions have an opportunity to function normally and shape an appropriate response to a stimulus or event (Barkley, 1997). In ADHD, an impulsive prepotent behavior that should be inhibited but is immediately reinforced interrupts these executive functions causing the problems with attention.

Lead and ADHD Symptoms

ADHD is known to have a significant neurological component, and a few different brain areas have been implicated in the different symptom sets. Because most of the executive functions discussed previously are thought to originate in the frontal lobe and

cortex, damage to neurons in this region caused by an accumulation of lead may result in impairments in executive functioning. Damage to brain structures like the basal ganglia, globus pallidus, and thalamus may be implicated in the severity of ADHD symptoms related to executive functioning (Mash & Barkley, 2003). In general, the basal ganglia is associated with regulation of movement as well as cognition and learning certain skills and is highly interconnected with the cerebral cortex. The caudate nucleus, part of the basal ganglia, is associated with learning and memory. The putamen is another region of the basal ganglia and is associated with motor movement. Disturbances in motor movement (hyperactivity or fidgeting) may originate in the basal ganglia but also implicate other brain areas involved in movement like the cerebellum. Lead in the brain may damage glial cells, which act as support cells for neurons by insulating neural axons, detoxifying harmful substances. They may also be involved in behavioral inhibition (Anderson, 2007; Masters, Hone, & Doshi, 1998). It has also been suggested that lead may interfere with the brain's normal process of pruning infrequently used neural connections. Lead may prevent the brain from removing unnecessary neural connections which may increase neural interference during information processing. The result of this might be over-responsiveness to stimuli as the child develops, expressed as impulsive behavior (Goldstein, 1992; Needleman et al., 1996).

Neurotransmitters are probably affected as well, but most of the data have come from animal studies. For example, lead exposure might inhibit N-Methyl-D-aspartic (NMDA) receptors in rats. By disrupting the reception of neurotransmitters like glutamate, learning and memory are disturbed (Nihei et al., 2000). It is also known that glutamate tends to be an inhibitory neurotransmitter and is found throughout the brain. If

NMDA receptors become damaged by lead, particularly in the frontal lobes, behavioral disinhibition may result. Needleman and colleagues (1996) have reported that lead toxicity is associated with interference in norepinephrine-mediated behavioral inhibition in a rodent model (Taylor et al., 1978). By interfering with inhibition at the neurochemical level, lead burden in the brain may cause unmediated responses to events or stimuli, which would appear as impulsivity. Dopaminergic disturbances have also been observed in the presence of lead burden (Cory-Slechta, 1997; Ris et al., 2003).

Specifically, Heijtz, Kolb, and Forssberg (2007) reported that in rats, damage to D1 dopamine receptors (D1R) are implicated in regulating motor and cognitive processes and that damage to these receptor sites by lead may be linked to motor disinhibition. This evidence may be supported by the fact that dopaminergic agonists like methylphenidate are often effective in the treatment of ADHD. Furthermore, it is known that the nucleus accumbens, a major dopamine-producing area, has strong ties to the prefrontal and frontal cortex. This pathway, beginning in the ventral tegmentum area and traveling through the nucleus accumbens to the prefrontal cortex and frontal lobes, is called the mesolimbic pathway of dopamine; it has been strongly associated with motivation and rewards (Ikemoto & Panksepp, 1999). It is possible that damage to D1 receptors along this “reward pathway” in the frontal lobes may be related to the impulsivity and problems with delayed gratification in ADHD (Heijtz, Kolb, & Forssberg, 2007).

CHAPTER II

REVIEW OF RELATED LITERATURE

A number of studies have examined the relation between lead burden and the components of ADHD in people. This meta-analysis attempted to include all of these published studies, but the following section will briefly summarize some exemplars of this research. In one of the earliest studies, David (1974) examined the relation between lower level lead concentrations and hyperactive symptoms in a group of medical outpatient children in New York. Children were divided into two groups, a hyperactive group and a nonhyperactive control group based on a doctor's diagnosis, a teacher report using the Conner's scale, and a parent report using the Wherry-Weiss-Peters scale. The average hyperactivity score was taken from all three reports to determine group assignment. Next, an analysis of lead was taken using blood samples and urine samples both before and after a penicillamine treatment. Additionally, a lead exposure questionnaire was completed for each child. The hyperactive group had significantly higher scores on blood, pre- and post-penicillamine urine, and lead questionnaire scores. Furthermore, over half of the hyperactive group had blood lead levels in a range between toxic and normal, which the author classified as raised. It was determined that a relation between low lead levels and hyperactivity exists and that lead burden above approximately 24.5 μ g/100mL should be attended to seriously (David, 1974).

