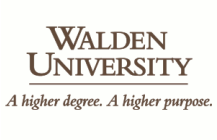

2018

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

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This is to certify that the doctoral dissertation by

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has been found to be complete and satisfactory in all respects,
and that any and all revisions required by
the review committee have been made.

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Abstract

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by

Megan Glenn Brown

MS, Mississippi State University, 2008

BA, Utica College of Syracuse University, 2005

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Abstract

Lead exposure during childhood is a significant global public health concern as the potential effects of exposure can result in the need for long-term treatment, diminished productivity in society, and financial strain on the health care system. There is strong evidence of a relationship between lead exposure and attention-deficit/hyperactivity disorder (ADHD); however, there is a gap in the current literature regarding the relationship between lead exposure and specific symptoms of ADHD and the strength of that relationship. The purpose of this meta-analysis was to examine and help quantify this relationship. Cohen's *d* was used as the standardized mean effect size measure for this study, and allowed for comparison of 2 groups on a specific measure. For the final analysis 20 studies were included that provided a comparison between lead exposure and overall ADHD, inattentive, or hyperactive/impulsive symptoms. The magnitude of the effect size of childhood lead exposure on ADHD symptoms was significant and of medium strength. There was significant variability in the research results for inattentive and hyperactive/impulsive symptoms, and it was hypothesized that this variability may be due to factors related to lead levels and covariates known to affect ADHD symptoms. Study results may contribute to positive social change by providing health care practitioners with a greater understanding of the effect of childhood lead exposure on ADHD symptoms, which they may use to achieve advancements in prevention and treatment. Improved prevention programs for lead exposure and early identification and treatment of related concerns may decrease negative outcomes, as well as the occurrence of ADHD symptoms on a population level, thus improving public health.

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Dedication

This dissertation is dedicated to my father, Dr. Thomas Glenn Brown, who passed away prior to its completion. Without his support and encouragement I would not have begun nor completed my doctoral degree, and his memory has kept me committed to this goal even when I felt discouraged.

Acknowledgments

I would like to thank Dr. McBride for his continued support and guidance throughout this process. I would also like to thank Dr. Little and Dr. Cabiria for their feedback and assistance.

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Chapter 1: Introduction to the Study

Introduction

Children are exposed to numerous environmental toxins throughout their daily lives with a host of medical and cognitive problems, such as cancer and intellectual disability, potentially resulting from this exposure (Grandjean & Landrigan, 2006). Lead, a heavy metal which can be present in materials such as paint, pipes, and gasoline, is one such environmental toxin (Agency for Toxic Substances and Disease Registry, 2011). If ingested, it is believed to cause numerous physical and cognitive problems, particularly at higher exposure levels (Mason, Harp, & Han, 2014). Despite widespread efforts in the United States (US) to decrease childhood lead exposure, the Centers for Disease Control and Prevention (CDC, 2012) estimated there are 500,000 children in the US between the ages of 1 year and 5 years who have blood lead levels that exceed the threshold believed to cause damage (5 micrograms per deciliter-μg/dL), and over 4 million households have conditions that are exposing children to lead (CDC, 2012).

Recently, researchers have found evidence suggesting there is no safe level of lead exposure and that damage to cognitive and behavioral functioning can occur at even low levels of exposure (Bellinger, 2008). In the US, children are frequently exposed to lead through dust or chips from lead-based paint (CDC, 2015), which is still present in many older homes that were built prior to the late 1970s when lead was removed from paint (CDC, 2014). Exposure can also occur through transfer from work facilities into the home (Newman, Jones, Page, Ceballos, & Oza, 2015). As Newman et al. (2015) noted, typical hand washing and laundry methods may not fully remove lead dust and, thus, may

serve as another source of exposure. There are numerous pathways for lead exposure that which make the task of prevention more complex.

Over three decades of research has consistently shown a correlation between exposure to lead, even at low-levels (less than 10 μg/dL), and intellectual impairments (Beattle et al., 1975; Canfield et al., 2003; Earl, Burns, Nettelbeck, & Baghurst, 2016; Henn et al., 2012; Mohan et al., 2014; Rodrigues et al., 2016). More recently, researchers have focused on the relationships between elevated lead levels and other cognitive and behavioral concerns, including lowered academic achievement and conduct problems (Marcus, Fulton, & Clarke, 2010; McCrindle, Green, & Sullivan, 2017; Strayhorn & Strayhorn, 2012).The potential impact of lead exposure on executive functioning skills, ADHD symptoms, autism, and externalizing problems is being investigated as well (see Boucher et al., 2012; Chiodo et al., 2007; Cho et al., 2010; Mohammed et al., 2015; Nigg et al., 2008; Roy et al., 2009). The greater breath of areas researchers are focusing on is indicative of the understanding that lead likely causes diffuse damage to the brain, and thus, the need to study a variety of cognitive, behavior, and executive domains beyond intelligence.

Although many studies have consistently revealed a significant effect of lead exposure during early childhood on diagnoses of ADHD and/or related symptomatology (see Braun, Kahn, Froehlich, Auinger, & Lamphear, 2006; Froehlich et al., 2009; Nigg et al., 2008; Nigg, Nikolas, Knottnerus, Cavanagh, & Friderici, 2010), there is disagreement regarding which individual symptoms and diagnosis subtypes have the strongest relationship with lead exposure. In some cases researchers have found lead exposure to

have a significant relationship with inattentive symptoms, but not hyperactive or impulsive symptoms (see Chiodo, Jacobson, & Jacobson, 2004; Chiodo et al., 2007; Roy et al., 2009). Contrary to these results, other researchers have found a significant relationship between lead exposure and hyperactive or impulsive symptoms, but not inattentive symptoms (see Boucher et al., 2012; Huang et al., 2016). Researchers such as Froehlich et al. (2009) and Braun et al. (2006) have also attempted to account for a variety of variables that could result in or mediate this relationship. The majority of researchers studying this issue have found significant results, even when accounting for these variables, which include both parental and child factors (e.g., birth weight, prenatal drug/alcohol exposure, maternal age, maternal IQ, parental education level, etc.). Inclusion of these variables is important to guard against a spurious relationship between lead exposure and ADHD symptoms being found.

Given the inconsistency in research finding (see Chiodo et al., 2004, 2007; Boucher et al., 2012; Huang et al., 2016; Roy et al., 2009), further research is needed in order to clarify the effect of lead exposure on ADHD diagnosis and symptoms. Attainment of this clarity may help researchers to decide what areas of lead exposure and ADHD need to be investigated next in order to continue the advancement of the field (Card, 2012; Lipsey & Wilson, 2001), and begin to formulate possible causal mechanisms behind the effect of lead exposure on ADHD symptomatology. Given the negative outcomes that have been associated with ADHD (see Chen et al., 2015; Kolla et al., 2016; Martin, 2014; Sasser, Kalvin, & Bierman, 2016; Sundquist, Ohlsson, Sundquist, & Kendler, 2015; Vitulano et al., 2014; Wymbs, Dawson, Suhr, Bunford,

Gidycz, 2017), understanding the effect of childhood lead exposure on ADHD symptoms could result in future advancements in prevention and treatment, as well as changes in social policy, through raising awareness of these public health concerns.

I will begin this chapter by providing brief background information on the current research on various aspects of ADHD and lead exposure. I will then present the problem statement and purpose of the study, followed by the research question and hypotheses. The nature of the study, including methodology and key variables, and relevant definitions will follow. I will then review the conceptual framework. The chapter will conclude with a discussion of the assumptions, limitations, and significance of the study.

Background

Research dating back over 30 years has consistently shown a correlation between exposure to lead, even at low-levels (less than 10 μg/dL), and intellectual impairments (see Canfield et al., 2003; Beattle et al., 1975; Earl et al., 2016). Researchers have also studied and in some cases found a significant relationship between lead exposure and other areas of cognitive, executive, and behavioral functioning (see Boucher et al., 2012; Chiodo et al., 2007; Cho et al., 2010; Marcus et al., 2010; McCrindle et al., 2017; Nigg et al., 2008; Roy et al., 2009; Strayhorn & Strayhorn, 2012). Specifically in regards to ADHD, researchers have studied lead exposures relationship to the diagnosis of ADHD, the related symptoms, and the related cognitive deficits (see Boucher et al., 2012; Chiodo et al., 2004, 2007; Cho et al., 2010; Froehlich et al., 2009; Huang et al., 2016; Nigg et al., 2008, 2010; Roy et al., 2009). Comparable to the research related to intellectual

functioning, more recent researchers examining the effects of lead exposure on ADHD symptoms have found an impact at similar low-levels of exposure (Braun et al., 2006).

ADHD Diagnosis and Lead Exposure

Braun et al. (2006) conducted a study examining the correlation between environmental toxins and diagnosis of ADHD in children ages 4 years to 15 years using data from The National Health and Examination Survey. It was found that higher lead levels during childhood were a significant predictor of ADHD diagnosis. Froehlich et al. (2009) also used data from a national survey, The National Health and Nutrition Examination Survey, and again higher lead levels were found to be a significant predictor of ADHD diagnosis, even when the analyses were conducted with only children whose blood lead levels were below 5 μg/dL.

In 2008 Nigg et al. had children in their sample evaluated by qualified professionals to determine whether a diagnosis of any subtype of ADHD, as well as other mental health disorders, was present. Overall, the ADHD combined type group was found to have significantly higher blood lead levels than the control group (no ADHD diagnosis); however, the ADHD predominately inattentive type group was not significantly different from either the ADHD combined type or control groups. Although the blood lead levels for the ADHD predominately inattentive type group were higher than in the control group, this difference did not reach significance. Unfortunately the limited number of children diagnosed with the predominately hyperactive-impulsive type was too small to include in the analyses. Nigg et al. (2010) conducted a similar study and

again found that blood lead levels were significantly associated with diagnosis of ADHD combined type, but not with diagnosis of ADHD predominately inattentive type.

Symptomatology of ADHD and Lead Exposure

Studies examining the diagnostic subtypes of ADHD have found a more robust correlation between lead exposure and ADHD combined type than with predominately inattentive type, suggesting there may be a differential impact of lead exposure on specific symptom categories (Nigg et al., 2008, 2010). Researchers have also examined the symptom clusters comprising the diagnosis of ADHD, rather than a formal diagnosis of ADHD. Cho et al. (2010) found a correlation between even very low lead levels and both the inattentive and hyperactive symptoms of ADHD in a sample of 8 year to 11 year old children. Boucher et al. (2012) examined a number of environmental contaminants including lead and mercury, both in regards to prenatal and postnatal exposure. The symptom cluster of the predominately hyperactive-impulsive type was more likely to be reported for children in the highest levels for prenatal mercury exposure and postnatal lead exposure. This study did not find a relationship between current blood lead level and the symptom cluster of the predominately inattentive type, although these symptoms were significantly more likely to be reported in children with higher prenatal mercury exposure (Boucher et al., 2012).

Contrary to the abovementioned results, Roy et al. (2009) only found a significant correlation between blood lead levels in children and inattentive ADHD symptoms, not hyperactive symptoms. This study also used teacher reports of child behavior on a number of questionnaires similar to the questionnaire used in Boucher et al. (2012).

Unlike other studies Roy et al. (2009) also examined the dose-response relationship seen between blood lead levels and attention, hyperactivity, anxiety, sociability, and overall executive functioning, with all these variables determined to have a linear relationship with blood lead levels.

Potential Confounding Variables

Research studies related to lead exposure and ADHD often include an analysis of potential confounding variables, such as birth weight, household income, maternal education, exposure to tobacco, and maternal drug/alcohol use (Boucher et al., 2012; Braun et al., 2006; Froehlich et al., 2009). Confounding variables are important to consider when evaluating the likelihood of causality in the relationship between lead exposure and ADHD as some of these variables are known to be predictive of ADHD. Several studies have considered tobacco exposure in the analyses, and although Braun et al. (2006) found a correlation between ADHD diagnosis and lead exposure even when prenatal tobacco exposure was accounted for, Cho et al. (2010) found that parent report of ADHD symptoms and lead exposure failed to reach significance when tobacco exposure was accounted for. It should be noted though, that teacher report of ADHD symptoms remained significantly associated with blood lead levels even when tobacco exposure was controlled (Cho et al., 2010).

It is unlikely that there is one single risk factor that all cases of ADHD can be attributed to, and in a literature review Thapar, Cooper, Eyre, and Langley (2013) identified the most consistently found risk factors to be genetic variations, extreme early adversity, lead exposure, and low birth weight/prematurity. All risk factors, however,

tended to have small effect sizes (Thapar et al., 2013). Similarly, Banerjee, Middleton, and Faraone (2007) reviewed the literature and found several toxins, including lead, to be consistently shown to correlate with ADHD. The complex nature of some risk factors and the potential for children to have multiple risk factors makes completing highly structured research that systematically accounts for potential cofounding variables important in advancing knowledge of lead exposure and ADHD.

Brief Note on Neurobiological Research

The conceptual framework of ADHD is based on behavioral and cognitive symptoms and not structural or functional deficits within the brain. Although the diagnosis of ADHD does not require any brain based deficits to be present, research has attempted to identify structural and functional differences in the brains of those diagnosed with ADHD compared to non-ADHD controls (Nigg, 2006). Examination of brain differences related to ADHD and lead exposure is an important piece in understanding the relationship between these variables. Thus, it is important to briefly highlight these structural and functional differences.

Nigg (2006) outlines several areas of the brain that research has found to be reduced in size or have different levels of activation in those diagnosed with ADHD compared to non-ADHD controls, including the prefrontal cortices, basal ganglia, cerebellum, and corpus callosum. In a comprehensive review of medical literature, Pasture, Mattos, Gasparetto, and Araujo (2011) found indications in many studies of differences between children with ADHD and controls in the following areas of the brain:

corpus callosum, portions of the basal ganglia, cerebellum, striatum, and frontal and temporal cortices.

Based on a meta-analysis of structural MRI studies conducted by Frodl and Skokauskas (2012), several areas within the basal ganglia, as well as the anterior cingulate cortex, were shown to have decreased gray matter volumes in children and adults diagnosed with ADHD as compared to non-ADHD control groups. Results of Lim et al. (2013) not only supported decreased volume in several areas of the brain for children with ADHD, including portions of the cerebellum, frontal cortex, and basal ganglia, but also found that these differences in brain structure were not present in children with autism spectrum disorders. This suggests these differences may be specific to ADHD and not psychopathology in general (Lim et al., 2013).

Researchers have found lead exposure to cause brain damage particularly in the prefrontal cortex, hippocampus, and cerebellum with damage being reflected in both the anatomical features of these brain regions and in the neurotransmitters (Finkelstein, Markowitz, & Rosen, 1998). More recently, researcher have found increased cell death in the cortex, hippocampus, portions of the basal ganglia, and thalamus in rats exposed to lead compared to controls (Sansar, Ahboucha, & Gamrani, 2011). Animal research has also shown increases in certain neurotransmitters, such as norepinephrine, in the frontal cortex, hippocampus, and striatum of mice with exposure to lead, prenatally and postnatally (Bijoor, Sudha, & Venkatesh, 2012). Research conducted using animals can help advance the understanding of the effect of lead on the brain through research methods that would be unethical to complete with human subjects.

Overview of and Gaps in the Knowledge Base

There is strong support seen in the available research for a relationship between lead exposure and the symptoms of ADHD (see Boucher et al., 2012; Chiodo et al., 2004; Cho et al., 2010; Nicolescu et al., 2010; Plusqellec et al., 2010). Preliminary comparisons suggest that this relationship is variable depending on the specific symptoms, diagnostic subtypes, and lead levels (see Boucher et al., 2012; Braun et al., 2006; Chiodo et al., 2004; Cho et al., 2010; Froehlich et al., 2009; Nicolescu et al., 2010; Nigg et al., 2008, 2010; Plusqellec et al., 2010; Roy et al., 2009). The significant correlation between the combined type of ADHD and lead exposure lends support to the impact being seen in both the inattentive and hyperactive/impulsive symptom clusters (Braun et al., 2006; Froehlich et al., 2009; Nigg et al., 2008, 2010). When the symptom clusters have been examined individually, results have shown a significant correlation with either hyperactive/impulsive symptoms or inattentive symptoms (Boucher et al., 2012; Roy et al., 2009), as well as with both symptom clusters (Cho et al., 2010).

The variability in research findings has resulted in a lack of clarity regarding the strength of the relationship between lead exposure and the different symptoms of ADHD (see Chiodo et al., 2004, 2007; Boucher et al., 2012; Huang et al., 2016; Roy et al., 2009). Inclusion of potential confounding variables in many studies may also have an impact on the variability seen across study results. It is unclear if any of these variables are moderating the relationship between lead exposure and ADHD symptoms. The present study intended to clarify these gaps in the current knowledge base, as well as help direct future research by synthesizing the current research that has been conducted in this area.

If lead exposure, at certain levels and/or ages of exposure, is uniquely related to the diagnosis of ADHD it would be expected that the brain abnormalities associated with ADHD would at least in part be those same brain regions impacted by lead exposure. Comparisons between the literature examining neurobiological correlates of ADHD and lead exposure reveal similarities in the brain regions identified as having abnormalities. Mainly the prefrontal cortex, basal ganglia, cerebellum, and striatum have been identified as having structural and functional differences in ADHD groups and lead exposure groups (Finkelstein et al., 1998; Nigg, 2006; Pasture et al., 2011).

Problem Statement

The increasing occurrence of ADHD in the US population and the incidence of lead exposure in childhood represent public health concerns that can have long-term consequences for afflicted children, their families, and the health care system (Chorozoglou et al., 2015; Kolla et al., 2016; Martin, 2014; Sasser et al., 2016; Silva, Colvin, Hagemann, Stanley, & Bower, 2014). Despite efforts by county, state, and federal agencies to eliminate the sources of lead exposure, researchers with the CDC report children in the US are continuing to be exposed to lead in larger numbers, in part due to over 4 million households having conditions that are exposing children to lead (CDC, 2012). The percentage of children with elevated lead levels has declined significantly; as Jones et al. (2009) noted, there was an estimated 84% decline from 1988-1991 rates to 1999-2004 rates.

Despite a decline in exposure rates, lead continues to be a notable public health concern (Jones et al., 2009). Sources of exposure are often not recognized until after a

child has been exposed (CDC, 2015). Given the preponderance of evidence that damage occurs at even very low levels of exposure (CDC, 2017), this is likely too late to prevent the negative consequences of exposure. The only known treatment for high lead levels is chelation, a technique used to remove lead from the body; however, this treatment does little for the long-term cognitive and behavioral impairments associated with low-level lead exposure (Meyer, Brown, & Falk, 2008). The lack of available treatments to revert the damage caused by lead and the difficulties involved in identifying sources of exposure makes research related to all areas of lead exposure crucial to improving overall public health.

Braun et al. (2006), using the population attributable fraction, estimated that 21.1% of the occurrences of ADHD in children between the ages of 4 years and 15 years in the US could be related to lead exposure with blood lead levels of at least 2.0 µg/dL. This percentage equates to approximately 290,000 ADHD cases potentially resulting from exposure to lead among children in that age range. As these numbers suggest, efforts to prevent exposure to lead could have wide spread implications for the incidence of ADHD in the population.

Within the majority of research, lead levels below 10 µg/dL are considered to be subthreshold or low levels of lead exposure (see CDC, 2017, Schnur & John, 2014, Surkan et al., 2007). In 2012, the CDC's decreased the reference level for damage to 5 µg/dL (Schnur & John, 2014), and future research will likely focus on these lower levels of lead exposure. In studying the relationship between lead exposure and ADHD, Braun et al. (2006) found significance even at these subthreshold levels of lead exposure. As

prevention programs improve and those children exposed to lead tend to be at lower levels, it will be important for researchers to focus on examining the potential effects of lead at these lower levels.

Other researchers have had conflicting results on the magnitude of the effect or the effect on specific symptoms of ADHD, such as inattention versus hyperactivity/impulsivity (Chiodo et al., 2007; Nigg et al., 2008). Further research is, thus, needed to systematically examine the available evidence for the effect of lead exposure on ADHD diagnosis and symptoms. There are numerous gaps in the current literature on ADHD and lead exposure, as well as gaps in the understanding of how this effect may occur. The present study was limited in that it was aimed at clarifying the magnitude of the effect size of lead exposure on ADHD symptoms through a meta-analysis of the currently available literature. I also examined potential mediating variables because there was significant variability in the initial study results for inattentive and hyperactive/impulsive symptom categories and lead exposure. Both estimating the magnitude of the effect size of lead exposure on ADHD symptoms and examining the factors related to variability are needed to decide the next steps in future research in this area.

Purpose of the Study

Lead exposure is a significant public health concern, with potentially wide ranging effects on the physical functioning and cognitive development of the exposed child (see Afeiche et al., 2011; Bartrem et al., 2014; Braun et al., 2006; Canfield et al., 2003; CDC, 2012). These potential effects can result in the need for long-term treatment,

diminished productivity in society, and financial strain on the health care system. There is strong evidence of a relationship between lead exposure and ADHD (see Boucher et al., 2012; Chiodo et al., 2004; Cho et al., 2010; Nicolescu et al., 2010; Plusqellec et al., 2010).

In the present study, I sought to examine and quantify the relationship between lead exposure and ADHD symptoms. The specific aim of this quantitative study was to estimate the magnitude of the effect size of childhood lead exposure on ADHD symptoms through a meta-analysis, as well as determine if there are any moderating variables (e.g., age of exposure and gender) that could be facilitating variability in research results. Researchers use quantitative meta-analysis research designs to advance the knowledge base and direct future research by systematically synthesizing and integrating the current research in a given field (see Card, 2012; Lipsey & Wilson, 2001). Examining whether there is a causal link between lead exposure and ADHD symptoms was beyond the scope of my research study. My study findings, however, may aid future researchers who seek to do so.

Research Question and Hypotheses

The main research question was, as follows: Based on a meta-analysis of available and selected research on the relationship between lead exposure (measured lead levels greater than 0 µg/dL) and ADHD symptoms (e.g., hyperactivity, inattention, etc.), is there a significant multi-study estimated effect size and if so, what is its magnitude?

H_o: There is no significant multi-study estimated effect size for the relationship between lead exposure and ADHD symptoms among children.

H_1: There is a significant multi-study estimated effect size for the relationship between lead exposure and ADHD symptoms among children.

Conceptual Framework

The central concept grounding the study was ADHD. Research related to ADHD has often been exploratory and descriptive with less development of comprehensive theories of ADHD (see Barkley, 1997; Nigg, 2006; Petersen & Posner, 2012). The symptoms and resulting impairment present in individuals diagnosed with ADHD is described in the Diagnostic and Statistical Manual of Mental Disorder (DSM) published by the American Psychiatric Association (2013). Attention deficit disorder first appeared in the third edition of the DSM published in 1980 and then was changed to attention-deficit/hyperactivity disorder in the revision published in 1987. Based on the DSM-V, there are three subcategories within the diagnosis of ADHD: predominately inattentive presentation, predominately hyperactive-impulsive presentation, and combined presentation (American Psychiatric Association, 2013). The DSM-V also provides diagnostic labels of other specified ADHD and unspecified ADHD if full symptom criteria is not met but symptoms and impairments are present (American Psychiatric Association, 2013). More detail regarding the diagnostic criteria for each subtype of ADHD is reviewed in Chapter 2.

Barkley (1997) outlined a neuropsychological theory of ADHD mainly grounded in the executive functions of the prefrontal lobe, specifically behavioral inhibition or self-control. Barkley postulated that the central impairment in behavioral inhibition experienced by individuals with ADHD subsequently causes dysfunction in the four

major domains of executive functioning (working memory; self-regulation of affect/motivation/arousal; internalization of speech; reconstitution). These executive functions are assumed to be under the control of the prefrontal cortex (Barkley, 1997).

Barkley (1997) focused on behavioral inhibition impairment as the primary deficit in ADHD, which then results in other executive functioning deficits; however, in other models, researchers have focused on attention systems as being deficient in ADHD (Nigg, 2006). The Posner-Petersen model of attention focuses on the vigilance system, which allows for the maintenance of a state of readiness for a certain stimulus to occur and requires both sustained attention and an alerting function when the stimulus presents itself (Petersen & Posner, 2012). The Posner-Petersen model focuses on attention itself, not specifically ADHD or other attention disorders (Petersen & Posner, 2012). Nigg (2006) reviewed ADHD research in light of such models and found that the alerting or arousal mechanism within the vigilance system is consistently impaired across research studies of ADHD, although the sustained attention function is not. This deficiency in alertness/arousal is also noted by researchers within their models of ADHD (see Barkley, 1997, Petersen & Posner, 2012) and for the conceptual framework of the present research.

Nature of the Study

The nature of this study was a quantitative design. I answered the research question using a meta-analysis of the available and selected research on childhood lead exposure and ADHD symptoms. I sought to determine (a) the multi-study estimated effect size of lead exposure on ADHD symptoms of inattention and

hyperactivity/impulsivity and (b) if any unexpected variability was present across the included research results. Such variability was present in the study findings, and thus, I identified and discussed moderators that could be related to this variability. It should be noted that, in this study, the effect size statistic was a measure of the magnitude of the relationship between lead exposure and ADHD symptoms and does not necessarily indicate a causal relationship of lead exposure on ADHD symptoms. As the authors of the included primary studies used a variety of methods and statistics, the focus of the present study was on the general relationship between lead exposure and ADHD and not specifically on a correlational or causal relationship.

A meta-analysis allows for organization and synthesis of the current research base and may provide statistically more powerful analysis than individual studies (Card, 2012). Researchers' use of meta-analysis can also determine whether the variability in results is statistically significant or simply represents not meaningful variations (Card, 2012). Depending on the heterogeneity of the available research, meta-analysis may also allow for a greater breath of possible moderators to be examined (Card, 2012). The synthesis of a current research base provided through the use of meta-analysis is also an important step in directing future research (Card, 2012). Overall, the benefits of using meta-analysis versus primary research are well suited for answering the present research question and clarifying the relationship between lead exposure and ADHD symptoms.

I searched online research databases from a variety of disciplines, including psychology, sociology, and medical/health science, to gather the sample of research studies included in the present meta-analysis. I also reviewed select conference programs

(e.g., American Psychological Association and Eastern Psychological Association), and contacted key researchers in this field, such as Joel T. Nigg and R. L. Canfield, to find unpublished research that may have been of relevance. In instances where the necessary statistical information was not provided in the research article, I used equations to transform the available type of results into those needed for the meta-analysis.

Procedure and Statistical Analyses

In the present meta-analysis, I used Cohen's *d* as the standardized mean effect size measure. Use of this statistic allowed for comparison of two or more groups (studies) on a specific measure, in this case those exposed to lead versus those not on measures of ADHD symptoms. This particular measure of effect size is useful for meta-analysis as it can be calculated post hoc from a variety of other reported statistics (Lipsey & Wilson, 2001). Use of this measure allowed me to include different statistics in the present meta-analysis. Lipsey and Wilson (2001) provided formulas to allow correlations, ANOVAs, and t-tests to be transformed into the standardized mean difference effect size, Cohen's *d*. Although use of Cohen's *d* as the standard mean effect size did not allow all relevant studies to be included in the present meta-analysis, this did maximize the number of included studies.

After I conducted a structured and thorough literature search and applied the inclusion and exclusion criteria to those studies, myself as well as a secondary researcher coded the data. Statistical analyses included the mean effect size, the standard error of the mean effect size, and the 95% confidence interval and a measure of homogeneity. The 95% confidence interval was used to determine whether the null hypothesis was accepted

or rejected, based on whether the null hypothesis value fell within that interval (Borenstein, Hedges, Higgins, & Rothstein, 2009).

Definitions

Attention-deficit/hyperactivity disorder: As outlined in the DSM-V (American Psychiatric Association, 2013), a diagnosis of ADHD is made through a categorical approach where an individual must exhibit a certain number of symptoms of either inattention or hyperactivity/impulsivity that are impairing their functioning in two or more domains.

Attributable fraction: The proportion of the overall occurrence of a disease or disorder in the population that can be attributed to a particular risk factor (WHO, 2016).

Executive functioning: The abilities used during goal-directed behavior including those needed to develop a goal, plan how to achieve it, and carry out those plans (Anderson, Jacobs, & Anderson, 2008). Anderson et al. (2008) outlined executive functioning to include "(a) anticipation and deployment of attention; (b) impulse control and self-regulation; (c) initiation of activity; (d) working memory; (e) mental flexibility and utilization of feedback; (f) planning ability and organization; (g) selection of efficient problem-solving strategies" (p. 4).

Hyperactive/impulsive symptoms: Per the DSM-V, hyperactivity/impulsivity symptoms are behaviors that represent excessive activity levels or inability to stop an impulsive and include such things as over activity, difficulty sitting still, acting impulsively, and talking excessively (American Psychiatric Association, 2013).

Inattention symptoms: Per the DSM-V, inattention symptoms are behaviors that represent a failure to attend appropriately and include such things as difficulty concentrating, distractibility, and disorganization (American Psychiatric Association, 2013)

Low-level lead exposure: Exposure to lead that has resulted in a blood, tooth, hair, or urine lead level that is below 10 μg/dL (CDC, 2017).

Study: For the purposes of the meta-analysis, a study "consists of a set of data collected under a single research plan from a designated sample of respondents" (Lipsey & Wilson, 2001, p. 76).

Assumptions

Although proving a causal relationship between lead exposure and ADHD was beyond the scope of this study, I did make an assumption regarding the potential causal link, which was, specifically, if lead, at some level, differentially or uniquely impacts the areas of the brain found to be abnormal in those with ADHD, then there is a strong case for lead causing ADHD. It is known that, at very high levels, lead can cause significant physical problems and death (Lidsky & Schneider, 2003), and it is likely that these higher levels are not in the range required for research in regards to the potential relationship with ADHD. Thus, I made an assumption that the relevant research for the present study will only have included lead exposure at lower and even subthreshold levels. I also assumed that the authors of the studies included in this meta-analysis all measured the same underlying effect of lead exposure on ADHD symptoms.

Scope and Delimitations

The scope of this study was restricted to research examining the relationship between early childhood lead exposure and ADHD symptoms, although not restricted in regards to the type of relationship (e.g., correctional, causal). This study was not intended to be an exhaustive analysis of all research related to the outcomes of lead exposure, but those related to the symptomatology of ADHD, specifically inattentive and hyperactive/impulsive symptoms. The included studies were restricted in regards to the age of participants, only including those using samples of children, but no other restrictions were placed based on population characteristics (e.g., gender, geographical region, socio economic status). This was done to increase the likelihood of heterogeneity being present in the sample of studies included, which consequently increased the potential moderators available for analysis and the generalizability of the results.

The scope of this study was also limited by the current research that has been conducted in this area, as well as access to the original research study and the statistical results necessary for meta-analysis. In order to allow the greatest number of studies to be included in this meta-analysis, statistical equations were used to transform the available statistics from the primary research into a common effect size measure. It was, however, anticipated that some research studies would have to be excluded due to the necessary effect size measure not being provided or not being able to be transformed from what was available.

Limitations

Limitations were present in this study due to the methodological approach used. The date collected for the present meta-analysis was limited by the availability of and access to the research that has been conducted in this area. The majority of research included in this study was gathered through searching published journal articles through electronic databases. Unfortunately, research is more often published when the results are significant and consistent with the researcher's hypotheses, which could bias the results and conclusions of studies, such as this, that gather data mainly from published studies. Specific authors or research labs known to conduct research in this area were attempted to be contacted to determine if relevant, unpublished research was available; however, no responses were received. A detailed description of the methods used to gather the studies included in the present meta-analysis is provided in Chapter 3.

Meta-analysis can also be limited by the quality of the research used for the analysis. Meta-analysis has the ability to overcome some methodological flaws that are present in the original studies, such as inadequate power; however, other flaws, such as the use of measures with poor validity or reliability, will be carried over to the meta-analysis. Lipsey and Wilson (2001) provide effect size adjustments that can be conducted prior to statistical analysis in order to account for biases or errors in the original studies. When studies with extreme outliers of effect size values were present, these studies needed to be examined for any reasonable explanation for the outlier and if none can be identified they should be removed from the analyses (Lipsey & Wilson, 2001).

Another important limitation of this study was the inability of the results to prove a causal link or mechanisms between lead exposure and ADHD. If the research indicates a significant effect size for lead exposure on ADHD symptoms, a causal mechanism can be postulated but not proven. It was important to identify and, when possible, address any moderating variables that could potentially result in a significant effect size for lead exposure on ADHD symptoms. However, regardless of whether these variables are accounted for, it is beyond the capability of this methodology to prove a causal relationship.

Significance

The symptoms associated with a diagnosis of ADHD have been correlated with academic difficulties, high school dropout, poor occupational functioning, and relationship concerns, as well as later mental health and substance abuse concerns (see Chen et al., 2015; Kolla et al., 2016; Martin, 2014; Sasser et al., 2016; Sundquist et al., 2015; Vitulano et al., 2014; Wymbs et al., 2017). Given the confluence of negative outcomes that can result from ADHD symptoms, it is important to gain greater understanding of the risk factors and possible causal mechanisms for development of these symptoms, including lead exposure. Although pediatricians and health departments may advise parents to have their children's lead levels checked yearly, these do not always ensure parents will follow through with consistent monitoring for lead exposure. Greater understanding of the effect of early childhood lead exposure on ADHD symptoms could result in future advancements in prevention and treatment, as well as changes to social policy (e.g., increases in insurance coverage and government services

for lead exposure). Increasing parents' understanding of the potential effect of lead exposure on children, even at low levels, is an important step in improving prevention and treatment. Although this study is narrowly focused on the relationship between lead exposure and ADHD symptoms, it is suspected that any improvements in prevention will decrease the occurrence of all cognitive impairments and negative outcomes associated with lead exposure, not only these ADHD symptoms hypothesized to be related to lead exposure (see Boucher et al., 2009; Chiodo et al., 2004; Cho et al., 2010; Nicolescu et al., 2010; Plusqellec et al., 2010).

Summary

In summary, lead exposure is a significant public health concern. Researchers at the CDC estimates that there are 500,000 children between the ages of one year and five years that have blood lead levels that exceed the threshold for damage and subsequent impairment (CDC, 2012). Due to the breadth of negative outcomes that have been linked with lead exposure, further research is needed to improve our knowledge and understanding of these potential outcomes including ADHD, as well as the mechanisms behind the correlations shown in research studies. Improving our knowledge is the first step in advancements in the prevention and treatment of lead exposure, which in turn could result in decreased prevalence rates of ADHD.

This study helped clarify and quantify the relationship between lead exposure and ADHD symptomatology through a meta-analysis of the current research in this area. Significant variability was identified in the results of these research studies, and I examined the potential moderating variables. It is important to note that proving a causal

link was beyond the scope of this study and the purpose here was to aid in directing future research in this area.

Chapter 2 presents an in-depth literature review of research pertaining to the relationship between lead exposure and ADHD symptomatology. I also discussed and analyzed research examining the effects of exposure to lead on diagnosis of ADHD, specific subtypes of ADHD, symptoms of ADHD, and executive functioning skills. I concluded Chapter 2 by summarizing the knowledge base in light of the present study.

Chapter 2: Literature Review

Introduction

Childhood lead exposure remains a significant public health concern despite widespread efforts in the United States to decrease the incidence of exposure. According to the CDC (2012), over 4 million households have conditions that are causing some of the estimated 500,000 cases of US children, ages of 1 year and 5 years, with blood lead levels above 5 micrograms per deciliter (μg/dL). In the majority of research on the topic, lead levels below 10 μg/dL are considered to be subthreshold or low levels of lead exposure, although the CDC has officially decreased the level of concern from 10 μg/dL to 5 μg/dL (CDC, 2012; Schnur & John, 2014). There is a wealth of evidence to support there is no safe degree of lead exposure and efforts need to be made to completely eliminate exposure (CDC, 2017).

A solid research base supporting the significant relationship between exposure to lead, even at low-levels (less than 10 μg/dL), and intellectual impairments exists (see Beattle et al., 1975; Canfield et al., 2003; Henn et al., 2012; Mohan et al., 2014; Rodrigues et al., 2016). Similar to researchers studying intellectual functioning, recent researchers examining the relationship between lead exposure and ADHD symptoms have found an impact even at low-levels of lead exposure (Braun et al., 2006). Researchers studying specific ADHD symptoms have found lead to have an impact even at sub-threshold levels (Braun et al., 2006). However, the research has not resulted in agreement on the magnitude of the effect or the effect on specific symptoms of ADHD, such as inattention versus hyperactivity/impulsivity (Chiodo et al., 2007; Nigg et al.,

2008). Further research is needed to investigate and clarify the relationship between childhood lead exposure and ADHD symptoms. The aim of the present quantitative study was to estimate the magnitude of the effect size of early childhood lead exposure on ADHD symptoms, as well as identify if there are any moderating variables (e.g., age of exposure, gender, etc.) that could be facilitating variability in the research results.

The majority of studies discussed in this chapter consistently support a significant relationship between lead exposure during early childhood and the diagnosis of ADHD and/or related symptomatology (Braun et al., 2006; Froehlich et al., 2009; Nigg et al., 2008, 2010), although exceptions to these significant findings are present. For instance, Cho et al. (2010) did not find a significant relationship between performance on several neurocognitive tasks or parental reports of ADHD symptoms and lead exposure after accounting for tobacco exposure. Researchers have also found a significant relationship between lead exposure with inattentive symptoms, but not hyperactive/impulsive symptoms, or vice versa (see Chiodo et al., 2004, 2007; Boucher et al., 2012; Huang et al., 2016; Roy et al., 2009).

Researchers using national surveys have been able to examine a wide range of ages and levels of lead exposure, as well as use samples with characteristics reflective of the national population. Using these national surveys, Braun et al. (2006) and Froehlich et al. (2009) both found elevated lead level, even levels below 5 μg/dL, to be a significant predictor of ADHD diagnosis. The authors of these studies did not differentiate between diagnostic subtypes of ADHD; they included children who were diagnosed with any of the three subtypes. Researchers for both of these studies also calculated the population

attributable fraction for children with higher lead levels. Braun et al. found that 21.1% of ADHD cases in children ages 4 years to 15 years could be attributable to lead levels greater than 2 µg/dL, equating to approximately 290,000 cases of ADHD in the US population. Similarly, Froehlich et al. estimated that 25.4% of ADHD cases in children ages 8 years to 15 years could be attributed to lead levels greater than 1.3µg/dL, equating to 598,000 cases. These estimates highlight the potential difference in ADHD prevalence that could result from improvements in the prevention of childhood lead exposure.

Other researchers have conducted studies examining the relationship between lead exposure and the diagnostic subtypes of ADHD. Nigg et al. (2008) found that those diagnosed with ADHD combined type had significantly higher blood lead levels than the control group (no ADHD diagnosis), but those with ADHD predominately inattentive type were not significantly different from either those with ADHD combined type or the control group. Nigg et al. (2010) confirmed these results with children whose lead levels were very low (below 3µg/dL). Boucher at al. (2012) found that children with lead levels greater than 1.6 µg/dL had significantly more reported symptoms of the predominately hyperactive-impulsive type, but not the symptoms of the predominately inattentive type.

The following literature review begins with a brief discussion of the relevant conceptual framework and the criteria and symptomatology associated with a diagnosis of ADHD. I then discuss the known and suspected effects of exposure to lead. In subsequent sections of this review, I discuss and synthesis research examining the effects of exposure to lead on diagnosis of ADHD, specific subtypes of ADHD, symptoms of

ADHD, and related executive functioning skills. I conclude the review with a brief discussion of causality and the need for continued research.

Literature Search Strategy

I conducted a literature search for this review using a number of databases available from Walden University's online library. These databases included Academic Search Complete, CINHAL Plus, MEDLINE, ProQuest Central, PsycARTICLES, PsycINFO, and PubMed. I also searched other university and college libraries, both online and physical, when full-text articles could not be found through the Walden Library databases. Key search terms were lead exposure or poisoning, attention-deficit/hyperactivity disorder or ADHD, inattention, hyperactivity, impulsivity, and executive functioning.

The scope of this literature review encompassed childhood lead exposure's relationship to ADHD diagnosis or symptomatology. Peer-reviewed literature, which included primary research articles and seminal or review works, was the main source of information for the review. I also gathered background information on lead exposure and ADHD by reviewing book and websites. I did not place restrictions on publication date, but did make efforts to focus on more recent research. Chapter 3 provides the detailed search methods used to find studies included in the meta-analysis, as well as the criteria for inclusion.

Conceptual Framework

The concept underlying the study was that of ADHD. The diagnosis of ADHD is made through a categorical approach where an individual must exhibit a certain number

of symptoms that are impairing their functioning in two or more domains (American Psychiatric Association, 2013). This approach to diagnosis is not theoretically driven and research related to ADHD has often been exploratory and descriptive with less development of comprehensive theories of ADHD (American Psychiatric Association, 2013). Likewise, research has provided some speculation on the neurobiological connection between lead exposure and ADHD, but to date no concrete theories have been developed. However, there are several seminal works related to ADHD that should be reviewed in order to provide a framework from which the symptoms and diagnosis of ADHD can be understood.

Barkley's Theory of ADHD

Barkley (1997) developed a seminal neuropsychological theory of ADHD grounded in the executive functions of the prefrontal lobe, specifically behavioral inhibition or self-control. Barkley attempted to integrate and expand upon the theories of Bronowski and Fuster to create this conceptual model of ADHD. Rather than a true attention deficit, Barkley postulated that the central impairment experienced by individuals with ADHD was in behavioral inhibition. He defined behavioral inhibition as the ability to stop a prepotent (common or typical) response or an ongoing response, as well as the ability to control for interfering stimuli. This impaired behavioral inhibition then, subsequently, causes dysfunction or disruption in four major domains of executive functioning; working memory, self-regulation of affect/motivation/arousal, internalization of speech, and reconstitution. These four executive functions are not believed to directly result from behavioral inhibition, but rather the ability to inhibit

behavior allows for these executive functions to occur at an optimal level. The last step Barkley postulated was that these four executive functions then act upon the motor control, fluency, and syntax of goal-directed behavior (Barkley, 1997).

Although Barkley (1997) presents a fairly substantial research base supporting these functions as being deficient in those with ADHD, he does recognize that further research, to clearly determine if the deficits indicated by this model are in fact present, was needed at that time. It is important to note that Barkley believed these executive functioning skills were under the control of the prefrontal cortex. This may help direct a future theoretical link between specific damage caused by lead exposure and development of ADHD symptoms (Barkley, 1997).

Attention Models

The Posner and Peterson model was originally published in 1990, and this model was recently revisited and updated based on the substantial research that has occurred over the past 20 years (Peterson & Posner, 2012). This model outlines three major networks within the attention system. The alerting network is responsible for the maintenance of attention over a period of time to a boring task. Peterson and Posner found evidence in the original studies reviewed that vigilance was controlled by the right cerebral cortex. When this area was revisited by Peterson and Posner norepinephrine stood out in the research as a significant pathway involved in alertness and these pathways were found in the frontal cortex and parietal regions. Inconsistency in the research between the involvement of the right hemisphere and thalamic versus the left hemisphere were reported and Peterson and Posner speculated that this may result from

more tonic or slower effects being right lateralized and phasic effects being left lateralized (Peterson & Posner, 2012).

The second network outlined by Peterson and Posner (2012) was that of orienting or the ability to direct attention at certain stimuli. Several areas have been implicated in regards to the orienting network with the cited research showing consensus with involvement of the frontal and posterior areas of the brain. The parietal areas are also cited as having involvement with orienting, as well as other forms of processing. Similar to the case of norepinephrine to the alerting system, the cholinergic system appears involved with the ability to orient. The involvement of this system appears to be located in the superior parietal lobe. Other areas including the temporoparietal junction and ventral frontal cortex are believed to play a role in orienting (Peterson and Posner, 2012).