Minder and colleagues (1994) measured the link between lead exposure and attentional problems in children. This pilot study used an X-ray technique to analyze hair samples of boys attending a special school for educational or learning problems. Children with probable known causes of attention problems (e.g., a parent with ADHD, head

trauma, pre- or perinatal complications, obvious lack of educational opportunity) were excluded from the research. A battery of paper-and-pencil tests assessing various aspects of attention and concentration, memory, and processing speed were assembled using subtests from the Neurobehavioral Evaluation System (NES), the Wechsler Intelligence Scale for Children-Revised (WISC-R), the Stroop test, Trail Making Tests A and B, and others. The greater the concentration of lead in the hair sample, the longer the reaction time and poorer performance on some of the tests of attention like the Trail Making Test B. The association remained even after potential confounding variables were accounted for, including socioeconomic status, age, and IQ (Minder et al., 1994).

Canfield and colleagues (2003) also examined the relation between low level lead burden and attention problems in children. This study sampled children from a larger, ongoing longitudinal study examining the effects of lead burden on neurobehavioral patterns. This particular research also examined the effects of lead on learning and memory. Gender was roughly equal in this sample (52% male). Blood lead levels were assessed over a period of 4 years at 6-month intervals. Children were given a battery of tests that primarily examined the child's attention level. Attention level was coded as either focused (serious facial expression, eye contact with work), settled (more open posture, less eye contact, unrelated verbalizations with the experimenter), or active inattention (prolonged lack of eye contact with the task, attempting to leave the task, or frequent fidgeting behavior). Lead burden was significantly associated with attention tasks requiring a child's sustained attention on the task but not during tasks that required children to switch their attention from one stimulus to another. Minder and colleagues

(2003) also noted that these associations occurred when controlling for confounding variables like socioeconomic status.

It should be apparent that there are many different ways to measure the various symptoms of ADHD. Additionally, there is heterogeneity in the various methods of assessing lead burden. The literature is further complicated by the influence of confounding variables that may act as moderators, such as socioeconomic status, age, gender, and IQ among others. Therefore, the aim of the present study was to investigate the relation between lead burden and the presence of ADHD symptoms by synthesizing the current findings from all English-language published studies of this association using meta-analytic techniques. Research has already determined there is a link between lead burden and symptoms of ADHD, and the goal of this study was to determine, on average, how large that relation is across studies and measures for each set of symptoms associated with ADHD. Based on the current literature, it was hypothesized that a meta-analysis of the findings would yield a statistically significant medium effect size across studies. For example, Mash and Barkley (2003) commented on the consistency of the correlation between lead and ADHD symptomatology across studies, although they describe this correlation as being small.

It was hypothesized that there would be significant heterogeneity among the studies and that several variables may moderate the relation between lead burden and components of ADHD. First, it was predicted that the methods used to assess lead burden would moderate the association between lead burden and ADHD symptomatology. More specifically, studies using hair analysis to measure the lead-ADHD association were predicted to exaggerate the relation between lead and ADHD symptoms causing it to

appear larger than the relation reported using other methods of lead assessment. This hypothesis was based on the findings of Marcus and colleagues (2010), who recently used similar techniques to study the relation between lead and conduct problems. Second, it was hypothesized that the year of publication would moderate the association between lead and ADHD symptoms. This prediction is based on the fact that over the last few decades, changes in public policy have reduced or eliminated the amount of lead used in commercial products. Therefore, the earlier studies should show a larger effect size because of the greater amount of environmental lead at the time of publication. Additionally, other possible moderators were examined, including age and gender, although it was unclear whether these variables would influence the lead-ADHD relation. The goal of this meta-analysis was to enhance knowledge of the etiology of ADHD symptoms, which is believed to have a strong genetic component, by increasing the understanding of one potential environmental component, lead burden.

CHAPTER III

METHODOLOGY

Compilation of Studies

Searches for relevant studies were conducted using the online journal databases PsychINFO and Medline. The search terms *lead (metal)*, *lead poisoning*, and *lead burden* were combined with various other terms including *ADHD*, *attention deficit*, *attention problems*, *hyperactivity*, and *impulsivity*. The search term *ADD* was also used in order to capture studies published before DSM criteria changed the name of the diagnosis. Furthermore, the researcher reviewed the reference sections of useful studies to generate more relevant articles for the analysis. In order to be included in the meta-analysis, the studies had to be written in English, provide codable statistics, and include a measure of a component of ADHD. It was not necessary that a diagnosis of ADHD be given in the studies that were included, just that at least one component (e.g., inattention, hyperactivity) was examined. Studies using animal models of ADHD were excluded as well as any single case designs of ADHD.

The aim of this meta-analysis was to examine the effects of lead burden on children and adolescents (who are still developing) and determine how lead relates to ADHD, which is generally viewed as a developmental disorder. Additionally, the CDC (1978) reported that the younger the individual, the greater the risk for lead poisoning, due to more inefficient metabolism, excretory pathways, and immunological systems. Therefore, studies of ADHD in adults were not included. Overall, 29 studies associating lead with a set of ADHD symptoms were included in the meta-analysis: 21 studies provided codable statistics for the lead-inattention association and 16 studies provided codable statistics for

the lead-hyperactivity/impulsivity association. All 29 studies were included in the meta-analysis for total ADHD symptoms. A total of 12,322 individual participants were included in this meta-analysis across all 29 studies.