The executive network was the final area outlined by Peterson and Posner (2012) and originally was considered target detection. This system reflects the point at which a stimulus enters into conscious awareness or is detected. The medial frontal cortex and the anterior cingulate cortex were the original areas implicated with the executive network; however, this area was elaborated on when Peterson and Posner revisited the model. Executive control has received substantial attention in recent years and although the anterior cingulate cortex continues to be recognized as playing a role, there are differing opinions on its exact involvement (Peterson & Posner, 2012).

Diagnostic Criteria for ADHD

Although the above mentioned theory and model are important in understanding a plausible relationship between lead exposure and ADHD, they do not form the basis for

how ADHD is defined or measured in research. Research in this area most often uses either formal diagnosis of ADHD or the presence of the diagnostic criteria symptoms as the dependent variable. Researchers and clinicians alike use diagnostic criteria set forth in the DSM-V to determine the presence of ADHD and its associated symptoms (American Psychiatric Association, 2013). A diagnosis similar to ADHD first appeared in the second edition of the DSM published in 1968 and was labeled hyperkinetic reaction of childhood. In the third edition, published in 1980, the diagnosis was listed as attention deficit disorder (ADD) and then in the revision of the third edition, published in 1987, the name was changed to ADHD. The International Statistical Classification of Diseases and Related Health Problems (ICD) published by the World Health Organization listed a similar diagnosis under the name hyperkinetic disorders (American Psychiatric Association, 2013).

The fifth edition of the DSM was recently published in 2013 (American Psychiatric Association, 2013) and thus, many relevant studies used the DSM-IV-TR criteria in research. Minimal changes were made to the symptoms descriptions for a diagnosis of ADHD in the DSM-V. Given these minimal change no concerns comparing research using either version of the DSM are raised (American Psychiatric Association, 2013).

Based on the DSM-V, there are three subcategories within the diagnosis of ADHD—predominately inattentive presentation, predominately hyperactive-impulsive presentation, and combined presentation (American Psychiatric Association, 2013). The inattention symptoms include difficulty sustaining attention, distractibility, forgetfulness,

and disorganization and the hyperactive/impulsive symptoms include over activity, difficulty sitting still, difficulty awaiting turn, and talking excessively. These are behavioral signs that can be observed by caregivers, teachers, and the individual themselves (American Psychiatric Association, 2013).

In order to meet criteria for combined presentation a person must present with six or more symptoms in each category, and for the individual subtypes a person must present with six or more symptoms only in that specific category (American Psychiatric Association, 2013). ADHD is considered a disorder that begins or is first present in childhood and thus, some of the symptoms must have been present prior to age 12 years, although symptoms may change as a child ages. The diagnosis also requires that the symptoms have been occurring for at least 6 months and are occurring in multiple settings. Diagnoses of unspecified or other specified ADHD can also be given if a person does not meet full criteria for one of the subtypes, but is showing impairment due to the presenting symptoms or if the symptoms began at or after 12 years of age. For any of the subtypes to be diagnosed the symptoms must be causing the individual clinically significant impairment in functioning in the school, work, or social settings (American Psychiatric Association, 2013).

The American Psychiatric Association (2013) estimates that five percent of children and two and a half percent of adults meet criteria for the diagnosis; however, the CDC estimates that 11 percent of children held an ADHD diagnosis in 2011 (CDC, 2016). ADHD symptoms can continue throughout the lifespan, although symptoms tend to improve into adulthood. If an individual no longer meets full criteria for the diagnosis

as they get older a modifier of "In Partial Remission" can be used (American Psychiatric Association, 2013).

Researchers studying lead exposure and ADHD have used both formal diagnosis of ADHD based on the DSM criteria and the individual symptoms described in the criteria (see Boucher et al., 2012; Chiodo et al., 2004; Cho et al., 2010; Nicolescu et al., 2010; Plusqellec et al., 2010). When the symptoms are the focus of the research often standardized ratings scales assessing the symptoms described in the diagnostic criteria are completed by parents/caregiver or teachers (see Boucher et al., 2012; Chiodo et al., 2004; Cho et al., 2010; Nicolescu et al., 2010). Due to the nature of a meta-analysis using existing literature as the sample, the present study closely aligns with the framework of the research in the field. The concept of ADHD and the associated symptoms in this study align with these that were investigated in the previous research.

Literature Review Related to Key Variables and/or Concepts

ADHD Evaluation and Treatment Overview

As outlined above, the DSM-V provides diagnostic criteria and specifications for health care professionals to follow when making a diagnosis of ADHD (American Psychiatric Association, 2013). According to the DSM-V, the prevalence rate of ADHD is approximately 5% in children (American Psychiatric Association, 2013) and of children receiving services from public mental health facilities 31% have a diagnosis of ADHD (Siegel, Laska, Wanderling, Hernandez, & Levenson, 2016). In addition to the symptoms of ADHD, those with the diagnosis often have co-morbid disorders or impairments including neuropsychological impairments, emotional dysfunction,

impairments in social and peer functioning, academic deficits, disruptive behavior disorders, mood and anxiety disorders, tic disorders, substance abuse, and motor coordination impairments (Tarver, Daley, & Sayal, 2014). Mellon et al. (2013) also found that children diagnosed with ADHD were 2.1 times more likely to be diagnosed with enuresis and 1.8 times more likely to be diagnosed with encopresis than those without a diagnosis of ADHD. Children diagnosed with ADHD also experience significant decreases in quality of life in physical and psychosocial domains (Lee et al., 2016).

Evaluations for ADHD can include several components such as clinical interviews with caregivers and patients, completion of standardized rating scales by caregivers, teachers, and patients, administration of psychological tests, and collection of information about overall functioning and medical history (Parker & Corkum, 2016). Parker and Corkum (2016) conducted a study of the usefulness of a parent and teacher standardized rating scale and a semi-structured diagnostic interview at predicting ADHD based on a more comprehensive evaluation. Based on 279 children with formal diagnoses of ADHD resulting from a comprehensive evaluation, the sensitivity and specificity of the semi-structured interview was high and 91.8% and 70.7%, respectively. For standardized ratings, the sensitivity was adequate (83.5%), however, the specificity was low (35.7%). While both these methods of evaluation can be useful as part of a comprehensive, diagnostic evaluation, these results clearly indicate standardized ratings should not be used independently to make a diagnosis of ADHD (Parker & Corkum, 2016). Edwards and Sigel (2015) found similar results with the accuracy of an attention problems scale of a standardized rating being lower than that needed to use the measure

independently. The need for best-practices, comprehensive assessment in the diagnosis of ADHD increases the societal cost of this disorder.

In addition to the cost of making an accurate diagnosis of ADHD, there can be significant costs of treatment once such a diagnosis has been made. Page et al. (2016) investigated the treatment costs for the use of pharmacological and behavioral interventions. Four treatment protocols were examined in this study where clients received two rounds of treatment either beginning with medication or behavioral treatment. For the second round participants either received continuation of the same treatment or switched to the alternative treatment. Overall, beginning with low intensity behavioral treatment cost less than beginning with medication. The average cost per child per year when beginning with behavioral treatment was $392 versus $1448 when beginning with medication. The cost of both treatments rose to $976 and $1701, respectively, when parent-time spent on treatment was included in the total cost (Page et al., 2016). Aside from the cost of treatment, there are often individual, organizational, and societal barrier to obtaining appropriate treatment (Wright et al., 2015). Caregiver and health care provider beliefs about ADHD symptoms, help-seeking behaviors, and differing access to treatment due to low SES can all significantly impact whether appropriate treatment is received (Wright et al., 2015).

A singular cause of ADHD has not been established and there are numerous potential causes including genetics, brain structure anomalies, prenatal chemical exposures and complications, perinatal complications, diet, environmental and parenting factors, and early deprivation and neglect (see Hanc et al., 2016; Pettersson et al., 2015;

Tarver et al., 2014). Hanc et al. (2016) investigated term of birth, birth weight, and Apgar scores in regards to future ADHD diagnosis and found that Apgar score had the highest predictive value for ADHD diagnosis. Pettersson et al. (2015) conducted a twin study, which found that one kilogram decrease in birth weight resulted in an increase of one unit on a parent rating of ADHD symptoms. The numerous possible causes or risk factors of ADHD complicate research into any one of these factors as it would be unlikely all risk factors could be accounted for in one study.

Lead Exposure Prevention and Treatment Overview

Lead, a heavy metal, at one time present in materials such as paint, pipes, and gasoline, is an environmental toxin. As mentioned the CDC estimated there are 500,000 children between the ages of one year and five years that have blood lead levels that exceed the threshold believed to cause damage (5 micrograms per deciliter-µg/dL) and over 4 million households have conditions that are exposing children to lead (CDC, 2012). Lead-based paint is often the target of prevention programs including the enactment of Lead-Based Paint Poisoning Prevention Act in 1971, but in 2002 there were over 9,000 industrial sites also releasing lead (Brink et al., 2013). Brink et al. (2013) found that ambient air lead levels were a significant predictor of elevated lead levels in children. The recent lead exposure through drinking water in Flint, Michigan provides evidence for another source of lead exposure that needs to be addressed through prevention programs (Hanna-Attisha, LaChance, Sadler, & Schnepp, 2016). Zartarian, Xue, Tornero-Velez, and Brown (2017) found that soil and dust were important exposure

avenues, but also developed a model to determine what a safe lead concentration in water would be in consideration of other exposure avenues.

Despite several avenues that may exposure children to lead most prevention programs focus on exposure through lead based paint in older homes, and lead screeners completed by pediatricians are often ineffective at identifying those at risk for exposure (Nicholson & Cleeton, 2016). In 2009, 27 of the 42 states that have CDC funded lead poisoning prevention programs within their health departments also enacted specific laws to help reduce or eliminate childhood lead poisoning (Kennedy, Lordo, Sucosky, Boehm, & Brown, 2016). Although the small sample size in Kennedy et al. (2016) likely decreased the power of the analysis, the results did not strongly support the effectiveness of new laws in decreases the incidence of lead exposure.

In Rochester, New York an amendment to the housing code was enacted that required rental properties built prior to 1978 to undergo lead inspections (Korfmacher, Ayoob, & Morley, 2012). If the property failed the inspection owners were required to make repairs. Only 6% of properties failed the visual inspection which was much less than expected and of those that passed a visual inspection 88% were negative for lead on a dust wipe test. These measures do appear to be reducing the lead hazards within the rental properties of Rochester (Korfmacher et al., 2012). New York State also began mandating lead screeners in children in 1992, which resulted in a significant increase in blood lead testing rates (Kennedy et al., 2014). Excluding New York City, the prevalence rates of elevated blood lead levels in children under 6 years old significantly declined from 1997 to 2011 in New York state. Examination of Monroe County, New York

specifically suggested that both efforts at increasing home inspections for lead hazards and screening of at-risk children have been effective at decreasing children with elevated blood lead levels (Kennedy et al., 2014).

The role of prevention is crucial due to the limited treatment options available for lead exposure and that those treatments may decrease lead levels, but not improve the damage caused by the lead (McKay, 2013). The Treatment of Lead-Exposed Children Trial examined the effect of succimer, a heavy metal chelating agent, on children between 12 and 33 months of age with blood lead levels between 20 and 44 mcg/dL. Although succimer was effective at decreasing blood lead level, there was no improvement on measures of cognitive abilities, behavior, or neuromotor speed for those treated with succimer (McKay, 2013). Research has also begun to examine potential protective factors for lead exposure and differing impacts of lead exposure on males and females has led to speculation that estrogen and estradiol may have protective effects (Khanna, 2015).

Known and Potential Effects of Lead Exposure

Research has consistently shown a correlation between exposure to lead, even at low-levels (less than 10 µg/dL), and intellectual impairments (see Canfield et al., 2003; Beattle et al., 1975; Henn et al., 2012; Mohan et al., 2014; Rodrigues et al., 2016). Canfield et al. (2003) also developed a linear model, which estimated that for every 10 µg/dL of lead exposure there would be a decline in IQ scores of four to six points. Research has also found significant correlations between elevated lead levels and lowered academic achievement and conduct problems (Marcus, Fulton, & Clarke, 2010;

McCrindle et al., 2017; Strayhorn & Strayhorn, 2012). Prenatal exposure to lead has also been found to be significantly correlated with delays in cognitive development and attention impairment (Neugebauer et al., 2015; Vigeh, Yokoyama, Matsukawa, Shinohara, & Ohtani, 2014).

More recent research has examined the potential impact of lead exposure on executive functioning skills, ADHD symptoms, and externalizing problems with some mixed results. Comparable to the research related to intellectual functioning, recent research on the correlation between lead exposure and ADHD symptoms has found an impact even at low-levels of lead exposure (Braun et al., 2006). The CDC currently reports 5 μg/dL as the cut-off for brain damage (CDC, 2012) and more recent research has examined the associations with lead levels much lower than this. However, the research has not resulted in agreement on the magnitude of the effect or the effect on specific symptoms of ADHD, such as inattention symptoms versus hyperactivity/impulsivity symptoms (see Chiodo et al., 2007; Nigg et al., 2008). Eubig, Aguiar, and Schantz (2010) reviewed human and animal studies related to lead and PCB exposure and domains impaired in ADHD. Overall, the authors of this review concluded that animal and human studies both support that lead impairs attention and response inhibition (i.e., impulsivity), as well as a correlation between lead exposure and ADHD diagnosis (Eubig et al., 2010). Further examination of the current research base and additional studies are needed to determine the specific outcomes correlated with lead exposure and whether there is any safe level of exposure.

ADHD Diagnosis and Exposure to Lead

Researchers studying lead exposure and ADHD have examined the correlation between blood lead levels and diagnosis of ADHD, as well as the individual symptoms comprising this diagnosis (Nigg et al., 2008, Morgan et al., 2001). In 2006 Braun et al. published a study examining the correlation between environmental toxins and diagnosis of ADHD in children ages 4 years to 15 years. The National Health and Examination Survey was conducted between 1992 and 2002 and included measurement of blood lead levels and parental reports of tobacco exposure, both of which are considered environmental toxins. Parental reports were also used to determine if a previous diagnosis of ADHD was present and any current or historic use of stimulant medication. Although blood lead levels were directly assessed, all other information was gathered through parental report. This could be considered a weakness of the study given parents' retrospective recall may not have been accurate, particularly of tobacco exposure prenatally. However, in regards to lead exposure, it was found that higher lead levels during childhood were a significant predictor of ADHD diagnosis (Braun et al., 2006).

Froehlich et al. (2009) also used data from a nation survey, The National Health and Nutrition Examination Survey, conducted between 2001 and 2004. Information regarding prenatal and current tobacco exposure, current lead exposure, ADHD diagnosis, birth weight, and other demographic information (e.g., gender, age, household income) was collected from parents. This study also showed higher lead exposure to be a significant predictor of ADHD diagnosis, even when the analyses were conducted with only children whose blood lead levels were below 5 μg/dL. Although lead exposure

remained a significant predictor of ADHD diagnosis even when prenatal tobacco exposure was accounted for, children who experienced both prenatal tobacco exposure and lead exposure were at eight times the risk for having an ADHD diagnosis than children who experienced neither exposure. As with Braun et al. (2006), the reliance on parental report is a weakness of this study. Both studies, Braun et al. and Froehlich et al., also used current lead exposure levels rather than a child's peak lead level or lifetime exposure to lead, which when looking at a dose-response relationship is an important factor to consider.

To avoid the potential inaccuracies caused by solely using parent report, Nigg et al. (2008) had children in their sample evaluated by qualified professionals to determine whether a diagnosis of ADHD, as well as other mental health disorders, was present. As each child was directly evaluated this study included diagnoses of ADHD combined type and ADHD predominately inattentive type. Unfortunately the number of children diagnosed with ADHD predominately hyperactive/impulsive type was too small to include in the analyses. Overall, researchers found the ADHD combined type group to have significantly higher blood lead levels than the control group (no ADHD diagnosis); however, the ADHD predominately inattentive group was not significantly different from either the ADHD combined type or control groups. Although the blood lead levels for the ADHD predominately inattentive group were higher than in the control group, this did not reach significance and suggests that lead exposure may have a differential impact on hyperactive/impulsive and inattentive symptoms (Nigg et al., 2008). These results were replicated in Nigg et al. (2010), which confirmed that blood lead levels were significantly

associated with diagnosis of ADHD combined type, but not with diagnosis of ADHD predominately inattentive type. In contrast to Nigg et al. (2008), this study included very low levels of lead exposure, below 3 μg/dL, and the significance of the association with ADHD combined type was maintained even at these very low levels of lead exposure (Nigg et al., 2010).

The results of Braun et al. (2006), among others, have been replicated in studies conducted in other countries. Wang et al. (2008) conducted a similar study with Chinese children, 4 years to 12 years old. Parental report was used to determine diagnosis of ADHD through a structured clinical interview, as well as gather data regarding tobacco exposure, SES, family history, and pregnancy/birth information. Based on this study, researchers concluded that lead exposure was a significant predictor of ADHD diagnosis even when a number of other known risk factors were accounted for in the analyses. The use of non-ADHD controls who were matched to the ADHD cases on a number of important variables (e.g., age, sex, SES) is an strength of the study, as this shows the correlation between lead exposure and ADHD is not the result of other variables that may be linked to both increased lead exposure and ADHD diagnosis (Wang et al., 2008). Wang et al. (2009) also looked at lead exposure in a population of Chinese children, ages 6 years to 12 years, but using a rating scale completed by the children's school supervisors as the measure of ADHD symptoms and diagnosis. These results did not show a significant difference between the ratings for those children exposed to lead and those that were not (Wang et al., 2009). These differing results may suggest that the measure used to identify ADHD symptoms can influence the results.

Yousef et al. (2011) conducted a similar study in the United Arab Emirates that analyzed several heavy metals in connection with ADHD diagnosis. Lead, mercury, arsenic, cadmium, copper, zinc, cobalt, manganese, chromium, antinomy, nickel, and molybdenum were all included in the study. Children ranged from 5 years to 15 years of age and exclusion criteria of mental retardation and autism were used. Significantly higher levels of lead, zinc, and manganese were present in children diagnosed with ADHD compared to controls (no ADHD diagnosis). When regression analysis was completed zinc levels were a better predictor of ADHD diagnosis than lead levels (Yousek et al., 2011). Ha et al. (2009) examined lead and mercury in a population of Korean children ages 6 years to 10 years. Both lead and mercury exposure were shown to increase risk for ADHD and no interaction effect was present between the two. The mean level of lead for the sample was very low at 1.8 μg/dL. The effect of lead on ADHD continued to be significant after accounting for household income, parent mental health, and place of residence, although the effect was lessened. A linear relationship was seen between increases in blood lead level and the severity of ADHD symptoms (Ha et al., 2009).

Kim et al. (2013) also examined lead and mercury, as well as cadmium in a sample of 5 year to 12 year olds that were diagnosed by a medical professional with ADHD. Initially blood lead levels were not significantly associated with ADHD diagnosis; however, after adjustment for covariates was made there was a significant association between lead and ADHD. Covariates included age, sex, race, prenatal tobacco and alcohol exposure, postnatal tobacco exposure, SES, and residence. The mean blood

lead level for the ADHD sample was 1.89 µg/dL and for the controls was 1.51 µg/dL. No significant effect of mercury or cadmium on ADHD diagnosis was found (Kim et al., 2013).

Individual Symptoms of ADHD and Exposure to Lead

Diagnosis of ADHD requires a variety of inattentive, disorganized, hyperactive, or impulsive symptoms to be present depending on the subtype (American Psychiatric Association, 2013). Studies examining the diagnostic subtypes of ADHD have found a more robust correlation with ADHD combined type than with predominately inattentive type suggesting there may be a differential impact of lead exposure on specific symptom categories (Nigg et al., 2008, 2010). Due to the limited number of cases of ADHD predominately hyperactive/impulsive type, however, no research could be found that included this subcategory and thus, it is not possible to draw any conclusions.

Support for a significant effect on inattention, impulsivity, and hyperactivity

Cho et al. (2010) examined lead and tobacco exposure in a sample of Korean children ages 8 years to 11 years. This study used both teacher reports of behavior and symptoms and children's performance on standardized measures of executive functioning. Cho et al. found a correlation between even very low lead levels in children and inattentive and hyperactive symptoms related to ADHD with the sample having a mean lead level of 1.9 µg/dL. As seen in other studies, such as Braun et al. (2006), this study also showed a consistent correlation even when other potentially confounding variables were accounted for (Cho et al., 2010).

Nicolescu et al. (2010) used parent and teacher rating scales that were specific to ADHD symptoms rather than measuring several areas of behavioral and emotional functioning. Researchers for this study used a sample of Romanian children 8 years to 12 years old and examined lead, mercury, and aluminum. Total ADHD scores, as well as scales of inattention, hyperactivity, and impulsivity, were significantly associated with lead exposure, but not with mercury or aluminum exposure. Results estimated that for a 2-fold increase in lead level there was an 11% and 16% increase in total ADHD ratings per parent and teacher reports, respectively. Parent reports showed the least impact on attention symptoms with a 2-fold increase in lead only causing a 4% increase in attention symptoms, but a 17% and 23% increase in hyperactive and impulsive symptoms, respectively. Teacher reports showed a more consistent increase in symptoms with a 2-fold increase in lead causing a 14% increase in attention and hyperactive symptoms and a 21% increase in impulsive symptoms (Nicolescu et al., 2010).

Hansen, Trillingsgaard, Beese, Lyngbye, and Grandjean (1989) used a continuous performance test to determine the potential effect of lead exposure in a cohort of first grade children. For the purposes of analysis children were put into a high lead group with lead levels greater than 18μg/dL and a control group with lead levels below 5 μg/dL. The high lead group had significantly more errors on a continuous performance test than the control group. However, the article related to this study did not specify whether this was based on total errors, omission errors, or commission errors and thus, it is not possible to determine whether these increased errors were a sign of inattention, impulsivity, or both (Hansen et al., 1989).

Plusquellec et al. (2010) found a correlation between impulsivity and activity level and lead exposure in a sample of 5 year old Inuit children. In this study a rating scale was completed by the examiner during the child's testing session to assess several areas of behavior. These sessions were also videotaped and later reviewed for coding of several other areas of behavior. Prenatal lead exposure and lead exposure at the time of assessment was collected. As mentioned activity level and impulsivity were significantly correlated with lead exposure, as were irritability and off task duration. These results suggest lead exposure has a negative effect on inattention, impulsivity, and hyperactivity (Plusquellec et al., 2010). Evidence for lead effecting inattentive, impulsive, and hyperactive symptoms was also present in the results of Fergusson, Fergusson, Horwood, and Kinzett (1988). Rating scales completed by both parents and teachers for 888 children at 8 years and 9 years old showed a significant correlation between dentine lead level and several symptoms related to activity and attention. Similar results were obtained across parent and teacher ratings and between the 8 year and 9 year old measures (Fergusson et al., 1988).

Fergusson, Horwood, and Lynskey (1993) separated lead levels into five groups ranging from 0 µg/dL to over 12 µg/dL. Researchers for this study, however, combined inattention and restlessness into one measure making it impossible to separate inattentive and hyperactive/impulsive symptoms of ADHD. Regardless, at both 12 and 13 years old there was a significant correlation between lead exposure and inattention/restlessness, as well as a small dose response relationship between increasing lead level and increasing severity of inattention/restlessness (Fergusson et al., 1993).

Hong et al. (2015) used parent and teacher ratings of inattentive, hyperactivity, and total ADHD symptoms and scores on a continuous performance test to determine the correlation with lead levels. Demographic information (age, sex, residential region, parental education, and socioeconomic status), as well as IQ scores, were also included in the analyses to determine if they moderated the correlation between lead levels and ADHD symptoms. Overall, lead levels were shown to be positively correlated with both parent and teacher ratings of inattentive, hyperactive, and total ADHD symptoms. Scores on the continuous performance test, however, only showed a significant correlation between lead levels and a measure of impulsivity, not inattention. Once adjusted for demographic information and IQ, the correlation between lead level and parent and teacher ratings was attenuated for all ratings, but more notably for inattentive symptoms (Hong et al., 2015).

Byun et al. (2013) investigated the relationship between lead exposure, mobile phone use, and ADHD symptoms. The study included 2422 from 27 elementary schools in various cities in Korea. Lead levels were measured at two time points and mobile phone use and ADHD symptoms were assessed through questionnaires completed by the children's parents or guardians. ADHD symptoms were measured using a Korean version of a standardized ADHD rating scale. Children were split into a low lead level group, below 2.35 μg/dL, and a high lead level group, above or equal to 2.35 μg/dL. The high lead level group had a significantly higher risk for ADHD symptoms than the low lead level group. Overall ADHD symptoms were measured and no results regarding specific symptom types was available (Byun et al., 2013).

Support for a significant effect on hyperactivity and impulsivity

Boucher et al. (2012) provides evidence for the correlation between lead exposure and ADHD hyperactive/impulsive symptoms in a population of Nunavik children (an area north of Montreal). Researchers in this study examined a number of environmental contaminants including lead and mercury, both with prenatal and postnatal exposure. Similar to Cho et al. (2010), Boucher et al. used teacher ratings of child internalizing, externalizing, and attention problems and ADHD diagnostic criteria, as well as including a number of potential confounding variables (e.g., maternal drug/alcohol use, maternal age, maternal education, etc.). The rationale for using teacher ratings was that the classroom provides an environment where ADHD symptoms are often seen and allows for comparisons across children; however, this is also a limitation of the study as a formal diagnosis of ADHD was not made by a qualified professional. Children's levels of both mercury and lead were distributed into three tertiles for analysis, with the first tertile having the lowest exposure. The symptoms of the predominately hyperactive-impulsive type were more likely to be reported for children in the third tertile for prenatal mercury exposure and for children in the second and third tertiles for postnatal lead exposure. Researchers did not find a relationship between current blood lead level and the symptoms of the predominately inattentive type, although these symptoms were significantly more likely to be reported in children with higher prenatal mercury exposure (Boucher et al., 2012).

Walkowiak et al. (1998) used a continuous performance test, as well as other neurobehavioral and intelligence measures, to examine the relationship between these

areas of functioning and lead and mercury levels in 6 year old children. Omission and commission errors within the continuous performance test were analyzed with borderline significant results for the relationship between lead levels and omission errors and significant results for commission errors being present. The results of Walkowiak et al. suggest that lead level has a stronger associated with impulsivity symptoms than with inattention symptoms, which is contrary to Chiodo et al. (2004) and Chiodo et al. (2007).

Kim, Yu, and Lee (2010) sampled school-aged Korean children using parent completed ratings of cognitive, emotional, and behavioral functioning. The sample was divided into two groups with low lead exposure and high lead exposure, but all had lead levels below 10 μg/dL Despite the overall low lead levels, the high lead exposure group had significantly higher ratings of hyperactive than the low lead level group. The overall mean lead level for all subjects was 2.68 μg/dL (Kim et al., 2010).

Stewart et al. (2006) assessed 167 children for their response inhibition and learning during a differential reinforcement of low rate tasks. Children's prenatal exposure to PCBs and post-natal exposure to methylmercury and lead were also assessed by researchers. All three types of exposure were found to be related to responding excessively and impaired performance. These results suggest that lead exposure, as well as PCB and methylmercury exposure, have a negative impact on response inhibition (Stewart et al., 2006).

Huang et al. (2016) examined a sample of 578 6 year to 13 year old Mexican children. Children's mothers completed standardized rating scales to assess ADHD symptoms and the children's current blood lead levels were measured. Researchers found

a significant correlation between blood lead levels and hyperactive and impulsive symptoms. They did not, however, find any significant association for inattentive or overall ADHD symptoms and lead exposure (Huang et al., 2016).

Support for a significant effect on inattention

Roy et al. (2009) found a significant relationship between blood lead levels in children and inattentive ADHD symptoms, but not hyperactive symptoms. Roy et al. used a sample of children 3 years to 7 years old from Chennai, India. Teacher reports of child behavior on a number of questionnaires similar to the questionnaire used in Boucher et al. (2012), but with the addition of a questionnaire assessing executive functioning skills, were included in the study. Roy et al. had the limitation of the questionnaires used not having been standardized for the specific population studied, which needs to be considered when analyzing the magnitude of the relationship seen. Interestingly, unlike many other studies discussed Roy et al. also examined the dose-response relationship seen between blood lead levels and attention, hyperactivity, anxiety, sociability, and overall executive functioning, with all these variables determined to have a linear relationship with blood lead levels. Increases in blood lead levels by far showed the largest impact on executive functioning, followed by anxiety, inattention, sociability, and hyperactivity, respectively. The mean lead level for the sample 11.4 μg/dL, which is slightly higher than the mean in most studies discussed. These results are important not just for providing further evidence for the relationship between lead exposure and ADHD, but examining the dose-response relationship between these variables (Roy et al., 2009).

Chiodo et al. (2004) examined a large variety of attention, executive functioning, intellectual, and teacher-rated behavioral measures in a population of African American, inner-city children. A continuous performance test was used to assess attention and two rating scales of general emotional/behavioral functioning and ADHD specific symptoms were also included. In regards to teacher ratings, lead exposure was significantly associated with higher overall ADHD symptoms and inattentive symptoms (on both rating scales), but not impulsive symptoms. On the continuous performance test lead exposure was associated with a decreased number of correct responses, which was considered a measure of sustained attention. It is also important to note that these results were consistent regardless of whether lead exposure was dichotomized at 5 μg/dL or 10 μg/dL, and the association for multiple outcomes was maintained with lead levels as low as 3 μg/dL (Chiodo et al., 2004). Chiodo et al. (2007) completed another study examining similar variables and measures including a continuous performance test and teacher ratings of inattention and impulsivity. These results also showed a significant correlation between lead exposure and teacher reported inattention symptoms, but not impulsive symptoms. A significant correlation between the number of omission errors on a continuous performance test and lead exposure was present, but not with the number of commission errors, which can be considered to measure sustained attention and impulsivity, respectively (Chiodo et al., 2007).

Boa et al. (2009) studied 7 year to 16 year olds in an area of China known to have been polluted by mine accidents and children's lead and zinc levels were assessed. Parents completed a version of the Child Behavior Checklist (CBCL) that had been

validated in Chinese. Lead and zinc were both shown to be strongly associated with all scales of the CBCL including attention problems. No specific scales for hyperactivity or impulsivity were part of the CBCL, but delinquent behavior and aggressive behavior were significantly associated with lead and zinc (Boa et al., 2009). Marlowe and Bliss (1993) used parent and teacher ratings to assess children's behavioral functioning across several areas including attention and acting out behavior, although a pure measure of hyperactivity/impulsivity was also not included. When these ratings were analyzed in regards to children's lead level, a significant association between lead and all scales was present. In particular, lead exposure was estimated to account for 30% of the variance in distractibility ratings based on teacher reports (Marlowe & Bliss, 1993).

Needleman, Riess, Tobin, Biesecker, and Greenhouse (1996) also used teacher completed rating scales, as well as parent completed scales to examine the relationship between lead exposure and behavior. This study separated the participants into low and high lead exposure groups for comparison and rating scales and lead levels were completed at two time points, 7 years and 11 years old. At 7 years old, there was not a significant difference between the groups on a scale of attention problems but at 11 years old a significant difference was seen with the high lead group showing more severe attention problems. Although this does suggest there is a greater negative impact of lead exposure at higher levels, the lack of a control group not exposed to lead hinders further conclusions (Needleman et al., 1996).

Bellinger, Leviton, Allred, and Rabinowitz (1994) studied prenatal and postnatal exposure to lead in relation to teacher completed ratings of emotional and behavioral

functioning. Although no association between prenatal lead exposure and increased problem behaviors was present, a significant association between postnatal exposure and problem behaviors was with no difference between internalizing and externalizing behaviors seen. Inattention falls within internalizing behavior category and had a modest association with postnatal lead exposure. No pure scale of hyperactivity or impulsivity was included, but associations were also seen on scales of nervous-overactivity, aggressive behavior, and self-destructive behavior (Bellinger et al., 1994).

Min et al. (2006) assessed 61 Korean children, ages 7 years to 16 years, on computer-based measures of neurobehavioral functioning. Five domains were tested and the children were also assessed for blood lead level. Additionally age, gender, and mother's performance were recorded. Blood lead levels were significantly correlated with measures of attention (measured by simple reaction time). The mean blood lead level for the children was 2.89 μg/dL (Min et al., 2006).

Surkan et al. (2007) examined the correlation between lead levels in children 6 years to 10 years old on a number of neuropsychological functions, including intelligence, achievement, working memory, and attention. Additional covariates of age, race, socioeconomic status, and maternal intelligence were included in the analyses. Children were placed into three groups based on lead levels; 1-2 μg/dL, 3-4 μg/dL, and 5-10 μg/dL. After adjustment for covariates, impairments in attention were significant for children with blood lead levels between 5 and 10 μg/dL. After children's intelligence was also adjusted for the most significant deficits in relation to lead levels was seen for spatial attention and executive functions (Surkan et al., 2007).

Support against a significant relationship between lead and ADHD symptoms

Chen, Cai, Dietrich, Radclife, and Rogan (2007) attempted to determine whether the effect of lead exposure on behavior was only resulting from the decreased intellectual abilities resulting from lead exposure. Rating scales that included an ADHD index and an individual scale of hyperactivity were the most relevant measures for the current topic. Both the ADHD index and the hyperactivity scale were significantly and negatively correlated with IQ, but not significantly correlated with lead level. These results did not show any significant relationship between lead exposure and ADHD symptoms. Behavioral symptoms, externalizing problems, internalizing problems, and school problems were significantly correlated with both IQ and lead leads, and in particular the correlation for school problems and externalizing problems was not mediated by IQ (Chen et al., 2007).

Cho et al. (2010) as discussed above did find a significant associated between lead levels and both inattention and hyperactivity using parent and teacher report. Urine cotinine was also included as a measure of tobacco exposure in the children sampled. After the results were adjusted for urine cotinine, the parent reported symptoms of ADHD were no longer significantly associated with lead level; however, the teacher reported symptoms remained significant.

Kordas et al. (2006) assessed a sample of 532 first grade children (less than 8 years old) on 14 measures of cognitive functioning, one being a freedom from distractibility index. Children's blood lead levels were also measured, as well as

additional participant information gathered. Prior to any adjustments, the freedom from distractibility factor was significantly correlated with lead levels; however, once adjustments were made for the covariates (gender, age, hemoglobin, family possessions, forgetting homework, house ownership, crowding, maternal education, birth order, family structure, arsenic exposure, tester, and school) the correlation no longer reached significant. Only measures of math performance, vocabulary, and memory continued to be significantly correlated with lead level once adjustments for the covariates were made (Kordas et al., 2006).

Executive Functioning Deficits Related to ADHD and Exposure to Lead

In addition to the above mentioned studies, several researchers have taken the approach of examining the relationship between lead exposure and specific deficits and impairments commonly found in those diagnosed ADHD rather than examining the diagnosis itself. Nigg et al. (2008) specifically examined cognitive control in children with lead exposure and a diagnosis of ADHD. Cognitive control was assessed on a stop task that required children to determine whether a letter flashed on a computer screen was an "X" or an "O" and press the corresponding key; however, if a tone sounded they were not to respond. This provided measures of the participant's response time and inhibitory control. Overall deficient response inhibition was found to be predicted by lead exposure and it was found that this deficit mediated the relationship between blood lead levels and hyperactive/impulsive symptoms. The effect of lead on cognitive control, specifically response inhibition, appears to be a significant factor in the hyperactive/impulsive symptoms that are seen in children diagnosed with ADHD (Nigg et al., 2008).

Cho et al. (2010) administered several neurocognitive assessments to children, as well as gathering parental and teacher reports of ADHD symptoms. Both blood lead levels and urinary cotinine levels were gathered to help determine the impact of lead exposure versus tobacco exposure. Initially blood lead levels were shown to be significantly related to omission errors, commission errors, and response time variability on a continuous performance task; however, when cotinine levels were controlled for this relationship was no longer significant. Cotinine levels were also significantly related to omission errors, commission errors, and response time variability on a continuous performance task, as well as to performance on the Stroop Word-Color Test and a trail making test, even when blood lead levels and other covariates were accounted for. These results suggest that tobacco exposure has a more significant effect on neurocognitive skills related to ADHD than lead exposure. However, as mentioned above, when examining inattentive and hyperactive symptoms of ADHD as reported by teachers the correlation with blood lead levels was significant even when all covariates were accounted for. Lead exposure may have a different effect on the diagnostic symptoms of ADHD and the neurocognitive and executive functioning skills related to this diagnosis (Cho et al., 2010).

Chiodo et al. (2007) found a significant association between lead exposure and several neurocognitive assessment results even when accounting for prenatal drug and alcohol use, including tobacco use. Chiodo et al. used a large sample of children, age 7 years, whose mothers had attended a prenatal clinic, which allowed information to be available regarding the child's prenatal exposure to drugs and alcohol, as well as other

potentially confounding variables. Children were assessed for intelligence, academic performance, ADHD symptoms (teacher report measure), behavior problems (teacher report measure), and attention and impulsivity (continuous performance test). After all covariates were accounted for blood lead levels were significantly related to intelligence scores, academic achievement, behavior problems, inattention, and hyperactivity. Lead levels, however, were not significantly related to impulsivity, which is contrary to Nigg et al. (2008), among others who have found lead exposure to be significantly related to hyperactivity/impulsivity and not inattention. When Chiodo et al. specifically examined the blood lead levels and the severity of these deficits and symptoms they were not able to identify a level of lead exposure that appeared "safe" or to be unrelated to these negative outcomes. This is an important finding when considering future regulations and preventative programs for lead exposure.

Academic Deficits, ADHD, and Exposure to Lead

The symptoms associated with a diagnosis of ADHD have been correlated with academic difficulties and high school dropout (Martin, 2014; Sasser et al., 2016). Sasser et al. (2016) followed a group of children from 3rd through 12th grade to examine the course of ADHD and whether these trajectories had different outcomes. The high trajectory group—significant symptoms across 3rd to 12th grade—had more arrests, higher unemployment rates, higher school dropout rates, and more antisocial behavior than those in the low trajectory group (i.e., no ADHD symptoms). The high trajectory group also was more likely than the low group to be rated by parents and teachers as inattentive, hyperactive, aggressive, emotionally dysregulated, and emotionally distressed, as well as

having greater life stress and more inconsistent parenting (Sasser et al., 2016). In line with these results Fried et al. (2016) found that 29.2% versus 7.7% individuals with and without ADHD repeated a grade, respectively. Individuals with ADHD were also 2.7 times more likely to drop out of high school than those without ADHD (Fried et al., 2016).

Researchers have also found a correlation between lead exposure and academic problems (see Amato et al., 2012; Blackowicz et al., 2016; Evens et al., 2015). Evens et al. (2015) examined the reading and math scores of 47,168 children in the Chicago Public School who had lead levels below 10 µg/dL. Results indicated there was a 1.32 fold increase in risk for reading and math failure with each increase of 5 µg/dL. A decrease in math and reading scores was seen as blood lead levels increased from 2 µg/dL to 9 µg/dL. Blackowicz et al. (2016) also studied a population of students within the Chicago Public School District, specifically 13,266 3rd grade Hispanic children. Researchers found similar results with a 0.55 point decrease in reading scores and a 0.48 point decrease in math scores for every 1 µg/dL increase in blood lead level. This study also showed that 7% and 13.7% of reading and math failure, respectively, could be attributed to elevated blood lead levels (Blackowicz et al., 2016).

A similar study in the Detroit Public School District was conducted by Zhang et al. (2013), which examined 3rd, 5th, and 8th grade students' performance on state math, reading, and science. For all tests there was a decrease in performance as blood lead levels during early childhood increased. There was an increased risk of scoring in the partially proficient or not proficient range on all three tests for children who had blood

lead level above 1 µg/dL compared to those with blood lead levels below 1 µg/dL (Zhang et al., 2013). Amato et al. (2012) also used performance on state tests as a measure of academic achievement in 4th grade children in Wisconsin, except this study examined moderate blood lead levels, specifically those in the 10 to 19 µg/dL range. Scores on all five sections of the Wisconsin Knowledge and Concepts Examination—math, reading, language arts, social studies, and science—were shown to be significantly worse among students with moderately elevated blood lead levels compared to those students not exposed to lead. Lead exposure appeared to have the largest effect on reading scores compared to the other five sections (Amato et al., 2012).

This research supports a correlation between both ADHD and academic deficits and lead exposure and ADHD (Amato et al., 2012; Blackowicz et al., 2016; Evens et al., 2015; Martin, 2014; Sasser et al., 2016; Zhang et al., 2013). These studies, however, did not examine potential confounding variables so it is not possible to determine whether lead has an impact on academic performance separate from the impact of ADHD and intellectual functioning. Regardless, this research highlights the potential long-term, negative consequences of childhood lead exposure.

Potential Confounding Variables

Lead exposure can often occur in conjunction with exposure to other environmental toxins, making it important to consider all possible exposures if the true impact of lead exposure on ADHD symptoms can be determined. Studies such as Boucher et al. (2012), Braun et al. (2006), and Cho et al. (2010) have included a number of possible confounding variables to provide a stronger argument for the impact of lead

exposure. These studies considered tobacco exposure in the analyses, and although Braun et al. found a correlation between prenatal tobacco exposure and ADHD diagnosis, a correlation was also found between ADHD diagnosis and lead exposure even when accounting for prenatal tobacco exposure. In order for causality between lead exposure and ADHD symptoms to be determined all possible third variables that may be influencing both lead exposure and ADHD symptoms need to be examined. This can present as a significant barrier to conducting research in this area as there are many prevalent environmental toxins that could potentially be impacting a child's development and symptom expression.

The Problem of Causality

Overall one of the largest downfalls of this line of research is that causality cannot be definitively proven, as researchers often examine correlations between lead exposure and negative outcomes. More evidence for the effect of lead exposure on symptoms of ADHD can be gathered from animal research. Morgan et al. (2001) exposed rats to low levels of lead and then administered a variety of tasks intended to measure sustained attention, response initiation, and reactivity to errors. It was found that even brief exposure to lead early in development resulted in deficits in sustained attention and an increase in reactivity to errors. It is important to note that these effects were not seen across all attention tasks completed and the effects did have small magnitudes. The results of Morgan et al., however, do add evidence to causality for the significant correlations seen in human research between lead exposure and ADHD symptoms and impairments. Animal research can be an important step in determining the areas of the

brain damaged by lead exposure and the causal mechanisms behind the effects of early childhood lead exposure on development.

Summary and Conclusions

The studies discussed reveal a significant relationship between lead exposure during childhood and diagnoses of ADHD and/or the related symptomatology (Braun et al., 2006; Froehlich et al., 2009; Nigg et al., 2008, 2010). One of the studies I found that did not support a significant relationship between these variables was Cho et al. (2010), which after accounting for tobacco exposure did not show a significant relationship between parent reports of ADHD symptoms and lead exposure. Chen et al. (2007) also did not find total ADHD scores or hyperactivity to be significantly associated with lead levels. Studies such as Froehlich et al. (2009) and Braun et al. (2006) have attempted to account for a variety of third variables that could be resulting in the significant effect or correlation. The majority of studies have shown significant results even when accounting for these variables including both parental and child variables (e.g., birth weight, prenatal drug/alcohol exposure, maternal age, maternal IQ, parental education level, etc.).

Despite disagreement regarding which individual symptoms and diagnosis subtypes have the strongest relationship with lead exposure, the research presented here clearly supports the presence of some relationship between lead exposure and ADHD. This disagreement, however, has resulted in a lack of clarity regarding the strength of the relationship between lead exposure and the various symptoms of ADHD. Additionally, given the inclusion in many studies of potential confounding variables, it is unclear if any of these variables are moderating the relationship between lead exposure and ADHD

symptoms and thus, resulting in some, or all, of the variability seen across study results. These two areas represent important gaps in the literature that the present meta-analysis will attempt to address.