Procedure

All studies were coded for sample size, mean age of participants, percentage of male participants, method of lead burden assessment (blood, hair, tooth, bone), component(s) of ADHD measured (inattention, hyperactivity-impulsivity, total ADHD symptoms), method(s) used to measure ADHD, and year of publication of the study. All effect sizes were converted into Pearson's product-moment correlation coefficients (Rosenthal, 1991). In order to correct for bias, all Pearson's r s were transformed using Fisher's Z_r transformation (Hedges & Olkin, 1985), then transformed back into Pearson's r for reporting. Effect sizes were weighted by sample size using the inverse variance weight sample size minus three (Lipsey & Wilson, 2001).

Because there are multiple facets of ADHD, different studies of ADHD measured and reported symptomatology in a variety of ways. If a study used both a dichotomous measure (e.g., a diagnosis) and a continuous measure (e.g., a rating scale) to measure ADHD symptoms, the effect size based on the continuous measure was used in the meta-analysis because it provides more information and greater variance than a dichotomous measure. If a study used multiple means of assessment for ADHD symptomatology, effect sizes were averaged. For example, 9 studies included both a parent and teacher report of a child's ADHD symptoms, and 4 studies used both questionnaires and performance measures (e.g., Continuous Performance Task). If a study used a measure that included subscales that measured a specific component of ADHD as well as gave an

estimate of total ADHD, both effect sizes were used. Additionally, some research might focus on a single aspect of ADHD. For example, 9 studies included a measure of inattention without including measures of hyperactivity and impulsivity and 6 studies provided measures of hyperactivity-impulsivity without including a measure of inattention. Three separate meta-analyses were conducted in order to use the largest amount of data from each article. One meta-analysis focused on effect sizes using Hyperactivity/Impulsivity data, a second meta-analysis focused on the Inattention domain, and a third meta-analysis used data from overall measures of ADHD and the combined-type domain. In the total ADHD symptoms meta-analysis, 7 studies provided an effect size for lead and total ADHD symptoms, but for the remaining studies that reported both inattention and hyperactivity-impulsivity effect sizes, these effect sizes were averaged to create a total ADHD symptoms effect size. If a study only reported on one aspect of ADHD (i.e., inattention but not hyperactivity-impulsivity), this effect size was used as an estimate of total ADHD. This was done in order to maximize the studies in the meta-analysis of lead and total ADHD symptoms.

Some studies reported only the simple correlation between lead burden and ADHD symptomatology. However, 6 studies included the correlation between lead burden and ADHD after controlling for covariates, including age, gender, IQ, or socioeconomic status. It is particularly common to control for covariates in studies like these in order to estimate the unique variance accounted for by lead burden (e.g., Nigg et al., 2008). Still other studies reported both the simple correlation of lead burden and ADHD symptomatology as well as the association controlling for covariates (e.g., Nigg et al., 2010). For the primary meta-analysis, the simple correlations were reported whenever

they were available. If they were unavailable or not reported, partial correlations between lead and ADHD symptoms that control for covariates were used instead. Supplementary meta-analyses using (a) only zero-order correlations and (b) only partial correlations were also conducted.

Statistical Procedures

Analyses were conducted using a maximum-likelihood random effects model, which is more conservative than a fixed effects model. By using a maximum-likelihood random effects model, the researcher was more able to generalize findings beyond the set of studies used in the meta-analysis. This model assumes that the studies used in the meta-analysis are only a sample of all possible studies that examine the association between lead burden and the components of ADHD (Field, 2003). A Q -test of homogeneity was performed to examine whether the results across studies came from similar or different populations. A significant Q -test indicates that the studies were heterogeneous rather than homogenous. A non-significant Q -test indicates that populations across studies were homogenous and that differences in effect sizes were largely due to sampling error rather than sample characteristics. I^2 (Higgins, Thompson, Deeks, & Altman, 2003) was computed to determine the percentage of variance that is attributable to the heterogeneity in populations across the studies. An I^2 of 0 indicates complete homogeneity, whereas an I^2 of 100 indicates complete heterogeneity.

A significant Q -test also indicates that moderating variables may explain the heterogeneity in samples. Hedges' (1982) meta-analytic analogue to an analysis of variance (ANOVA) was used to test the effects of potential categorical moderators, such as method of lead burden assessment. Finally, Hedges and Olkin's (1985) meta-analytic

analogue to a regression was used to test the effects of continuous moderators, such as year of publication or mean age of the sample. These analyses were all conducted using SPSS statistical programs created by Lipsey and Wilson (2001) specifically for meta-analysis.