There is a third gap in the current literature that is important to consider, although addressing it is beyond the scope of the present meta-analysis. Due to the ethical implication of carrying out a true experimental design most research has not focused on identifying a causal link between exposure to lead and ADHD symptoms. Animal studies have provided some support for and insight into a causal link. The complex nature of executive functions in humans in general, and specifically in regards to those implicated in ADHD, makes it more difficult to draw parallels between animal and human research in this area.

Meta-analysis in general allows for organization and synthesis of the research base in a certain area (Card, 2012). The purpose of the present meta-analysis was to estimate the magnitude of the effect size of early childhood lead exposure on ADHD symptoms. Through the systematic synthesis of the current research base in the area of lead exposure and ADHD the estimated effect size magnitude—or strength—was determined for ADHD symptoms. This addressed the first gap in the current literature base identified above. Meta-analysis can also determine whether the variability in results is statistically significant or simply represents non-meaningful variations, and if significant, determine what variables are likely to be causing that variability (Card, 2012). Such variability was found in the research related to lead exposure and ADHD

symptoms, and I identified some relevant moderators, thus addressing the second identified gap in the literature base.

In addition to directly addressing the gaps in the literature related to the strength of the relationship between lead exposure and specific ADHD symptoms and the impact of confounding variables, the present meta-analysis attempted to direct future research toward areas that may prove to be the most fruitful. Although beyond the scope of the present meta-analysis, determining the most relevant moderating variables is also an important step in the designing of research that could identify a causal link between lead exposure and ADHD. Chapter 3 presents a detailed methodology for the present meta-analysis including the research design and rationale, data collection, and statistical analysis.

Chapter 3: Research Method

Introduction

Researchers' use of quantitative meta-analysis research designs can contribute significantly to the current research base by synthesizing and integrating the available research in a given area. This allows for expansion of knowledge and conclusions made by the original researcher, as well as the identification of gaps and areas in need of further research (see Card, 2012; Lipsey & Wilson, 2001). I intended the present study to achieve these goals in the area of childhood lead exposure and ADHD symptoms. The aim of the present quantitative study was to estimate the magnitude of the effect size of childhood lead exposure on ADHD symptoms through a meta-analysis, as well as determine if there were any moderating variables (e.g., age of exposure, gender, etc.) that could be facilitating variability in the research results.

I will discuss the research design and rationale for the present study next, followed by the methodology. I will include the search strategies, inclusion and exclusion criteria, and statistical analyses, as well as the procedures for data collection and coding. Lastly, I will discuss any potential threats to validity and ethical concerns.

Research Design and Rationale

Overview of Meta-Analysis

Meta-analysis is a quantitative research method used by researchers to synthesize primary research studies, wherein those primary results are used as the data for analysis (Card, 2012). For primary research in this area data is collected directly from human participants for analysis; however, in a meta-analysis the results of existing studies is the

collected and analyzed data. Stated differently, the data used in this present research were derived from the statistical results reported in the primary studies included in the meta-analysis, rather than measurements on a dependent variable from a sample of human participants. Like primary research that includes different sample sizes, the number of studies included in a meta-analysis can differ greatly from hundreds of studies to just a few (Card, 2012). Additionally, the research procedures for meta-analysis are comparable to primary studies in that the development of research questions, the collection and coding of data, and statistical analysis are required.

Although the specific statistical comparison used for a meta-analysis is dependent upon the type of data collected and the statistics commonly used in the primary studies, it will most often reflect a type of effect size (Card, 2012). Primary researchers in the area of lead exposure and ADHD symptoms have used a variety of statistics including correlations, odds ratios, regression, ANOVA or ANCOVAs, t-tests, and so forth (see Chiodo et al., 2007; Bellinger et al., 1994; Yule, Urbanowicz, Lansdown, & Millar, 1984). For the present study I used a standard mean differences statistic to analyze the results of the included studies.

I used Cohen's *d* as the common effect size measure for the present study. When necessary, I used statistical equations to compute Cohen's *d* from the statistic provided in the results of the primary study. Using a standard mean differences statistic allowed studies to be included in the present meta-analysis that provided different statistics. By including studies with a variety of statistics, and methods, I was able to examine the

general relationship between lead exposure and ADHD symptoms rather than only a correlational or causal relationship through the present meta-analysis.

The present meta-analysis was not meant to be an exhaustive analysis of all research related to the outcomes of lead exposure. I focused solely on research related to the symptomatology of ADHD, specifically inattention and hyperactive/impulsive symptoms. Even within this narrow focus, there were time constraints that may have resulted in some relevant research being excluded. For instance, at the time of completion no responses had been received from the authors in this field who had been contacted regarding unpublished research.

Justification for Research Design

The aim of the present quantitative study was to estimate the magnitude of the effect, an overall effect size, of childhood lead exposure on ADHD symptoms through a meta-analysis, as well as identify if there were any moderating variables (e.g., age of exposure, gender, etc.) that could be facilitating variability in the research results. Meta-analysis allows for the results of multiple studies to be synthesized and combined in order to expand upon the conclusions of those studies (see Card, 2012; Lipsey & Wilson, 2001). In comparison to primary research, meta-analysis often provides a significantly larger sample size by combining the samples of those individual studies (see Card, 2012; Lipsey & Wilson, 2001). Thus, it can provide a more powerful analysis than was possible in the primary studies. In areas such as lead exposure and ADHD, where the results of studies appear inconsistent, a meta-analysis is likely able to provide a better understanding of this variability than another primary study (see Card, 2012; Lipsey &

Wilson, 2001). By providing a standardized method to combine and analyze the results of numerous studies, researchers using meta-analysis have the potential to examine a larger breadth of moderating or confounding variables and determine what variables might be having a significant effect on the relationship between the independent and dependent variables (see Card, 2012; Lipsey & Wilson, 2001).

This type of structured review and synthesis of the current research in any given area is an important step in researchers directing future research toward more meaningful pursuits (see Card, 2012; Lipsey & Wilson, 2001). For instance, if I was able to identify a moderating variable for the effect of lead exposure through the present meta-analysis, a worthwhile endeavor would be to allocate more resources into research of the moderating effect of that variable. The identification and understanding of moderating variables to lead exposure can also greatly assist researchers in the integration of protective factors into preventative programs.

Methodology

Population

The population for the present meta-analysis was all studies conducted that included the variables of lead exposure and ADHD symptoms in children. The target population for the studies included in the meta-analysis was children, male and female, under the age of 18 years (i.e., birth to 17 years old) who had been exposed to lead. No restrictions on the population based on race, ethnicity, or country of residence were placed on the study population.

Search Procedure for Meta-Analysis

For the present meta-analysis, I employed procedures from literature searching that are outlined by Card (2012). As discussed by Card, conducting an adequate literature search requires the use of electronic and print materials. In regards to electronic searching, I searched several electronic databases including, but not limited to, PsycINFO, PsycARTICLES, Academic Search Premier, MedLine, CINAHL Plus, PubMed, and Dissertation Abstracts. I used the following key words and combinations of these key words to search these electronic databases: attention-deficit/hyperactivity disorder, ADHD, inattention, attention, hyperactivity, impulsivity, executive functioning, lead, lead poisoning, and lead exposure. I determined that searching just the word lead resulted in a larger numbers of relevant studies being identified compared to searching lead poisoning or exposure, which appeared to exclude some relevant studies.

After I completed these search methods, I conducted backward and forward search techniques of the articles identified as relevant (Card, 2012). I conducted backward searching by reviewing the reference lists of these articles to identify any additional articles of relevance. I completed forward searching by searching for any articles that cited the identified article (Card, 2012). It should be noted that this method of forward searching can only be conducted for databases that have this function, but was able to be completed for all identified relevant articles. Although book chapters are not included in the meta-analysis, any identified as regarding a relevant area of research I also subjected to backward and forward searching to identify any additional relevant research articles.

In the case that the full-text for any article was not available electronically and could not be retrieved through the library system, the authors were to be contacted to attempt to retrieve the full-text; however, I was able to retrieve full-text for all relevant articles by using a variety of databases. In order to reduce the "file drawer affect" common authors were also contacted to request any unpublished research (see Appendix A) (Card, 2012), but unfortunately I did not received any responses.

A variety of statistics were included in the primary research in this area (e.g., correlations, odds ratios, regression, ANOVA, t-tests, etc.), and in order to allow the greatest number of studies to be included in this meta-analysis I used statistical equations to transform the available statistics from the primary research into a common effect size measure. These transformations were completed by the statistical analysis software.

Once I conducted all above-mentioned search strategies, I then reviewed the identified articles to determine their relevance for the present study. I used the inclusion and exclusion criteria to determine the final sample of articles included in the present meta-analysis. I again used the key search terms to search the main databases toward the end of the study to ensure no new articles had been published during the course of the present study.

Inclusion and Exclusion Criteria

I thoroughly reviewed all identified research articles to determine whether all inclusion criteria were fulfilled. Six inclusion criteria were used based on the variables being studied, as well as the ability for the needed effect size statistic to be generated from the reported data (Card, 2012).

1. No stipulations were placed on research regarding publication. The inclusion of both published and unpublished studies is important to reduce a publication bias and the inclusion of only published studies would increase the potential for artificial inflation of effect sizes due to the tendency for studies that have found significant effects to be published more often than those with non-significant effects (Card, 2012).
2. The study must include a measure of lead exposure during childhood. This can be through blood draw, tooth, hair, or urine as the medium for assessment of lead levels. Measurement of lead exposure must occur during childhood (less than 18 years old).
3. The study must include a psychometric measure of the child's symptoms related to ADHD (e.g., inattention/distractibility, hyperactivity/impulsivity). There are no restrictions regarding the psychometric measure in regards to the party completing it (e.g., parent, caregivers, teacher). The psychometric measure does not need to be completed concurrently with the measure of lead exposure, but does need to be completed during childhood (less than 18 years old).
4. The study will need to include and report statistical data that reflect the appropriate effect size or enough information to compute the appropriate effect size (Card, 2012). The number of participants for each group in the study will also have to be provided.
5. The study must provide enough information that the standard error for the effect size can be calculated (Lipsey & Wilson, 2001).

Data Collection and Coding

Once I collected the sample of studies deemed appropriate for the present meta-analysis, I developed a coding manual based on the characteristics of the studies that were imputed for analysis (see Appendix B). I coded all the studies chosen for inclusion in the meta-analysis, and a second investigator independently coded the studies prior to data being entered into the statistical analysis software.

Potential study characteristics included.

The present meta-analysis included potential moderating variables when available; however, the specific variables were limited to those that were reported by the studies. Sample characteristics including gender, age, and location from each study were included when available. Other potential moderating variables I considered were lead level and symptom measure (parents vs. teachers report, objective test).

Operationalization

The variable of lead exposure is defined as the presence of lead in the child's system, which has resulted in a lead level greater than 0 μg/dL. The lead level itself can be measured through a blood, tooth, or hair sample. For purposes of the present meta-analysis, the ADHD symptom variables of inattention and hyperactivity/impulsivity were defined as the presence of a standardized measure of those symptoms. Although the studies included in the present meta-analysis may differ in the instrument used to measure ADHD symptoms, it was assumed that all studies were measuring a similar underlying construct of inattention and hyperactivity/impulsivity. The underlying construct of inattention is assumed to include symptoms such as difficulty concentrating,

distractibility, and disorganization. The underlying construct of hyperactivity/impulsivity is assumed to include symptoms such as over activity, difficulty sitting still, and talking excessively.

Data Analysis Plan

Software used for analyses.

I conducted the statistical analyses for the present meta-analysis using the Comprehensive Meta Analysis Version 3.0 software. This software was developed by Michael Borenstein, Larry Hedges, Julian Higgins, and Hannah Rothstein and is available for purchase through the website www.meta-analysis.com.

Research question and hypotheses.

The research question to be answered by the present study investigated the relationship of lead exposure and ADHD symptoms and was as follows:

Research Question: Based on a meta-analysis of available and selected research on the relationship between lead exposure (measured lead levels greater than 0 μg/dL) and ADHD symptoms (e.g., hyperactivity, inattention, etc.), is there a significant multi-study estimated effect size and if so, what is its magnitude?

H_o: There is no significant multi-study estimated effect size for the relationship between lead exposure and ADHD symptoms among children.

H_1: There is a significant multi-study estimated effect size for the relationship between lead exposure and ADHD symptoms among children.

Standard mean difference effect size statistic.

Although the primary studies in this area used a variety of statistical methods (e.g., correlation, odds ratio, t-test, ANOVA/ANCOVA), it is assumed that, despite the use of different statistical methods, all primary studies included estimated the same effect of lead exposure on ADHD symptoms. Thus, I made attempts to use all available studies in this meta-analysis regardless of the statistic used in the primary study. Despite these efforts, there were a number of studies that had to be excluded for statistical reasons.

The present meta-analysis used the *d* family of effect sizes, which typically measures the difference between two groups on a certain measure. There are three effect size statistics included within the *d* family; Glass's delta, Cohen's *d*, and Hedge's g (Card, 2012), and for the present meta-analysis, Cohen's *d* was utilized. The standard formula for calculating Cohen's *d* is the difference between means of two groups divided by the standard deviation of the population. This particular statistic is useful for meta-analysis because it is possible for Cohen's *d* to be calculated post hoc from a wide variety of other statistical tests, including t-test, one-way ANOVA, and correlation coefficients (Lipsey & Wilson, 2001). Due to the variability in statistics used in the primary research in this area, the choice of an effect size statistic that can be calculated from several statistics is important to allow the maximum number of studies to be included in the meta-analysis. It should be noted that due to the inclusion of studies with various statistical methods, the estimated multi-study effect size was reflective of a general relationship between lead exposure and ADHD, and not a specifically causal or correlational relationship.

Lipsey and Wilson (2001) provide formulas for the direct calculation or estimation of the standardized mean difference effect size (ES_{sm}) from other statistics. The estimate of ES_{sm} from a correlation (r) can be calculated as follows:

$$ES_{sm} = \frac{2r}{\sqrt{1 - r^2}}$$

To calculate the ES_{sm} from an ANOVA the formulas when the sample size of each group is known and when the total sample size is known are as follows, respectively:

$$ES_{sm} = \sqrt{\frac{F(n_1 + n_2)}{n_1 n_2}} \text{ or } ES_{sm} = 2\sqrt{\frac{F}{N}}$$

To calculate the ES_{sm} from a t-test the formulas when the sample size of each group is known and when the total sample size is known are as follows, respectively:

$$ES_{sm} = t\sqrt{\frac{(n_1 + n_2)}{n_1 n_2}} \text{ or } ES_{sm} = \frac{2t}{\sqrt{N}}$$

By using one standardized measure of effect size the results from studies that differed in variable definitions and specific psychometric measures can be synthesized in one meta-analysis (Lipsey & Wilson, 2001). For example, in the present meta-analysis this standard measure of effect size allowed studies to be compared that used various measures of inattention and hyperactivity/impulsivity (e.g., parent report, teacher report, observation, objective test). It was anticipated that findings from these measures were most likely reported as T-scores, scaled scores, or standard scores and thus, standardization is critical for combining of these results.

Common corrections to the effect size statistic were considered depending on the studies included in the present meta-analysis in order to address possible biases (Lipsey

& Wilson, 2001). First, studies based on small sample sizes tend to result in a slightly increased effect size value. Second, if extreme outliers in the distribution of effect sizes are present either removing them from the analysis or adjusting them needed to be considered. A close examination of the study characteristics was conducted to attempt to determine the cause of the outlier and thus, determine whether removing the outlier from the meta-analysis or adjusting it was most appropriate (Lipsey & Wilson, 2001).

Planned data analysis.

I used a fixed model for combining effect sizes in the present meta-analysis. After all effect sizes for the included studies were calculated, the weighted mean effect size was calculated. The formula for computed the weighted mean effect size is

$$\overline{ES} = \frac{\Sigma(\omega_i ES_i)}{\Sigma\omega_i}.$$

In this formula, the effect size from each study (ES_i) was multiplied by its inverse variance weight (ω_i) and then summed. The sum was then divided by the sum of the inverse variance weights to produce the mean effect size (Lipsey & Wilson, 2001).

A 95% confidence interval for the mean effect size was then calculated, which indicated the range of effect sizes that the true effect size for the population was likely to fall within 95% probability (Lipsey & Wilson, 2001). To compute the confidence interval the standard error of measurement for the mean effect size had to first be calculated. The formula to compute the standard error is

$$SE_{\overline{ES}} = \sqrt{\frac{1}{\Sigma\omega_i}}.$$

The standard error of measurement for the mean effect size ($SE_{\overline{ES}}$) was then multiplied by a critical z-value determined by the chosen confidence level. This value was then subtracted and added to the mean effect size to determine the lower and upper bounds of the confidence interval.

Lastly, a homogeneity analysis was conducted to determine if the distribution of effect sizes was within the expected range given sampling error (Lipsey & Wilson, 2001). The Q statistic was used to compute homogeneity and the formula is

$$Q = \sum \omega_i (ES_i - \overline{ES})^2.$$

Interpreting Cohen's d.

There are commonly used standards for interpreting the magnitude of the effect size that were established by Cohen (as cited in Lipsey & Wilson, 2001). Based on those standards the following ranges were used for interpretation of Cohen's *d* in the present meta-analysis: small $ES \leq 0.20$, medium = 0.50, and large $ES \geq 0.80$. The confidence interval was then used to determine if the null hypothesis was accepted or rejected for the research question (Borenstein et al., 2009); in other words whether the multi-study estimated effect size of lead exposure on ADHD symptoms reached significance. If the value of the null hypothesis was within the 95% confidence interval *p* was greater than 0.05 and the null hypothesis was accepted. If the value of the null hypothesis was outside the 95% confidence interval *p* was less than 0.05 and the null hypothesis was rejected. For a fixed effects model the null hypothesis is that the true effect size is zero (Borenstein et al., 2009).

Threats to Validity

It is important to note that a meta-analysis may contain the same threats to validity that are present in the original studies. There are some threats to validity that a meta-analysis can overcome such as inadequate power. Others, however, are transferred from the original studies to the meta-analysis. For instance, if the original studies used psychometric measures with poor validity that threat was maintained in the meta-analysis. During the coding process for the studies included in the meta-analysis I attempted to identify any threats to validity, but no significant validity concerns were identified aside from studies with small samples.

Ethical Procedures

I received approval for the present meta-analysis from the Institutional Review Board (IRB) at Walden University. The data collected for the present meta-analysis was collected through review of primary studies and thus, the meta-analysis itself did not have any human participants. The data collected from the primary studies included statistical results and sample sizes, which were anonymous in nature and I, nor the secondary researcher, had access to any confidential data from the primary studies. Nonetheless, the data collected for the present meta-analysis were housed in a locked filing cabinet I maintained and the electronic data was housed on my computer with password protection.

The primary studies included in the present meta-analysis were conducted on human subjects and I made an assumption that these studies met appropriate ethical standards and received approval from their receptive IRBs. If any ethical concerns were

identified in the primary studies they were to be discussed when interpreting the results of the present meta-analysis. I did not, however, identify any ethical concerns in the reviewed studies.

Summary

In Chapter 3 I provided an explanation of the methodology that was used for the present meta-analysis, as well as some details on data collection, coding, and analysis. First, I discussed the justification for the methodology and then presented the research question and hypothesis. I followed this by an outline of the literature search procedures for the meta-analysis and the exclusion and inclusion criteria for studies. Next I outlined the statistical analyses for the present meta-analysis. I determined that Cohen's *d* would be the measure of effect size used, and I described the planned analyses, as well as interpretation of Cohen's *d*. Lastly, I briefly discussed any threats to validity.

I provide more detailed information on the data collection and the sample included in the meta-analysis in Chapter 4. I also present the results of all statistical analyses. I conclude by discussing a summary of the answers to the research question.

Chapter 4: Results

Introduction

As presented in the preceding chapters, there is strong evidence of a relationship between lead exposure and ADHD (see Boucher et al., 2012; Chiodo et al., 2004; Cho et al., 2010; Nicolescu et al., 2010; Plusqellec et al., 2010). The purpose of this study was to examine and potentially help quantify this relationship. The specific aim of this quantitative meta-analysis was to estimate the magnitude of the effect size of childhood lead exposure on ADHD symptoms through a meta-analysis, as well as determine if there are any moderating variables (e.g., age of exposure, gender, etc.) that could be facilitating variability in research results.

The main research question was, as follows: Based on a meta-analysis of available and selected research on the relationship between lead exposure (measured as lead levels greater than 0 μg/dL) and ADHD symptoms (e.g., hyperactivity, inattention, etc.), is there a significant multi-study estimated effect size, and if so, what is its magnitude?

H_o: There is no significant multi-study estimated effect size for the relationship between lead exposure and ADHD symptoms among children.

H_1: There is a significant multi-study estimated effect size for the relationship between lead exposure and ADHD symptoms among children.

The purpose of this chapter is to present the results of this meta-analysis. First, I review the search method by which the research studies included were found, and then present the number of studies meeting inclusion and exclusion criteria. I then present

descriptive data regarding the sample of included studies and comparison to excluded studies. Lastly, I present the results of the meta-analysis and main research question.

Data Collection

Search Methods

The search methods I used are described in detail in Chapter 2, and I did not deviate from these methods. I conducted the search between May 2017 and December 2017. First, I conducted the electronic database searches using those key terms presented in Chapter 2. Once I completed all electronic searches, I subjected those studies identified as relevant to forward and backward searching. Second, I reviewed conference programs; however, this search was limited because some past programs were not accessible. Most conferences only provide online access to the most recent conference. Third, I reviewed the authors of all identified studies, and contacted several to determine if any additional unpublished research relevant to the current meta-analysis existed. To date, I have not received any responses from contacted authors.

Coding

I and the secondary researcher systematically coded all included studies as described in the coding manual referenced in Chapter 3. I and the secondary researcher then compared the coding for consistency. Discrepancies were discussed and the final data were agreed upon by both researchers.

For studies that included multiple measures of ADHD symptoms, I made a decision regarding which data would be used in the meta-analysis. I based this decision on a variety of information. First, I reviewed the studies to determine if the necessary

information to include in the meta-analysis was provided for all measures, and if not, I chose the measure based on this availability. Next, I gave priority to the measure that included the largest number of participants. Lastly, since the majority of studies included were based on a parent rating, I chose this type of measure over other rating forms.