CHAPTER IV

ANALYSIS OF DATA

Primary Analyses

The average r across all 29 studies was .19, which was statistically significant (95% CI = .12-.26; $Z = 5.11$, $p < .001$). This value is equivalent to a d of .39 and is considered a medium effect size (Cohen, 1988). There was significant heterogeneity across studies, $Q(28) = 427.42$, $p < .001$, $I^2 = 93.45$, suggesting that they do not all derive from the same population and that their results should not be averaged without considering the influence of moderators. The average r across all 21 studies that reported the relation between lead and inattention was .16, which was also statistically significant (95% CI = .12-.19; $Z = 9.09$, $p < .001$). This value is equivalent to a d of .32 and is considered a medium effect size (Cohen, 1988). There was not significant heterogeneity across the 21 studies that provided measures of inattention, $Q(20) = 30.41$, $p = .064$, $I^2 = 34.23$. Due to the lack of sufficient heterogeneity across studies that provided measures of inattention, no moderation analyses were conducted. Finally, the average r across all 16 studies that reported the relation between lead and hyperactivity-impulsivity was .15, which was statistically significant (95% CI = .10-.19; $Z = 6.30$, $p < .001$). This value is equivalent to a d of .30 and is considered a medium effect size (Cohen, 1988). There was significant heterogeneity across the 16 studies that reported the relation between lead and hyperactivity-impulsivity, $Q(15) = 29.28$, $p = .015$, $I^2 = 48.77$. This result indicates that these studies may not all derive from the same population and that their results should not be averaged without considering the influence of moderating variables.

Secondary Analyses

There were 12 studies of inattention that provided effect sizes controlling for covariates. In these studies, the average r was .14 (95% CI = .096-.174; $Z = 6.63$, $p = < .001$). In these studies, there was no significant heterogeneity, $Q(11) = 17.33$, $p = .0986$, $I^2 = 36.53$. For the 6 studies of inattention that provided both zero-order and partial correlations controlling for covariates, the average zero-order correlation between lead and inattention was .16 and the average partial correlation between lead and inattention was .14. There was no evidence that covariates explained the relation between lead and inattention in these studies. There were 6 studies of hyperactivity-impulsivity that provided effect sizes controlling for covariates. In these studies, the average r was .10 (95% CI = .04 -.16; $Z = 3.23$, $p = .001$). These studies also did not demonstrate significant heterogeneity, $Q(5) = 10.04$, $p = .0742$, $I^2 = 50.20$. For the 4 studies of hyperactivity-impulsivity that provided both zero-order and partial correlations controlling for covariates, both the average zero-order correlation and the average partial correlation between lead and hyperactivity-impulsivity symptoms was .11. Therefore, there was no evidence that covariates explained the association between lead and hyperactivity-impulsivity symptoms.

Table 1

General Information on Studies that Examined the Lead/ADHD Symptoms Association

Reference	N	Lead Measure	Inattention ES (r) ^a	Hyperactive-Impulsive ES (r) ^a	Total ADHD ES (r) ^a
Braun et al. (2006)	1674	Blood	--	--	.51 ^b
Canfield et al. (2003)	170	Blood	(.25)	--	(.25)
Canfield et al. (2004)	174	Blood	(.22)	--	(.22)
Chiodo et al. (2007)	452	Blood	.20 (.16)	-.04 (-.02)	.08 (.07)
Cho et al. (2010)	639	Blood	.15 (.09)	.16 (.12)	.16 (.11)

Table 1 (continued).

Reference	N	Lead Measure	Inattention ES (r) ^a	Hyperactive -Impulsive ES (r) ^a	Total ADHD ES (r) ^a
Counter et al. (2009)	35	Blood	.46	--	.46
David (1974)	91	Blood	--	.22	.22
Fergusson et al. (1993)	878	Hair	.20 (.12)	--	.20 (.12)
Fraser et al. (2006)	110	Blood	.14	.27	.21
Froehlich et al. (2009)	2588	Blood	--	--	.26 ^b
Kahn et al. (1995)	116	Blood	--	--	-.03 ^b
Marlowe & Errerra (1982)	55	Tooth	.28	.29	.29
Minder et al. (1994)	43	Tooth	.28	--	.28
Needleman et al. (1979)	158	Hair	.19	.17	.18
Needleman et al. (1996)	212	Bone	(.06)	(.04)	(.05)
Nicolescu et al. (2010)	83	Blood	.31	.23	.28 ^b
Nigg et al. (2008)	150	Blood	.18	.28	.24 ^b
Nigg et al. (2010)	236	Blood	.15 (.13)	.18 (.16)	.17 (.15)
Plusquellec et al. (2007)	169	Blood	(.18)	--	(.18)
Ris et al. (2004)	195	Blood	-.001 (.114)	--	.001 (.114)
Roy et al. (2009)	814	Blood	(.24)	(.13)	(.16) ^b
Rummo et al. (1979)	90	Blood	--	(.11)	(.11)
Silva et al. (1988)	579	Blood	.13	.17	.15
Šovčíková (1995)	393	Blood	.09	--	.09
Thomson et al. (1989)	501	Blood	--	.08	.08
Vibha et al. (1996)	100	Blood	--	.24	.24
Wang et al. (2008)	1260	Blood	--	--	.54 ^b
Wasserman et al. (2001)	191	Blood	(.06)	--	(.06)
Yule et al. (1984)	166	Blood	.17 (.18)	.16 (.19)	.17 (.19)

^a Effect sizes computed with covariates appear in parentheses. ^b Studies that provided Total ADHD effect sizes.