Inclusion Criteria

I found all the studies identified as relevant through electronic database searches and subsequent backward and forward searches. I then thoroughly read and coded these research articles for the inclusion and exclusion criteria as outlined in Chapter 2. In total, I identified 74 studies as relevant to the current topic of lead exposure and ADHD symptoms based on title and abstract review. After I more thoroughly reviewed these for inclusion/exclusion criteria, I found 20 studies that meet the inclusion criteria for this meta-analysis.

Of the 74 identified studies, the largest number were excluded for not having an appropriate measure of ADHD symptoms. Twenty-five studies were excluded for failure to meet this criterion. When I more thoroughly reviewed these studies, many studies were excluded because they included a measure of attention that was conflated with measures of other abilities, such as using a digit span subtest as a measure of attention or only providing an overall behavior score from parent or teacher rating scales.

Of the 74 identified studies, only four did not include an appropriate measure of lead exposure. In three cases, the researchers used lead exposure as a confounding variable or covariate instead of the primary measure in the study. In the other excluded study, only a measure of prenatal lead exposure was included.

Of the 74 identified studies, eight were excluded because they did not include enough statistical information for the necessary data to be calculated. An additional 17 studies were excluded for use of a type of statistical analysis that could not be included in the current meta-analysis. A regression analysis was used in the majority of these studies, while one used statistical equation modeling.

Population Characteristics

I determined descriptive characteristics for the 45 studies that included both a measure of lead exposure and a measure of overall ADHD, inattentive, and/or hyperactive/impulsive symptoms. Only four studies (9%) included measures of overall ADHD, inattentive, and hyperactive/impulsive symptoms; three studies (7%) included only a measure of overall ADHD symptoms. Nineteen of the studies (42%) included both a measure of inattentive and hyperactive/impulsive symptoms, 13 (29%) included only a measure of attentive symptoms, and six (13%) included only a measure of hyperactive/impulsive symptoms. These percentages are slightly different than those in the final meta-analysis sample. Of the 20 studies included in the meta-analysis, four (20%) included measures of all symptoms categories, nine (45%) included a measure of both inattention and hyperactivity/impulsivity symptom categories, three (15%) included only a measure of overall ADHD symptoms, three (15%) included only a measure of inattention, and one (5%) included only a measure of hyperactivity/impulsivity.

These studies used a variety of measures of lead exposure including blood, urine, hair, and teeth, although the majority of studies used a blood sample to determine lead exposure (69%). Measures of overall ADHD, inattentive, and hyperactive/impulsive

symptoms were measured using ratings forms completed by parents, teachers, or study examiners. Several studies also used objective psychological tests to measure these symptoms, most often a continuous performance test. Thirteen of the studies included multiple measures of symptoms. The most common measure used was a rating form completed by parents with 25 of these studies including such a measure. Seventeen studies included a rating form completed by teachers, 13 studies included an objective test, and only 4 included a rating form completed by an examiner.

When considering only those studies included in the final meta-analysis, the majority continued to use a rating form completed either a parent (11 studies) or a teacher (seven studies). Only two studies included a rating form completed by an examiner and three included an objective test. There was also one study where it was not clearly indicated who completed the rating form. Descriptive information regarding these studies is provided in Table 1.

These studies were also examined in regards to whether they found a significant relationship between lead exposure and the symptoms categories examined. First, of the seven studies that included a measure of overall ADHD symptoms all indicated there was a significant relationship. Also, all seven of these studies were included in the final meta-analysis.

Second, of the 36 studies that included a measure of inattention 22 had a significant relationship between lead exposure and inattention. Of the 16 studies that included a measure of inattention and were included in the final meta-analysis, 13 had a significant relationship between lead exposure and inattention. Overall 61% of these

studies showed a significant relationship, where as 81% showed a significant relationship when only those studies included in the final meta-analysis were considered.

Third, of the 29 studies that included a measure of hyperactivity/impulsivity, 18 had a significant relationship between lead exposure and hyperactivity/impulsivity. Of the 14 studies that included a measure of hyperactivity/impulsivity and were included in the final meta-analysis, nine had a significant relationship between lead exposure and hyperactivity/impulsivity. Overall 62% of these studies showed a significant relationship and 64% showed a significant relationship when only those studies included in the final meta-analysis were examined.

When overall percentages are examined, a very similar percentage of studies had a significant relationship between lead exposure and inattention that had a significant relationship between lead exposure and hyperactivity/impulsivity. This percentage was consistent when considering only the hyperactivity/impulsivity symptom studies that were included in the final meta-analysis. When considering only the inattention studies, however, the percentage of studies showing a significant relationship increased. Descriptive information regarding these studies is also provided in Table 1.

Table 1

Descriptive Information for All Studies

Title	Lead measure	Symptoms	Measure type	Significance
Relationships Between Blood Lead, Behaviour, Psychometric, and Neuropsychological Test Performance in Young Children[a]	Blood	Inattention; hyperactive/impulsive	Objective test	Inattention - S; hyper/impul - NS
A Longitudinal Study of Dentine Lead Levels, Intelligence, School Performance and Behaviour, Part III. Dentine Lead Levels and Attention/Activity [a]	Teeth	Overall; inattention; hyperactive/impulsive	Parent rating	Overall - S; inattention - S; hyper/impul - S;
Blood Lead, Intelligence, Reading Attainmnet, and Behaviour in Eleven Year Old Children in Dunedin, New Zealand[a]	Blood	Inattention; hyperactive/impulsive	Parent rating	Inattention - S; hyper/impul - S
Teachers' Ratings of Children's Behaviour in Relation to Blood Lead Levels [a]	Blood	Inattention; hyperactive/impulsive	Teacher rating	Inattention - S; hyper/impul - S
Effects of Early Childhood Lead Exposure on Academic Performance and Behaviour of School Age Children [a]	Blood	Inattention; hyperactive/impulsive	Rating (unclear who completed)	Inattention - NS; hyper/impul - NS
Blood Lead Levels and Specific Attention Effects in Young Children [a]	Blood	Inattention; hyperactive/impulsive	Objective test	Inattention - S; hyper/impul - NS
Low-Level Lead Exposure, Executive Functioning, and Learning in Early Childhood [a]	Blood	Inattention	Examiner rating	Inattention - S
Early Dentine Lead Levels and Subsequent Cognitive and Behavioural Development [a]	Tooth	Inattention	Parent & teacher rating	Inattention - S
Variation in an Iron Metabolism Gene Moderates the Association Between Blood Lead Levels and Attention-Deficit/Hyperactivity Disorder in Children [a]	Blood	Inattention; hyperactive/impulsive	Parent rating	Inattention - S; hyper/impul - S
Neurodevelopmental Effects of Postnatal Lead Exposure at Very Low Levels [a]	Blood	Overall; inattention; hyperactive/impulsive	Teacher rating	Overall - S; inattention - S; hyper/impul - NS;

Title	Lead measure	Symptoms	Measure type	Significance
Attention-Deficit/Hyperactivity Symptoms in Preschool Children from an E-waste Recycling Town: Assessment by the Parent Report Derived from DSM-IV [a]	Blood	Overall; inattention; hyperactive/impulsive	Parent rating	Overall - S; inattention - S; hyper/impul - S;
The Relationship between Lead Exposure, Motor Function, and Behaviour in Inuit Preschool Children [a]	Blood	Inattention; hyperactive/impulsive	Examiner rating	Inattention - NS; hyper/impul - S
The Relationship between Hair Zinc and Lead Levels and Clinical Features of Attention-Deficit Hyperactivity Disorder[a]	Hair	Inattention; hyperactive/impulsive	Objective test	Inattention - S; hyper/impul - S
Effects of Blood Lead and Cadmium Levels on the Functioning of Children with Behaviour Disorders in the Family Environment[a]	Blood	Inattention; hyperactive/impulsive	Parent rating	Inattention - NS; hyper/impul - S
Pre- and Postnatal Lead Exposure and Behavior Problems in School-Aged Children[a]	Tooth	Inattention	Teacher rating	Inattention - S
Lead and Hyperactivity Revisited: An Investigation of Nondisadvantaged Children[a]	Urine	Hyperactive/impulsive	Parent & teacher rating	Hyper/impul - NS
Association Between Lower Level Lead Concentrations and Hyperactivity in Children[a]	Urine	Overall	Parent rating	Overall - S
Hair Lead Levels Related to Children's Classroom Attention-Deficit Behavior[a]	Hair	Overall	Parent & teacher rating	Overall - S
Low Blood Levels of Lead and Mercury and Symptoms of Attention Deficit Hyperactivity in Children: A Report of the Children's Health and Environment Research (CHEER) [a]	Blood	Overall	Parent rating	Overall - S
Environmental Exposure to Lead, but Not Other Neurotoxic Metals, Related to Core Elements of ADHD in Romanian Children: Performance and Questionnaire Data[a]	Blood	Overall; inattention; hyperactive/impulsive	Parent & teacher rating	Overall - S; inattention - S; hyper/impul - S;
Changed Plasma Levels of Zinc and Copper to Zinc Ratio and Their Possible Associations with Parent- and Teacher-Rated Symptoms in Children with Attention-Deficit Hyperactivity Disorder	Blood	Inattention; hyperactive/impulsive	Parent & teacher rating	Inattention - NS; hyper/impul - NS
Behavioral and Neurological Effects of Symptomatic and Asymptomatic Lead Exposure in Children	Blood	Hyperactive/impulsive	Parent rating	Hyper/impul - S

Title	Lead measure	Symptoms	Measure type	Significance
Blood-Lead Levels and Children's Behaviour - Results from the Edinburgh Lead Study	Blood	Hyperactive/impulsive	Teacher rating	Hyper/impul - S
Prenatal Methylmercury, Postnatal Lead Exposure, and Evidence of Attention Deficit/Hyperactivity Disorder among Inuit Children in Arctic Quebec	Blood	Inattention	Teacher rating	Inattention - NS
Effect of Environmental Exposure to Lead and Tobacco Smoke on Inattentive and Hyperactive Symptoms and Neurocognitive Performance in Children	Blood	Inattention; hyperactive/impulsive	Parent & teacher rating; objective test	Inattention - S; hyper/impul - S
Environmental Lead Exposure and Attention Deficit/Hyperactivity Disorder Symptom Domains in a Community Sample of South Korean School-Age Children	Blood	Inattention; hyperactive/impulsive	Parent & teacher rating; objective test	Inattention - NS; hyper/impul - S
Childhood Blood Lead Levels and Symptoms of Attention Deficit Hyperactivity Disorder (ADHD): A Cross-Sectional Study of Mexican Children	Blood	Inattention; hyperactive/impulsive	Parent rating	Inattention - NS; hyper/impul - S
Confirmation and Extension of Association of Blood Lead with Attention-Deficit/Hyperactivity Disorder (ADHD) and ADHD Symptom Domains at Population-Typical Exposure Levels	Blood	Inattention; hyperactive/impulsive	Parent & teacher rating	Inattention - S (only teacher); hyper/impul - S (only parent)
Lead Exposure and Behavior Among Young Children in Chennai, India	Blood	Inattention; hyperactive/impulsive	Teacher rating	Inattention - S; hyper/impul - NS
The Conjoint Influence of Home Enriched Environment and Lead Exposure on Children's Cognition and Behaviour in a Mexican Lead Smelter Community	Blood	Hyperactive/impulsive	Parent & teacher rating	Hyper/impul - S
Response Inhibition and Error Monitoring during a Visual Go/No-Go Task in Inuit Children Exposed to Lead, Polychlorinated Biphenyls, and Methylmercury	Blood	Inattention; hyperactive/impulsive	Objective test	Inattention - S; hyper/impul - S
Mineral Status, Toxic Metal Exposure and Children's Behaviour	Hair	Inattention	Parent rating	Inattention - NS
Blood Lead Concentrations and Children's Behavioral and Emotional Problems: A Cohort Study	Blood	Inattention	Parent & teacher rating	Inattention - NS
Lead Exposure, Attentional Outcomes, and Socioenvironmental Influences	Blood	Inattention	Parent rating; objective test	Inattention - NS

Title	Lead measure	Symptoms	Measure type	Significance
Contribution of Maternal Smoking During Pregnancy and Lead Exposure to Early Child Behavior Problems	Blood	Inattention	Parent rating	Inattention - NS
A Pilot Study of Blood Lead Levels and Neurobehavioral Function in Children Living in Chennai, India	Blood	Inattention; hyperactive/impulsive	Teacher rating	Inattention - NS; hyper/impul - NS
Neurobehavioral Function and Low-level Metal Exposure in Adolescents	Blood	Inattention	Objective test	Inattention - NS
Neuropsychological Dysfunction in Children with Chronic Low-level Lead Absorption	Blood	Hyperactive/impulsive	Examiner rating	Hyper/impul - NS
Early Exposure to Lead and Neuropsychological Outcome in Adolescence	Blood	Inattention	Objective test	Inattention - S (only boys)
Lifetime Low-level Exposure to Environmental Lead and Children's Emotional and Behavioral Development at Ages 11-13 Years: The Port Pirie Cohort Study	Blood	Inattention	Parent rating	Inattention - S (for girls only)
Impairment of Psychological Functions in Children Environmentally Exposed to Lead	Blood	Inattention	Objective test	Inattention - S
The Association Between Lead and Micronutrient Status, and Children's Sleep, Classroom Behavior, and Activity	Blood	Inattention; hyperactive/impulsive	Examiner rating; objective test	Inattention - NS; Hyper/Impul - NS
Failure to Find Hyperactivity in Preschool Children with Moderately Elevated Lead Burden	Blood	Hyperactive/impulsive	Parent rating; objective test	Hyper/Impul - NS
Cognitive and sensorimotor functions in 6-year-old children in relation to lead and mercury levels: Adjustment for intelligence and contrast sensitivity in computerized testing	Blood	Inattention; hyperactive/impulsive	Objective test	Inattention - S; Hyper/Impul - S
Hair Element Concentrations and Young Children's Classroom and Home Behavior	Blood	Inattention	Parent rating	Inattention - S

Note. S = Significant, NS = nonsignificant, Hyper/Impul = hyperactivity/impulsivity.
[a]Studies that were included in the meta-analysis.

Chapter 4: Results

Descriptive Statistics

Overall ADHD symptom sample.

Seven studies were included in the final meta-analysis to determine the relationship between overall symptoms of ADHD (both inattention and hyperactive/impulsive symptoms combined). The measures included in these studies to assess overall ADHD symptoms were standardized ratings completed by either a parent and/or teacher. The data used in the meta-analysis came from parent ratings for four of the studies and teacher ratings for two of the studies. One study included both parent and teacher ratings and it did not clearly indicate which rating form the presented data came from. Measures of lead included use of the participants' blood, hair, urine, or teeth to measure lead exposure.

These seven studies included a total of 1865 participants that ranged in age from 3 years to 12 years. The majority of studies did not provide a breakdown of participants by gender, but for those that did the majority of participants were male. Of those studies that provided gender information, males ranged from 51% to 61% of the sample.

Locations of the studies were international and thus, included a wide range of ethnic and racial groups. Given the common causes of lead exposure, many study samples were of low socioeconomic status. Table 2 provides descriptive data regarding the sample of studies examining overall ADHD symptoms and lead exposure.

Table 2

Descriptive Information for Studies Included in Analysis of Overall ADHD Symptoms

Title	Author (Year)	Sample Size	Males	Ages	Location
Association Between Lower Level Lead Concentrations and Hyperactivity in Children	David (1974)	91	55	mean 7 years (no spread given)	Brooklyn, NY, USA
Hair Lead Levels Related to Children's Classroom Attention-Deficit Behavior	Tuthill (1996)	277	NR	6.5-7.5 years	Western Massachusetts City, USA
Low Blood Levels of Lead and Mercury and Symptoms of Attention Deficit Hyperactivity in Children: A Report of the Children's Health and Environment Research (CHEER)	Ha, Kwon, Lim, Jee, Hong, Leem, Sakong, Bae, Hong, Roh, & Jo (2009)	104	NR	6-10 years	South Korea
Environmental Exposure to Lead, but Not Other Neurotoxic Metals, Related to Core Elements of ADHD in Romanian Children: Performance and Questionnaire Data	Nicolescu, Petcu, Cordeanu, Fabritius, Schlumpf, Krebs, Kramer, & Winneke (2010)	83	42	8-12 years	Bucharest and Pantelimon, Romania
Attention-Deficit/Hyperactivity Symptoms in Preschool Children from an E-waste Recycling Town: Assessment by the parent report derived from DSM-IV	Zhang, Huo, Ho, Chen, Wang, Wang, & Ma (2015)	243	141	3-7 years	Guangdong, China
Neurodevelopmental Effects of Postnatal Lead Exposure at Very Low Levels	Chiodo, Jacobson, & Jacobson (2004)	179	NR	7.5 years	Inner city, USA
A Longitudinal Study of Dentine Lead Levels, Intelligence, School Performance and Behaviour, Part III. Dentine Lead Levels and Attention/Activity	Fergusson, Fergusson, Horwood, & Kinzett (1988)	888	NR	8-9years	Christchurch, New Zealand

Note. NR = Not reported.

Inattention symptoms sample.

Sixteen studies were included in the final meta-analysis to determine the relationship between lead exposure and inattentive symptoms. As discussed above, the measures included in these studies to assess inattention were standardized ratings completed by either a parent or teacher, rating completed by the examiner, or an objective test of attention. Measures of lead included use of the participants' blood, hair, or teeth to

measure lead exposure, but the majority of studies determined lead exposure through blood test.

These 16 studies included a total of 6443 participants that ranged in age from 2 years to 18 years. The majority of studies did not provide a breakdown of participants by gender, but for those that did the majority of participants with male. Of those studies that provided gender information, males ranged from 50% to 83% of the sample. The majority of study samples included children between 5 years and 13 years old. Three studies included adolescents and three studies included preschool age children (2-4 years).

Locations of the studies were international and thus, included a wide range of ethnic and racial groups. Given the common causes of lead exposure, many study samples were of low socioeconomic status. Table 3 provides descriptive data regarding the sample of studies examining inattention symptoms and lead exposure.

Table 3

Descriptive Information for Studies Included in Analysis of Inattentive Symptoms

Title	Author (Year)	Sample size	Males	Ages	Location
Relationships between blood lead, behaviour, psychometric and neuropsychological test performance in young children	Harvey, Hamlin, Kumar, Morgan, & Spurgeon (1988)	98	NR	5.5years	Birmingham (inner city), UK
A Longitudinal Study of Dentine Lead Levels, Intelligence, School Performance and Behaviour, Part III. Dentine Lead Levels and Attention/Activity	Fergusson, Fergusson, Horwood, & Kinzett (1988)	888	NR	8-9years	Christchurch, New Zealand
Blood Lead, Intelligence, Reading Attainment, and Behaviour in Eleven Year Old Children in Dunedin, New Zealand	Silva, Hughes, Williams, & Faed (1988)	535	NR	11 years	Dunedin, New Zealand

Title	Author (Year)	Sample size	Males	Ages	Location
Blood Lead Levels and Specific Attention Effects in Young Children	Chido, Covington, Sokol, Hannigan, Jannise, Ager, Greenwald, & Delaney-Black (2007)	464	NR	7 years	Detroit, MI, USA
Early Dentine Lead Levels and Subsequent Cognitive and Behavioural Development	Fergusson, Horwood, & Lynskey (1993)	891	NR	6-8 years for lead; 12-13 years for attention measure	Christchurch, New Zealand
Variation in an Iron Metabolism Gene Moderates the Association Between Blood Lead Levels and Attention-Deficit/Hyperactivity Disorder in Children	Nigg, Elmore, Natarajan, Friderici, & Nikolas (2016)	269	156 approxi mately	6-17 years	Michigan, USA
Neurodevelopmental Effects of Postnatal Lead Exposure at Very Low Levels	Chiodo, Jacobson, & Jacobson (2004)	164	NR	7.5 years	Inner city, USA
The Relationship between Lead Exposure, Motor Function, and Behaviour in Inuit Preschool Children	Fraser, Muckle, & Despres (2006)	101	NR	5 years	Nunavik, Quebec, Canada
The Relationship between Hair Zinc and Lead Levels and Clinical Features of Attention-Deficit Hyperactivity Disorder	Shin, Kim, Oh, Shin, & Lim (2014)	41	34	5-15 years	urban areas of Seoul, Korea
Effects of Blood Lead and Cadmium Levels on the Functioning of Children with Behaviour Disorders in the Family Environment	Szkup-Jablonska, Karakiewicz, Grochans, Jurczak, Nowak-Starz, Rotter, & Prokopowicz (2012)	73	NR	2-18 years	Szczecin, Poland
Low-Level Lead Exposure, Executive Functioning, and Learning in Early Childhood	Canfield, Kreher, Cornwell, & Henderson (2003)	157	82 approxi mately	4.5 years	Rochester, NY, USA
Attention-Deficit/Hyperactivity Symptoms in Preschool Children from an E-waste Recycling Town: Assessment by the parent report derived from DSM-IV	Zhang, Huo, Ho, Chen, Wang, Wang, & Ma (2015)	243	141	3-7 years	Guangdong, China
Environmental Exposure to Lead, but Not Other Neurotoxic Metals, Related to Core Elements of ADHD in Romanian Children: Performance and Questionnaire Data	Nicolescu, Petcu, Cordeanu, Fabritius, Schlumpf, Krebs, Kramer, & Winneke (2010)	83	42 approxi mately	8-12 years	Bucharest and Pantelimon, Romania
Effects of Early Childhood Lead Exposure on Academic Performance and Behaviour of School Age Children	Chandramouli, Steer, Ellis, & Emond (2009)	488	276	2.5 years for blood; 7-8 years behavior measures	Bristol, UK
Pre- and Postnatal Lead Exposure and Behavior Problems in School-Aged Children	Bellinger, Leviton, Allred, & Rabinowitz (1994)	1782	898	6 years	Boston, MA, USA

Title	Author (Year)	Sample size	Males	Ages	Location
Teachers' Ratings of Children's Behaviour in Relation to Blood Lead Levels	Yule, Urbanowicz, Lansdown, & Millar(1984)	166	NR	6-12 years	London, UK

Note. NR= Not reported

Hyperactive/impulsive symptom sample.

Fourteen studies were included in the final meta-analysis to determine the relationship between lead exposure and hyperactive/impulsive symptoms. The majority of studies included in this analysis were also included in the analysis of inattention symptoms, with only one additional study included that only examined hyperactivity. The measures included in these studies to assess hyperactive/impulsive symptoms were standardized ratings completed by either a parent or teacher, rating completed by the examiner, or an objective test of attention. Measures of blood lead included use of the participants' blood, hair, or teeth to measure lead exposure, but the majority of studies determine lead exposure through blood test.

These 14 studies included a total of 3788 participants that ranged in age from 2 years to 18 years. The majority of studies did not provide a breakdown of participants by gender, but for those that did the majority of participants with male. Of those studies that provided gender information, males ranged from 51% to 83% of the sample. The majority of study samples include children between 5 years and 12 years old. Three studies included adolescents and two studies included preschool age children (2-4 years).

Locations of the studies were international and thus, included a wide range of ethnic and racial groups. Given the common causes of lead exposure, many study

samples were of low socioeconomic status. Table 4 provides descriptive data regarding the sample of studies examining hyperactive/impulsive symptoms and lead exposure.

Table 4

Descriptive Information for Studies Included in Analysis of Hyperactive/Impulsive Symptoms

Title	Author (Year)	Sample size	Males	Ages	Location
Relationships between blood lead, behaviour, psychometric and neuropsychological test performance in young children	Harvey, Hamlin, Kumar, Morgan, & Spurgeon (1988)	99	NR	5.5 years	Birmingham (inner city), UK
A Longitudinal Study of Dentine Lead Levels, Intelligence, School Performance and Behaviour, Part III. Dentine Lead Levels and Attention/Activity	Fergusson, Fergusson, Horwood, & Kinzett (1988)	888	NR	8-9years	Christchurch, New Zealand
Blood Lead, Intelligence, Reading Attainmnet, and Behaviour in Eleven Year Old Children in Dunedin, New Zealand	Silva, Hughes, Williams, & Faed (1988)	535	NR	11 years	Dunedin, New Zeland
Blood Lead Levels and Specific Attention Effects in Young Children	Chido, Covington, Sokol, Hannigan, Jannise, Ager, Greenwald, & Delaney-Black (2007)	466	NR	7 years	Detroit, MI, USA
Variation in an Iron Metabolism Gene Moderates the Association Between Blood Lead Levels and Attention-Deficit/Hyperactivity Disorder in Children	Nigg, Elmore, Natarajan, Friderici, & Nikolas (2016)	269	156 approximately	6-17 years	Michigan, USA
Neurodevelopmental Effects of Postnatal Lead Exposure at Very Low Levels	Chiodo, Jacobson, & Jacobson (2004)	169	NR	7.5 years	Inner city, USA
The Relationship between Lead Exposure, Motor Function, and Behaviour in Inuit Preschool Children	Fraser, Muckle, & Despres (2006)	101	NR	5 years	Nunavik, Quebec, Canada
The Relationship between Hair Zinc and Lead Levels and Clinical Features of Attention-Deficit Hyperactivity Disorder	Shin, Kim, Oh, Shin, & Lim (2014)	41	34	5-15 years	urban areas of Seoul, Korea
Effects of Blood Lead and Cadmium Levels on the Functioning of Children with Behaviour Disorders in the Family Environment	Szkup-Jablonska, Karakiewicz, Grochans, Jurczak, Nowak-Starz, Rotter, & Prokopowicz (2012)	73	NR	2-18 years	Szczecin, Poland
Attention-Deficit/Hyperactivity Symptoms in Preschool Children from an E-waste Recycling Town: Assessment by the parent report derived from DSM-IV	Zhang, Huo, Ho, Chen, Wang, Wang, & Ma (2015)	243	141	3-7 years	Guangdong, China

Title	Author (Year)	Sample size	Males	Ages	Location
Environmental Exposure to Lead, but Not Other Neurotoxic Metals, Related to Core Elements of ADHD in Romanian Children: Performance and Questionnaire Data	Nicolescu, Petcu, Cordeanu, Fabritius, Schlumpf, Krebs, Kramer, & Winneke (2010)	83	42 approximately	8-12 years	Bucharest and Pantelimon, Romania
Effects of Early Childhood Lead Exposure on Academic Performance and Behaviour of School Age Children	Chandramouli, Steer, Ellis, & Emond (2009)	488	276	2.5 years for blood; 7-8 years bx measures	Bristol, UK
Teachers' Ratings of Children's Behaviour in Relation to Blood Lead Levels	Yule, Urbanowicz, Lansdown, & Millar (1984)	166	NR	6-12 years	London, UK
Lead and Hyperactivity Revisited: An Investigation of Nondisadvantaged Children	Gittelman & Eskenazi (1983)	167	NR	6-12years	Suburban areas of NYC, USA

Note. NR = Not Reported

Statistical Assumptions

The primary studies included in the analysis used a variety of statistical methods in the original analyses and measures of ADHD symptoms. I made an assumption that despite the use of different statistical analyses and measurements, all the included primary studies are estimating the same effect of lead exposure on ADHD symptoms. Given the inclusion of studies with different statistical analyses, I also made an assumption that the estimated multi-study effect size is reflective of a general relationship between lead exposure and ADHD, and not a specifically causal or correlational relationship.

Primary Analysis

Based on a meta-analysis of the relationship between lead exposure (measured lead levels greater than 0 μg/dL) and overall ADHD symptoms, the estimated standard mean difference effect size is 0.363. The standard error is 0.048 and there is a 95% confidence interval of 0.269 to 0.457. Thus, the null hypothesis is rejected because zero is

not within the confidence interval of the estimated effect size (Borenstein et al., 2009). Figure 1 provides a forest plot of the estimated effect size and individual effect sizes for each study, as well as the 95% confidence intervals.

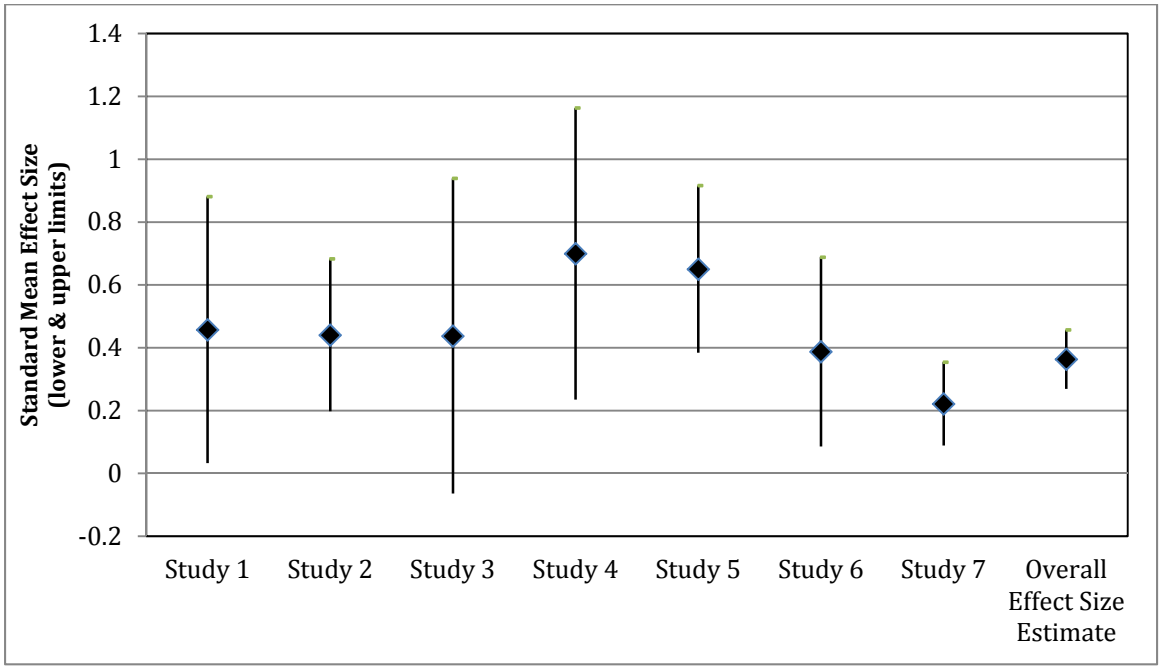

Figure 1. Effect sizes and 95% CIs for lead exposure and overall ADHD symptoms.

Based on a meta-analysis of the relationship between lead exposure (measured lead levels greater than 0 µg/dL) and inattention symptoms of ADHD, the estimated standard mean difference effect size is 0.308. The standard error is 0.029 and there is a 95% confidence interval of 0.252 to 0.364. Thus, the null hypothesis is rejected because zero is not within the confidence interval of the estimated effect size (Borenstein et al., 2009). Figure 2 provides a forest plot of the estimated effect size and individual effect sizes for each study, as well as the 95% confidence intervals.

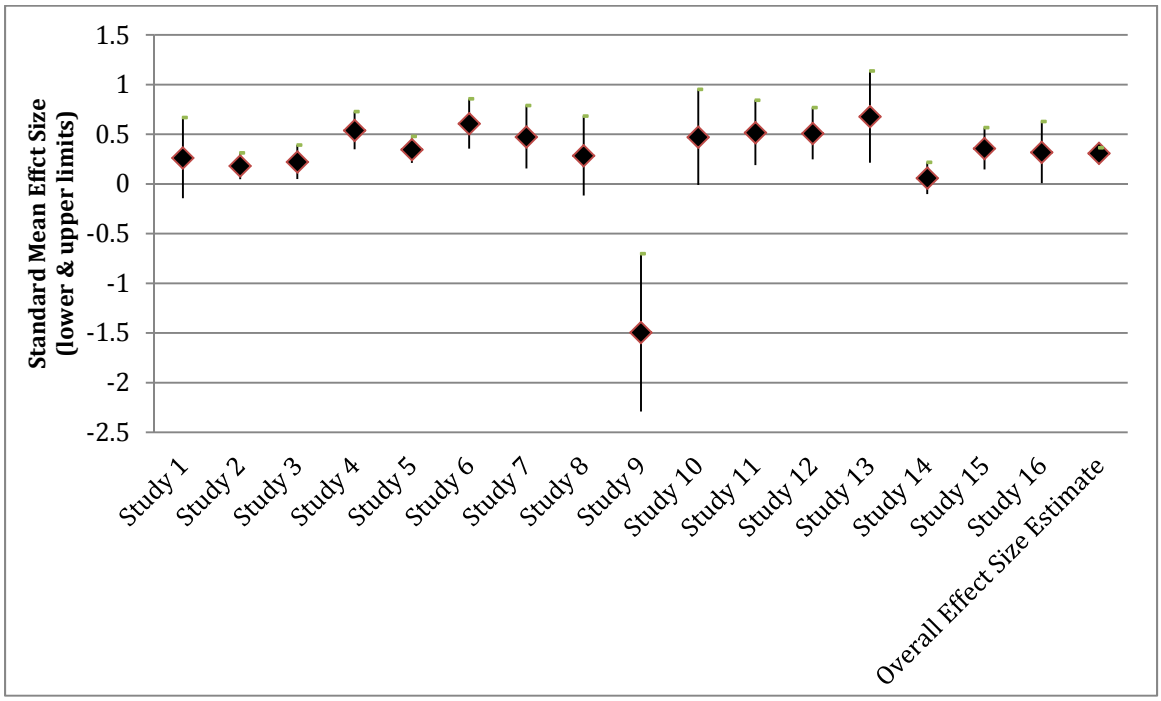

Figure 2. Effect sizes and 95% CIs for lead exposure and inattention symptoms.

Based on a meta-analysis of the relationship between lead exposure (measured lead levels greater than 0 μg/dL) and hyperactive/impulsive symptoms of ADHD, the estimated standard mean difference effect size is 0.231. The standard error is 0.033 and there is a 95% confidence interval of 0.167 to 0.295. Thus, the null hypothesis is rejected because zero is not within the confidence interval of the estimated effect size (Borenstein et al., 2009). Figure 3 provides a forest plot of the estimated effect size and individual effect sizes for each study, as well as the 95% confidence intervals.

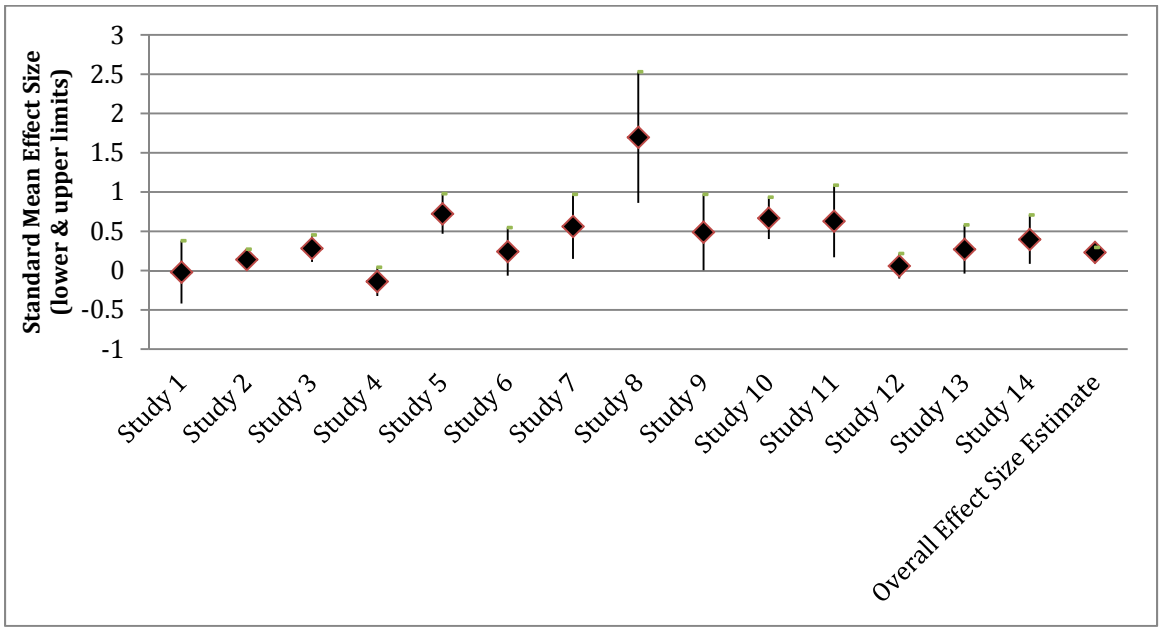

Figure 3. Effect sizes and 95% CIs for lead exposure and hyperactive/impulsive symptoms.

Post Hoc Analysis

A homogeneity analysis was conducted to determine if the distribution of effect sizes is within the expected range given sampling error for each primary analysis (Lipsey & Wilson, 2001). For the analysis of overall ADHD symptoms Q statistic was 11.551 with a p-value of 0.073. Thus, the sample of studies included in the overall ADHD symptom analysis does not have significant heterogeneity.

For the analysis of inattention symptoms Q statistic was 53.25 with a p-value of 0.000. Thus, the sample of studies included here has significant heterogeneity. There was one notable outlier in the sample that was a study based on a sample of children diagnosed with ADHD and did not include any control children with lead exposure. When this study is removed from the analysis, the Q statistic remained significant with a

p-value of 0.003. For the analysis of hyperactive/impulsive symptoms Q statistic was 68.141 with a p-value of 0.000. Thus, the sample of studies included here also has significant heterogeneity.

Summary

In summary, the null hypothesis has been rejected and there is a significant relationship between lead exposure and overall ADHD symptoms, and both the inattentive and hyperactive/impulsive symptom categories. Based on the estimated effect size, these relationships are of medium strength with the relationship between lead exposure and overall ADHD symptoms being the highest, followed by inattention symptoms and hyperactive/impulsive symptoms.

Both the inattention and hyperactive/impulsive symptoms samples possessed significant heterogeneity, but the overall ADHD symptom analysis was homogeneous. The studies included in the inattentive and hyperactive/impulsive symptoms analyses were thus examined for moderating variables that may account for that variability. I discuss that heterogeneity and moderating variables in Chapter 5.

I begin Chapter 5 by briefly reiterating the purpose and nature of the study and the key findings. I then discuss the findings in light of previous research in the area and how these findings extend the current knowledge. I present the interpretation the findings in the context of the conceptual framework as well. I then discuss limitations of the current study and recommendations for future studies, and lastly, I present the implications of the current findings.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

The preceding chapters provided strong evidence for a significant relationship between lead exposure and ADHD (see Boucher et al., 2012; Chiodo et al., 2004; Cho et al., 2010; Nicolescu et al., 2010; Plusqellec et al., 2010). The purpose of this study was to examine and help quantify this relationship. The specific aim of this quantitative meta-analysis was to estimate the magnitude of the effect size of childhood lead exposure on ADHD symptoms through a meta-analysis, as well as determine if there are any moderating variables (e.g., age of exposure, gender, etc.) that could be facilitating variability in research results.

The results of the primary analysis for the present study show a significant relationship between lead exposure during childhood and overall symptoms of ADHD. The estimated effect size for that relationship was of medium strength. Similarly when the symptom categories of ADHD (inattention and hyperactivity/impulsivity) were individually analyzed, lead exposure was also shown to have a significant relationship with both inattentive and hyperactive/impulsive symptoms. The estimated effect size for these relationships was also in the medium range.

Secondary analyses of homogeneity indicate the sample of studies for overall ADHD was homogeneous, meaning the individual study effect sizes were not significantly different from one another. Analysis of homogeneity for the individual symptoms categories, however, indicate that both for inattentive and hyperactive/impulsive symptoms the sample was heterogeneous. Thus, moderating

variables were considered and I examined the potential impact these may have had on the research.

Interpretation of Findings

Extension of Current Knowledge

Researchers examining childhood lead exposure and ADHD symptoms have not found agreement on the magnitude of the effect or the effect on inattention symptoms versus hyperactivity/impulsivity symptoms of ADHD (see Chiodo et al., 2007; Nigg et al., 2008). The primary goal of the present study was to quantify the relationship between lead exposure and ADHD symptoms by systematically combining these previous research studies. The results of the present study do support a significant relationship between childhood lead exposure and ADHD symptoms, including overall, inattentive, and hyperactive/impulsive symptoms.

Due to the variability in results from previous studies in this area, the present results both confirm and disconfirm the knowledge base on lead exposure and ADHD symptoms. In regards to research of inattentive and hyperactive/impulsive symptoms, researchers in approximately 60% of the studies found a significant relationship between lead exposure and these ADHD symptom categories. Researchers found a significant relationship with lead exposure for all studies that included an overall measure of ADHD symptoms. Similarly, researchers examining the diagnostic subtypes of ADHD have found a more robust correlation between lead exposure and ADHD combined type than predominately inattentive type suggesting there may be a differential impact of lead exposure on specific symptom categories (Nigg et al., 2008, 2010). I was not able,

however, to find research that included the ADHD predominately hyperactive/impulsive type to provide a confirmation.

The present meta-analysis results, which included studies with significant and nonsignificant results, is better conceptualized as an extension of the current knowledge rather than a confirmation or disconfirmation of previous research. The significant relationship found in the present study between lead exposure and overall ADHD symptoms further confirms previous studies in this area, all of which also were significant (see Chiodo et al., 2004; David, 1974; Fergusson et al., 1988; Ha et al., 2009; Nicolescu et al., 2010; Tuthill, 1996; Zhang et al., 2015). Although not all studies of the inattentive and hyperactive/impulsive symptoms categories have resulted in the presence of a significant relationship with lead exposure (see Canfield, Kreher, Cornwell, & Henderson, 2003; Chandramouli, Steer, Ellis, & Edmond, 2009; Chiodo et al., 2004, 2007; Fergusson et al., 1988, 1993; Fraser, Muckle, & Despres, 2006; Gittelman & Eskenazi, 1983; Harvey, Hamlin, Kumar, Morgan, & Spurgeon, 1988; Millar et al., 1984; Nicolescu et al., 2010; Nigg, Elmore, Natarajan, Friderici, & Nikolas, 2016; Shin, Kim, Oh, Shin, & Lim, 2014; Silva, Hughes, Williams, & Faed, 1988; Szkup-Jablonska et al., 2012; Yule et al., 1984; Zhang et al., 2015), the fact that the present study did, even when including nonsignificant results, provides strong support, I believe, that a significant relationship does exist.

One hypothesis for why the present meta-analysis indicates a significant relationship between lead exposure and inattentive and hyperactive/impulsive symptoms categories when not all previous studies have is the increased power of the present study

resulting from the higher number of participants. By systematically combining previous studies, I was able to include a much larger sample than authors of the primary studies. The present analyses of inattentive and hyperactive/impulsive symptoms included several thousand participants. As power increases, however, there is also an increase in the chances that a type I error might occur (Faber & Fonseca, 2014). Given the heterogeneity that was present in these samples of studies, examination of possible moderating variables is an important next step for future researchers.

Heterogeneity and Possible Moderating Variables

The studies included in the analysis of lead exposure and overall ADHD symptoms were homogeneous, while those in the analyses of inattentive and hyperactive/impulsive symptoms were heterogeneous. The homogeneity of the overall ADHD sample and the heterogeneity of the inattentive and hyperactive/impulsive symptom samples are expected if the significance of the individual studies are examined. All those identified studies that included a measure of overall ADHD symptoms found a significant relationship with lead exposure. In the case of inattentive and hyperactive/impulsive symptoms, of the studies identified only approximately 60% found a significant relationship with lead exposure.

There were numerous covariates included in the sample of studies for the present meta-analysis; with some studies having included many and some included none. The differing inclusion of covariates is one possible reason for the heterogeneity. Covariates in these studies included child characteristics (e.g., age, gender, race, prenatal concerns), parental characteristics (e.g., education, IQ, marital status, age), and family

characteristics (e.g., SES, home environment, family size, housing). Table 5 provides covariates for each study, as well as any reported inclusion and exclusion criteria.