It was hypothesized that the method of lead assessment would moderate the lead-ADHD relation. Specifically, studies relying on hair analysis of lead burden would overestimate this relation when compared to studies using blood, tooth, or bone analysis. A random effects model analogue to the ANOVA indicated that method of lead assessment did not contribute to the variability across studies, $Q_B(3) = 1.42$, $p = .701$; $Q_H(25) = 25.71$, $p = .423$. The studies that used hair analysis to estimate lead burden did not report significantly larger associations between lead and overall ADHD symptoms ($r = .27$, $k = 3$) than did studies using blood lead levels ($r = .19$, $k = 23$) or dentine lead

levels ($r = .19$, $k = 2$). Only one study provided estimates of lead burden using bone x-ray techniques ($r = .48$, $k = 1$; Needleman et al., 1996). Furthermore, a second random effects model analogue to the ANOVA was conducted comparing the effect sizes based on hair analysis to that of the remaining studies. There were no significant difference between groups, $Q_B(1) = 0.54$, $p = .46$; $Q_H(27) = 25.83$, $p = .53$. The average effect size of studies that did not use hair analysis was $r = .19$ (95% CI = .13-.25, $Z = 6.15$, $p < .001$). The small number of total studies using hair analysis compiled in this meta-analysis and a lack of statistical power may be responsible for the absence of significant results. Furthermore, too few studies of the association between lead and hyperactivity-impulsivity used hair samples to assess lead burden ($k = 2$). The lack of variability in assessment method prevented hair from being analyzed as a moderator in these studies.

The year of publication was hypothesized to moderate the relation between lead and ADHD symptoms, with older studies yielding larger effect sizes. Year of publication did not moderate the association between lead and ADHD symptoms ($k = 29$; $\beta = .237$; $B = .004$ [SE = .003]; $Z = 1.25$, $p = .21$). Furthermore, when treated as a continuous moderator, the meta-analytic equivalent to a regression revealed that year of publication did not significantly moderate the association between lead and hyperactive-impulsive symptomatology, ($k = 16$; $\beta = -.083$; $B = -.0006$ [SE = .002]; $Z = -.32$, $p = .75$).

While searching for possible moderators, it was discovered that sample size moderated the relation between lead and total ADHD symptoms. There was a large range in sample sizes. The smallest sample size was $n = 35$ (Counter, Buchanan, & Ortega, 2009) and the largest sample size was $n = 2588$ (Froehlich et al., 2009). Studies with larger samples yielded larger effect sizes ($k = 29$; $\beta = .486$; $B = .0001$ [SE = .0001]; $Z =$

2.88, $p = .004$). Further analysis of the sample sizes revealed that three outliers were responsible for this effect. These studies were outliers in that they contained extremely high correlations between lead and total ADHD symptoms. When studies by Froehlich and colleagues (2009; $n = 2588$), Braun and colleagues (2006; $n = 1674$), and Wang and colleagues (2008; $n = 1260$) were removed from the model, a larger sample no longer indicated a stronger relation between lead and total ADHD ($k = 26$; $\beta = .144$; $B < .0001$ [$SE < .0001$]; $Z = .831$, $p = .41$). Furthermore, total sample size did not appear to moderate the association between lead and hyperactivity-impulsivity, ($k = 16$; $\beta = -.3751$; $B = -.0001$ [$SE = .0001$]; $Z = -1.468$, $p = .14$).

Demographic Variables

Age groups in this meta-analysis ranged from very young children to adolescents. The youngest mean age was 1.0 (Plusquellec et al., 2007) and the oldest mean age was 15.6 (Ris et al., 2004). Despite this wide range, age did not moderate the relation between lead burden and total ADHD symptomatology ($k = 23$; $\beta = .113$; $B = .005$ [$SE = .009$]; $Z = .52$, $p = .60$). Additionally, age did not moderate the relation between lead and hyperactivity-impulsivity symptoms ($k = 11$; $\beta = .4340$; $B = .020$ [$SE = .0125$]; $Z = 1.57$, $p = .12$).

There was also no evidence that gender moderated the relation between lead and ADHD symptoms. Despite ADHD symptoms being much more prevalent in boys than girls, when percentage of male participants was treated as a continuous variable, the meta-analytic analog to a regression revealed that it did not moderate the association between lead and total ADHD symptoms ($k = 24$; $\beta = .188$; $B = .002$ [$SE = .002$]; $Z = .89$, $p = .37$). Additionally, percentage of male participants did not appear to moderate the

association between lead and hyperactivity-impulsivity symptoms ($k = 15$; $\beta = -.026$; $B = -.0002$ [SE = .002]; $Z = -.095$, $p = .9241$) in this subset of studies.

CHAPTER V

DISCUSSION OF RESULTS

Despite its focus on aggressive behaviors, the original Byers and Lord (1943) lead study included several case descriptions of children who exhibited inattentive and hyperactive or impulsive behavior. Descriptions of children who are “inattentive, restless, and inaccurate in work” by the teachers interviewed by Byers and Lord (1943; p. 481) seem consistent with teachers’ descriptions of children who might meet criteria for an ADHD diagnosis today. The results of this meta-analysis indicate that lead burden in children and adolescents contributes to the development of the attention problems and hyperactivity-impulsivity symptoms associated with ADHD. These results supported the first hypothesis that lead burden would be moderately related to the ADHD symptoms of inattention and hyperactivity-impulsivity. Beyond genetic predisposition, it would appear that lead exposure, and over time, lead burden has a significant impact on a child’s ability to inhibit prepotent responses to a stimulus or maintain sustained focus on one particular task. ADHD symptomatology, by definition, must begin before the age of seven years old (i.e., early childhood) and lead exposure and burden typically affects children most severely because their brains are still developing. Considering what we already know about how dangerous lead exposure can be regarding cognitive development (e.g., Needleman & Gastonis, 1990), it makes sense that lead burden might also be implicated in other neurological disorders like ADHD. Some authors have argued that environmental factors, like lead, may activate a genetic predisposition toward attention problems or hyperactivity-impulsivity (Nigg et al., 2008; Waldman & Gizer, 2006).

One of the most important findings from this meta-analysis was that a moderate effect size was found for both the lead-inattention and lead-hyperactivity/impulsivity associations even after controlling for covariates. Out of the 29 studies in the meta-analysis, 12 included effect sizes with covariates partialled out of the lead-inattention association, and 6 included effect sizes with covariates partialled out of the lead-hyperactivity/impulsivity association. We certainly know that lead exposure is related to a number of covariates, particularly variables like low SES (e.g., low-income housing containing lead-based products, neighborhoods near industrial areas). Almost all studies in these analyses controlled for SES, and other common covariates were maternal IQ, child IQ, ethnicity, parental education level, and family size. These results indicate that covariates do not explain the lead-ADHD symptoms association and that such a relation exists beyond the influences of certain covariates. This information leads researchers closer to establishing the lead-ADHD symptoms association as a causal one.

Given the fact that the earlier a study was published, the more lead was in the environment at the time, it was hypothesized that the year of publication might moderate the association between lead and ADHD. However, year of publication did not appear to moderate this association, and the years during which lead was much more common in the environment did not seem to amplify the association between lead and ADHD symptoms. These results demonstrate that even if the amount of environmental lead decreased as a function of time, the magnitude of the effect stayed the same across time, which may be evidence that the lead-ADHD symptoms relation is linear. Additionally, it is important to note that some longitudinal studies may have assessed lead burden

throughout a child's lifetime, and year of publication might not reflect the year of exposure (e.g., Needleman et al., 1996; Ris et al., 2004).

Across the 29 studies in the meta-analysis, unfortunately, there was not enough heterogeneity in lead assessment methods to determine if the method used to assess lead burden was a moderator of the lead-ADHD association. Out of the 29 studies, only 3 used tooth analysis, 2 used hair analysis, and 1 used X-ray techniques to analyze bones; the remaining 23 studies all used blood analysis. The hypothesis that studies using hair sampling would appear to magnify the association between lead and ADHD symptoms was based on the findings of Marcus et al. (2010). In their meta-analysis of the association between lead burden and conduct problems, they found that hair analysis seemed to exaggerate the relation between lead and conduct problems. They noted that this may be due to the fact that hair analysis is subject to external treatments or washing (EPA, 2006), and that overall hair analysis is generally more inaccurate than blood analysis of lead (Smith, 1985). They also noted that the three studies using hair samples in their meta-analysis were all conducted by the same first author. In this study, the two hair-lead studies were conducted by two different research teams.

Unexpectedly, it was observed that sample size moderated the association between lead and ADHD symptoms. In this meta-analysis, studies with larger samples appeared to generate a stronger relation between lead and total ADHD ratings. Upon a closer inspection, it was noted that this moderation was drastically influenced by three outliers and that, when the outliers were removed, the relation vanished. These three outliers (Braun et al., 2006; Froehlich et al., 2009; Wang et al., 2008) all used diagnostic status (i.e., ADHD had been diagnosed or not diagnosed) or some other dichotomous measure

(e.g., currently taking stimulant medication) to measure the presence or absence of total ADHD. Furthermore, two of these studies (Braun et al., 2006; Froehlich et al., 2009) reported the association between lead burden and ADHD as adjusted odds ratios. This estimate of effect size is sometimes used when data are artificially or naturally dichotomized, such as a child whose blood lead level is above or below a certain cutoff point or the diagnostic status of ADHD (Haddock, Rindskopf, & Shadish, 1998). It is possible to transform odds ratios into Pearson's product-moment correlations, but Bonett (2007) reported that this transformation is only approximate. It is possible that the transformation of effect sizes for the purposes of this meta-analysis led to an overestimation of the association.

Limitations of the Current Study

Although the present meta-analysis provides insight into the lead-ADHD symptoms relation, there are some limitations that should be discussed. One limitation might be that this meta-analysis was restricted by the small number of studies ($k = 29$) included in the final analysis. This meta-analysis was dependent upon both the usefulness of the search terms as well as the effectiveness of the electronic databases in finding relevant articles. Despite best efforts, some research articles returned by the databases could not be procured in time through inter-library loan for the final analysis. The quality of research returned may also have varied considerably. For example, some of the studies in this meta-analysis were published by research teams who had previously contributed several articles about lead exposure to the field. These studies tended to include information about covariates and all relevant demographic data used in subsequent analyses. Other studies might have been a research team's first foray into the lead literature and,

therefore, were not as well organized and lacked information about covariates or demographics. However, all studies were published in peer-reviewed journals, guaranteeing at least adequate scholarly quality.

Furthermore, lead research generally is marked by a variety of limitations because individuals can never be experimentally exposed to lead on purpose to measure the outcomes. Because it is harmful and unethical to experimentally test the effects of lead exposure on people, researchers have typically relied either on experimental animal models or quasi-experimental studies of people. In human subjects research, investigators also typically try to analyze the impact of covariates, or confounding variables, in order to extrapolate the unique effect of lead on ADHD symptoms. However, not all of the studies used in this meta-analysis provided information about lead's unique effect.

Needleman and colleagues (1996, p. 368) pointed out that lead levels tend to be higher in children and adolescents who have more "non-lead risk factors" for attention problems. Lead is most common in low SES environments—in older buildings or near factories or industrial areas. Socioeconomic status is associated with a variety of confounding variables, including parental IQ, parental education, number of parents in the home, or family size. Several studies in this meta-analysis controlled for covariates, and the significant association between lead and inattention, hyperactivity-impulsivity, and total ADHD symptoms remained. The fact that the association between lead and ADHD symptoms remained statistically significant even after a number of covariates are controlled is a curious one. It is interesting that even after controlling for variables like IQ, age, and family characteristics, the association remained almost identical across several studies. This implies that the association between lead and ADHD symptoms

might be causal. This is consistent with findings observed in animal models. For example, monkeys treated with lead appeared to demonstrate difficulty inhibiting responses and behaved differently than controls (Rice, 2005). Additionally, a study by Silbergeld and Goldberg (1973) revealed that rats treated with lead were observed to be more than three times as hyperactive as control rats. Furthermore, cognitive impairments as a result of lead exposure, such as lower IQ, have been well-documented by research (e.g., Needleman & Gatsonis, 1990). These results suggest the association to be a causal one. It is important to remember that environmental toxins like lead are certainly not the only cause of attention problems or hyperactive and impulsive behavior and that the etiology of ADHD is complex. It is well known that ADHD symptoms are strongly genetically linked. However, for a disorder so strongly linked to genetic variability, the association between lead burden and ADHD symptoms uncovered by this meta-analysis is quite impressive.

Directions for Future Research

Future studies of the lead-ADHD symptoms association should make every attempt to control for various covariates in order to clarify the lead-ADHD association. It is known that lead levels tend to be higher in children who are exposed to “non-lead risk factors” (Needleman et al., 1996, p. 368). In this meta-analysis of 29 studies, only 12 studies provided information about the lead-ADHD symptoms association with the effects of covariates partialled out. Studies should attempt to address variables like SES, gender, IQ, and age of exposure (if it was an acute and documented event in the child’s life) at the very least. Maternal and paternal characteristics like IQ, education, and parenting styles may also be important covariates. If future research can document the

relation between lead and ADHD symptoms beyond the influence of these common covariates, it may be better established that lead affects the development of ADHD-related symptoms in a causal way.

Future research may also move in the direction of ascertaining prenatal lead levels and attempting to connect very early lead exposure with later cognitive or behavioral development. One study in this meta-analysis (Plusquellec et al., 2007) collected prenatal lead data through the assessment of maternal blood and hair lead levels as well as the assessment of blood lead levels in the child's umbilical cord. According to Needleman (2009), it is known that lead crosses the placenta via blood. Lead probably affects children at least as much as adults because their brains are still in critical stages of development. Assessing blood lead levels prenatally may provide even more insight into how lead can adversely affect developing children as well as help identify children who may be at risk for cognitive delays or behavioral problems later in life.

Future research in lead burden and ADHD symptomatology might also focus on whether this relation is linear or if there is a certain threshold related to ADHD symptoms. The focus of this meta-analysis was designed to elucidate the association, not explain exactly how lead is related to the symptomatology. Several authors have argued that the lead-ADHD symptoms association is indeed a linear one and that a larger "dose" of lead is related to more problems with inattention or hyperactivity-impulsivity. In contrast, other studies support the idea that this association is non-linear and that a certain threshold of lead burden is associated with the presence of ADHD symptomatology (e.g., Chiodo et al., 2007) but that larger amounts of lead may not necessarily increase symptomatology. Additionally, it is possible that problems with inattention and

hyperactivity are associated with different threshold “doses.” For example, Chiodo and colleagues (2007) reported that blood lead levels as low as $5\mu\text{g/dL}$ were associated with inattention but not impulsivity, which required a slightly higher amount of lead. This particular issue cannot be studied experimentally (i.e., groups of children cannot be purposefully exposed to varying amounts of lead and then observed) but carefully controlled longitudinal designs might be able to produce data useful for answering these questions regarding the role of age and duration of exposure, as well as how the association changes based on these variables. Such research would almost certainly be very costly in time, effort, and money but would also provide better information on the mechanisms by which lead affects cognitive and behavioral development than does the current literature.

CHAPTER VI

SUMMARY

The results of this meta-analysis indicate that a significant moderate association exists between lead burden and the inattention and hyperactive-impulsive symptoms of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents. Across the 29 studies in this analysis, there was an average r of .19 for the association between lead and both inattention and hyperactivity-impulsivity. Interestingly, Marcus et al. (2010) recently found an identical association between lead and conduct problems in children and adolescents. This relation is also strikingly similar to the effect size lead-Full Scale IQ association of $r = -.152$ reported by Needleman and Gatsonis (1990). Thus, as reported by Mash and Barkley (2003), it appears that lead exposure and burden have a moderate but consistent impairing effect across a variety of domains of cognition and behavior. As more research is conducted in this area, a clearer picture of this relation will develop, as the field works toward confirming these associations as causal. Furthermore, despite drastic changes in public policy over the last 40 years, it would appear, based on some of the more recent studies in this meta-analysis, that the problem of lead exposure and burden in children has not yet been fully eliminated in North America or around the world. Although a reduction in lead has been associated with a reduction in crime and violence (e.g., Nevin, 2000; Stretsky & Lynch, 2001) as well as increased IQ (i.e., the Flynn effect; Hagan, Drogin, & Guilmette, 2008), rates of ADHD may be increasing (CDC, 2010). This pattern suggests that the pathogenesis of ADHD is complex and multifactorial and that further exploration of the association between ADHD symptomatology and neurotoxins such as lead is necessary.

APPENDIX A

LEAD/ADHD SYMPTOMS DESCRIPTIVE INFORMATION (CODING SHEET)

1. Study Number:
2. Full Reference for the study (APA style):
3. Type of Publication
 - 1 = journal
 - 2 = book chapter
 - 3 = thesis/dissertation
4. Publication year:
5. Region:
 - 1 = American
 - 2 = European (note country/language)
 - 3 = Canada
 - 4 = Other (list)
6. Sample
 - 1 = adolescent (~14-18)
 - 2 = primary school (~6-13)
 - 3 = preschool (~2-5)
7. Mean age:
8. # of subjects:
9. Population
 - 1 = general
 - 2 = psychiatric
10. Geographical factors
 - 1 = urban
 - 2 = suburban
 - 3 = rural
 - 4 = not reported
 - 5 = mixed (must be specifically reported mixed by article)
11. Gender
 - 1 = mixed
 - 2 = male
 - 3 = female

11a. % male:

12. Pb method of assessment

- 1 = blood
- 2 = hair
- 3 = teeth
- 4 = x-ray
- 5 = environmental (e.g., air)

13a. Inattention symptoms

- 1 = self-report scales + Name of scales
- 2 = other report (parent, teacher, etc.) + Name of scales
- 3 = performance tasks + names
- 4 = diagnosis of ADHD, Inattentive Type (yes or no)

13b. Hyperactivity/Impulsivity symptoms

- 1 = self-report scales + Name of scales
- 2 = other report (parent, teacher, etc.) + Name of scales
- 3 = performance tasks + names
- 4 = diagnosis of ADHD, Hyperactive-Impulsive type (yes or no)

12. All relevant statistics (e.g., t, F, r, etc.)

May copy and paste relevant tables here

13. List relevant statistics as well as covariates here.

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