Table 5

Covariates and Inclusion/Exclusion Criteria for Studies Included in Analysis

Title	Inclusion/exclusion	Covariates
A Longitudinal Study of Dentine Lead Levels, Intelligence, School Performance and Behaviour, Part III. Dentine Lead Levels and Attention/Activity	—	Maternal and paternal education levels; family socio-economic standards; family social environment; child's perinatal history; child's school experiences; factors related to lead exposure; factors relating to sampling of teeth; age at which tooth was shed; the position of the shed deciduous tooth
Neurodevelopmental Effects of Postnatal Lead Exposure at Very Low Levels	—	Prenatal alcohol/drug/cigarette use; SES; age, marital status, & years of education of the primary caregiver; child's gender and parity; number of children in the household; parenting quality; primary caregiver's vocabulary; caregiver's level of depression; crowded living conditions; disruption in caregiving; primary caregiver psychological symptoms; severity of personality disorder (if any) for the caregiver; family function; the Life Events Scale for the primary caregiver and child; domestic violence; age of examiner; age of child
Attention-Deficit/Hyperactivity Symptoms in Preschool Children from an E-waste Recycling Town: Assessment by the parent report derived from DSM-IV	—	Nutrition intake; residence; household tobacco smoke exposure; father's work relating to e-waste; parents' education levels; monthly household income
Association Between Lower Level Lead Concentrations and Hyperactivity in Children	Excluded children with psychosis or significant neurological diseases	—

Title	Inclusion/exclusion	Covariates
Hair Lead Levels Related to Children's Classroom Attention-Deficit Behavior	—	Child's health status clinic visits, illness, medication & vitamin use; diagnosed hyperactivity; low birth weight or premature birth; residence; education & occupation of the main wage earner; child's gender & ethnicity
Low Blood Levels of Lead and Mercury and Symptoms of Attention Deficit Hyperactivity in Children: A Report of the Children's Health and Environment Research (CHEER)	—	Birth weight; residential area; education levels of parents; household income; history of parental neuropsychiatric disease; parental marital status; maternal prenatal smoking or alcohol intake
Environmental Exposure to Lead, but Not Other Neurotoxic Metals, Related to Core Elements of ADHD in Romanian Children: Performance and Questionnaire Data	—	Study area; gender, age, computer experience, handedness, eye problems, number of siblings of child; parental education; prenatal smoking/alcohol consumption; family psychopathology
Relationships between blood lead, behaviour, psychometric and neuropsychological test performance in young children	Born in hospital of two European parents; be legitimate; weigh at least 2500g at birth; mother between 20 and 29 years of age at the timeof the birth; English first language	—
Blood Lead, Intelligence, Reading Attainmnet, and Behaviour in Eleven Year Old Children in Dunedin, New Zealand	—	SES; maternal cognitive ability & depression; overall disadvantage; maternal age; child age & ordinal position; child intelligence & reading

Title	Inclusion/exclusion	Covariates
Teachers' Ratings of Children's Behaviour in Relation to Blood Lead Levels	—	—
Effects of Early Childhood Lead Exposure on Academic Performance and Behaviour of School Age Children	—	Gender; child's IQ; maternal educational; home ownership; maternal smoking; home facilities score at 6 months; paternal SES; Family Adversity Index,; parenting attitudes at 6 months
Blood Lead Levels and Specific Attention Effects in Young Children	Singleton gestation; not HIV positive, without multiple congenital malformations; African American race; only one child per mother included in study	Child's age & gender; marital status; maternal age at prenatal check; number of children in home; SES; drug/alcohol/cigarette use in home & prenatally; maternal IQ; quality of home environment; maternal custody
Low-Level Lead Exposure, Executive Functioning, and Learning in Early Childhood	—	Child's gender, birth weight, gestational age, & birth order; maternal race, IQ, marital status, education, prenatal smoking, & SES; home environment
Early Dentine Lead Levels and Subsequent Cognitive and Behavioural Development	—	Gender; ethnicity; family size; maternal & paternal education; SES; maternal emotional responsiveness; avoidance of punishment; number of schools attended; residence in old housing

Title	Inclusion/exclusion	Covariates
Variation in an Iron Metabolism Gene Moderates the Association Between Blood Lead Levels and Attention-Deficit/Hyperactivity Disorder in Children	Healthy children; no psychotropic medication; no ASD or ID diagnosis; no history of head injury	Child age; race; SES; ODD/CD; iron hemoglobin; HFE mutations
The Relationship between Lead Exposure, Motor Function, and Behaviour in Inuit Preschool Children	Biological mother was the primary caretaker, had undergone full-termpregnancy, child's birth weight was of at least 2500 g with no neurological or developmental disorder and no severe chronic disease known	SES; education level of primary caregiver; number of children and adults in home; maternal psychological distress; maternal non-verbal reasoning abilities; intra-family violence; quality of intellectual stimulation; maternal reproductive history; prenatal and postnatal exposure to mercury (Hg) and organochlorine compounds (OCs); prenatal exposure to alcohol/illicit drugs/tobacco; iron deficiency; blood nutrients
The Relationship between Hair Zinc and Lead Levels and Clinical Features of Attention-Deficit Hyperactivity Disorder	ADHD diagnosis/healthy controls; IQ above 70; no medication or supplement use; no other psychiatric or major medical concerns	—
Effects of Blood Lead and Cadmium Levels on the Functioning of Children with Behaviour Disorders in the Family Environment	Diagnosis of behavior disorders such as hyperactivity, impulsiveness and attention deficit disorder	—
Pre- and Postnatal Lead Exposure and Behavior Problems in School-Aged Children	—	Family's sociodemographic characteristics; mother's general medical & reproductive history; course of pregnancy labor and delivery; child's neonatal status; at time of assessment additional info on sociodemographic status and child's medical & behavior histories

Title	Inclusion/exclusion	Covariates
Lead and Hyperactivity Revisited: An Investigation of Nondisadvantaged Children	(1) Nondisadvantaged hyperactive children; (2) normal children; and (3) nondisadvantaged children with a developmental disorder other than hyperactivity (learning-disabled children).	SES; child's race, age, and gender; paternal IQ; prenatal/perinatal complications

Note. SES = Socioeconomic status; HFE = Human factors engineering

Although studies often included similar covariates, the means by which these covariates were measured varied. For instance, measures of the home environment, parenting skills, and parent mental health were not consistently determined by the same questionnaire making comparisons difficult. Other covariates were more static, such as number of people in the home and education level, allowing for easy comparison of their inclusion across studies. One consistent variable included across studies was a measure of socioeconomic status through household income, caregiver education, and/or caregiver occupation. The second most common covariate was a measure of prenatal and perinatal complications, specifically prenatal exposure to substances (alcohol, cigarettes) and low birth weight. The inclusion of these covariates is particularly important given that they are also known to be associated with ADHD (see Han et al., 2015; Joelsson et al., 2016; Russell, Ford, Williams, & Russell, 2016; Sucksdorff et al., 2015), and thus not accounting for them within a study could lead to a spurious association between lead exposure and ADHD symptoms.

Of these two most common covariates, six out of the seven studies included in the analysis of overall ADHD symptoms used a measure of SES and five out of the seven used a measure of prenatal/perinatal concerns. The common inclusion of these covariates across most studies in the overall ADHD analysis is one hypothesis for the homogeneity of these studies. When the studies included in the inattentive and hyperactive/impulsive analyses are examined there is larger variability, particularly in regards to prenatal and perinatal concerns. Of the 16 studies included in the analysis of inattentive symptoms, 12 included a covariate measure of socioeconomic status but only seven included a covariate

measure of prenatal or perinatal concerns. For the hyperactive/impulsive analysis studies, 10 of the 14 included a covariate measure of socioeconomic status and 6 included a covariate measure of prenatal or perinatal concerns. One study did include low birth weight as an exclusion criterion, although it did not use prenatal/perinatal concerns as a covariate. A summary of this information can be found in Table 6.

Table 6

Significance and Covariate Inclusion for Studies Included in Analysis

Title	Significance	SES measure	Prenatal/ perinatal concern
A Longitudinal Study of Dentine Lead Levels, Intelligence, School Performance and Behaviour, Part III. Dentine Lead Levels and Attention/Activity	Overall - S inattention - S hyper/impul - S	X	X
Neurodevelopmental Effects of Postnatal Lead Exposure at Very Low Levels	Overall - S inattention - S hyper/impul - NS	X	X
Attention-Deficit/Hyperactivity Symptoms in Preschool Children from an E-waste Recycling Town: Assessment by the parent report derived from DSM-IV	Overall - S inattention - S hyper/impul - S	X	
Association Between Lower Level Lead Concentrations and Hyperactivity in Children	Overall - S		
Hair Lead Levels Related to Children's Classroom Attention-Deficit Behavior	Overall - S	X	X
Low Blood Levels of Lead and Mercury and Symptoms of Attention Deficit Hyperactivity in Children: A Report of the Children's Health and Environment Research (CHEER)	Overall - S	X	X
Environmental Exposure to Lead, but Not Other Neurotoxic Metals, Related to Core Elements of ADHD in Romanian Children: Performance and Questionnaire Data	Overall - S inattention - S hyper/impul - S	X	X
Relationships between blood lead, behaviour, psychometric and neuropsychological test performance in young children	Inattention - S hyper/impul - NS		
Blood Lead, Intelligence, Reading Attainmnet, and Behaviour in Eleven Year Old Children in Dunedin, New Zealand	Inattention - S hyper/impul - S	X	
Teachers' Ratings of Children's Behaviour in Relation to Blood Lead Levels	Inattention - S hyper/impul - S		
Effects of Early Childhood Lead Exposure on Academic Performance and Behaviour of School Age Children	Inattention - NS hyper/impul - NS	X	

Title	Significance	SES measure	Prenatal/ perinatal concern
Blood Lead Levels and Specific Attention Effects in Young Children	Inattention - S hyper/impul - NS	X	X
Low-Level Lead Exposure, Executive Functioning, and Learning in Early Childhood	Inattention - S	X	X
Early Dentine Lead Levels and Subsequent Cognitive and Behavioural Development	Inattention - S	X	
Variation in an Iron Metabolism Gene Moderates the Association Between Blood Lead Levels and Attention-Deficit/Hyperactivity Disorder in Children	Inattention - S hyper/impul - S	X	
The Relationship between Lead Exposure, Motor Function, and Behaviour in Inuit Preschool Children	Inattention - NS hyper/impul - S	X	X
The Relationship between Hair Zinc and Lead Levels and Clinical Features of Attention-Deficit Hyperactivity Disorder	Inattention - S hyper/impul - S		
Effects of Blood Lead and Cadmium Levels on the Functioning of Children with Behaviour Disorders in the Family Environment	Inattention - NS hyper/impul - S		
Pre- and Postnatal Lead Exposure and Behavior Problems in School-Aged Children	Inattention - S	X	X
Lead and Hyperactivity Revisited: An Investigation of Nondisadvantaged Children	Hyper/impul - NS	X	X

Note. SES = Socioeconomic status; S = Significant; NS = Nonsignificant, Hyper/Impul = Hyperactive/impulsive

The lead levels of the sample included in the studies was also considered a possible cause of the heterogeneity seen in these studies. Overall, all studies included generally low levels of lead exposure with mean lead levels for the study sample most often being below the recommended limit put forth by the CDC. It has been hypothesized that lead exposures effect on ADHD symptoms has a similar dose response relationship as that seen with lead exposure and intellectual functioning (see Banner & Kahn, 2014; Tuthill, 1996). Tuthill (1996) investigated such a hypothesis and found support for such a relationship. When participants were separated into 6 groups based on lead levels, a

consistent increase in teacher-reported distractibility, disorganization, non-persistence, dependence, frustration, day dreaming, inability to follow sequences, and low overall functioning was seen as lead levels increased. A similar pattern was also seen in regards to teacher reported hyperactivity and impulsivity, although the increase in reported symptoms with increased lead exposure was more variable (Tuthill, 1996).

The lead levels for each study are reported in Table 7, and when available the mean, standard deviation, and range are provided. The mean lead levels for the majority of studies were relatively low, but individual levels within the studies ranged from 0 to 52 µg/dL. If there is truly a dose response relationship between lead exposure and ADHD symptoms, it is likely that the heterogeneity found in the present meta-analysis is, at least partially, resulting from the differing severities of lead exposure present in the studies. The fact that there was also variability in the lead levels found in the studies included in the analysis of overall ADHD despite these studies being found to be homogeneous, however, does not support this hypothesis. This is clearly an area in need of further research to confirm the presence of a dose response relationship.

Table 7

Lead Levels for Each Study

Title	Mean	Lead level SD	Range
A Longitudinal Study of Dentine Lead Levels, Intelligence, School Performance and Behaviour, Part III. Dentine Lead Levels and Attention/Activity	—	—	—
Neurodevelopmental Effects of Postnatal Lead Exposure at Very Low Levels	5.4 µg/dL	3.3 µg/dL	1-25 µg/dL
Attention-Deficit/Hyperactivity Symptoms in Preschool Children from an E-waste Recycling Town: Assessment by the parent report derived from DSM-IV	7.9 µg/dL	—	5.1-16.9 µg/dL

Title	Mean	Lead level SD	Range
Association Between Lower Level Lead Concentrations and Hyperactivity in Children	Means per group ranged from 22.16 - 41.06 µg/dL	—	—
Hair Lead Levels Related to Children's Classroom Attention-Deficit Behavior	—	—	0-11.99 ppm (>3 ppm considered high)
Low Blood Levels of Lead and Mercury and Symptoms of Attention Deficit Hyperactivity in Children: A Report of the Children's Health and Environment Research (CHEER)	1.8 mg/dL	1.71 mg/dL	—
Environmental Exposure to Lead, but Not Other Neurotoxic Metals, Related to Core Elements of ADHD in Romanian Children: Performance and Questionnaire Data	—	—	1.1-14.2 mg/dL
Relationships between blood lead, behaviour, psychometric and neuropsychological test performance in young children	0.63 µmol/l	0.2 µmol/l	0.2 - 1.4 µmol/l
Blood Lead, Intelligence, Reading Attainmnet, and Behaviour in Eleven Year Old Children in Dunedin, New Zealand	11.4 µg/dL (boys); 10.4 (girls)	—	—
Teachers' Ratings of Children's Behaviour in Relation to Blood Lead Levels	13.25 µg/dL	—	7-32 µg/dL
Effects of Early Childhood Lead Exposure on Academic Performance and Behaviour of School Age Children	—	—	Majority below 10 µg/dL
Blood Lead Levels and Specific Attention Effects in Young Children	5 µg/dL (majority below 10)	3 µg/dL	—
Low-Level Lead Exposure, Executive Functioning, and Learning in Early Childhood	6.49 µg/dL	—	1.7-20.8 µg/dL
Early Dentine Lead Levels and Subsequent Cognitive and Behavioural Development	6.2 µg/g	3.7 µg/g	—
Variation in an Iron Metabolism Gene Moderates the Association Between Blood Lead Levels and Attention-Deficit/Hyperactivity Disorder in Children	Average consistent with that reported by CDC	—	—
The Relationship between Lead Exposure, Motor Function, and Behaviour in Inuit Preschool Children	5.3 µg/dL	4.9 µg/dL	—
The Relationship between Hair Zinc and Lead Levels and Clinical Features of Attention-Deficit Hyperactivity Disorder	ADHD = 0.14 mg/100g; Control = 0.21 µg/100g	—	—
Effects of Blood Lead and Cadmium Levels on the Functioning of Children with Behaviour Disorders in the Family Environment	1.971 µg/dL	—	.6-10.1 µg/dL
Pre- and Postnatal Lead Exposure and Behavior Problems in School-Aged Children	3.4 µg/g	—	0.1-28.9 µg/g
Lead and Hyperactivity Revisited: An Investigation of Nondisadvantaged Children	—	—	2-52 µg/dL

Note. SD =Standard deviation; µg/dL = Micrograms per deciliter; ppm = Parts per million; mg/dl = Milligrams per deciliter; µmol/l = Micromole per liter; µg/g = Micrograms per gram

Conceptual Framework Interpretation

The concept underlying the present study was that of ADHD, a diagnosis made through a categorical approach where an individual must exhibit a certain number of symptoms that are impairing their functioning in two or more domains (American Psychiatric Association, 2013). This approach to diagnosis is not theoretically driven and research related to ADHD has often been exploratory and descriptive with less development of comprehensive theories of ADHD. The present study examined research focused on the symptoms of ADHD, rather than the formal diagnosis, and the results need to be interpreted in consideration of symptoms rather than formal diagnosis.

The present meta-analysis found a significant relationship between lead exposure and overall ADHD symptoms, inattentive symptoms, and hyperactive/impulsive symptoms. As discussed the studies included mainly used standardized rating scales of these symptoms or objective measures of these symptoms (see Table 1 for individual study information). The symptoms examined in the present study are just part of the diagnostic criteria required for a formal diagnosis of ADHD, albeit a fundamental part of the diagnosis. The present study, and those previous studies examined in this area, support that children exposed to lead have a greater chance of exhibiting behaviors and impairments consistent with the symptoms of an ADHD diagnosis and thus, can be assumed to have a greater chance of actual diagnosis. Braun et al. (2006) and Froehlich et al. (2009) calculated the population attributable fraction for children with lead exposure

and found that 21.1% and 25.4% of ADHD cases, respectively, could be attributable to exposure to lead. This equates to 290,000 to 598,000 cases of ADHD in the US population.

There are several theories of attention and ADHD, that although are not directly used in the diagnosis of ADHD, are important to consider when looking at attention impairments. Two theories highlighted herein were Barkley (1997), a seminal neuropsychological theory of ADHD based upon deficits in behavioral inhibition or self-control, and Posner and Peterson model of an attention system (Peterson & Posner, 2012). Barkley defined behavioral inhibition as the ability to stop a common or an ongoing response, as well as the ability to control for interfering stimuli. Impairment in behavioral inhibition then causes dysfunction in executive functioning; working memory, self-regulation of affect/motivation/arousal, internalization of speech, and reconstitution. These areas of dysfunction are considered responsible for the behavioral impairments and symptoms reported or measured in the assessment of ADHD symptoms, such as those examined in the present study.

The Peterson and Posner model described the alerting, orienting, and executive networks that control attention (Peterson & Posner, 2012). In this model, the behavioral impairments and symptoms considered indicative of ADHD can result from dysfunction in any or all of these three networks. As I discussed in Chapter 2, an understanding of these theories of attention and what brain regions or functions are responsible for attention may help direct a future theoretical link between specific damage caused by lead exposure and development of ADHD symptoms

Limitations of the Study

There are several important limitations to consider when interpreting the present results. First, one of the largest downfalls of this line of research is that causality cannot be definitively proven, as research often examines correlations between lead exposure and negative outcomes. This is true of the present study sample, as none of the included research can be considered to prove a causal relationship between lead exposure and ADHD symptoms. Thus, the present meta-analysis also is only able to support a significant relationship between lead exposure and ADHD symptoms and not a causal one. Meta-analysis can also be limited by the quality of the research used for the analysis; however, no significant concerns were identified in the included studies for the present meta-analysis.

In regards to generalizability, the specific populations represented in the samples of those included studies need to be considered. The present results are limited to children with the majority of studies focus on preschool and elementary age children. The mean lead levels for the samples of children were also generally low. The present significant relationship found between lead exposure and ADHD symptoms cannot be generalized to adolescents or adults or those with high lead exposure. The studies samples, however, were significantly diverse in regards to gender, ethnicity, and country of residence increasing the generalizability of these results.

Recommendations

The present results of this study provide evidence of a significant relationship between childhood lead exposure and ADHD symptoms, which is adequate to warrant

additional research in this area. Given the present results show significant heterogeneity in the analysis of inattentive and hyperactive/impulsive symptom categories, additional research in these specific areas is recommended. Many of the studies included numerous covariates, and thus, additional research focusing on the potential moderating relationship of the variables known to be risk factors for ADHD (e.g., birth weight/prematurity, low SES, prenatal tobacco exposure) is recommended.

Additionally, the hypothesis regarding a dose response relationship between lead exposure and ADHD symptoms warrants further investigation. Studies focusing on the breath and severity of ADHD symptoms in a population with varying degrees of lead exposure, including analysis of lifetime exposure rather than single points of exposure are recommended. Although the CDC has set a threshold of 5 μg/dL for lead exposure concern, there is evidence to suggest there is no safe level and extended exposure may be of greater concern than short-term exposure. Research has shown that the negative impact on IQ persists into adulthood (Reuben et al., 2017), and further longitudinal research to determine both the impact of extended exposure and whether these ADHD symptoms persist into adulthood is also recommended.

Implications

In recent years, there has been an increased focus on the impact of mental health concerns on children, adolescents, and adults and the long term consequences of untreated mental health concerns. The symptoms associated with a diagnosis of ADHD have been correlated with academic difficulties, high school dropout, poor occupational functioning, and relationship concerns, as well as later mental health and substance abuse

concerns (see Chen et al., 2015; Martin, 2014; Kolla et al., 2016; Sasser et al., 2016; Sundquist et al., 2015; Vitulano et al., 2014; Wymbs et al., 2017) and those with ADHD are also at greater risk of developing other mental health concerns later in life (see Brook, Brook, Zhang, Seltzer, & Finch, 2013; Humphreys et al., 2013; Michielsen et al., 2013). Given the confluence of negative outcomes that can result from ADHD symptoms, it is important to gain greater understanding of the risk factors and possible causal mechanisms for development of these symptoms, including lead exposure.

The present study has the opportunity to raise awareness for both the public health concern lead poses and individual and societal consequences of ADHD. As the knowledge base increases regarding the harmful effects of lead exposure, individuals, communities, and governments will have a basis for developing and implementing better prevention, identification, and treatment programs. Prevention programs are the most important defense against the long term consequences of lead exposure. However, for those already exposed, expanding knowledge regarding what those consequences are is important. By further establishing the relationship between lead exposure and ADHD symptoms, the present study can be used to help ensure physicians and other health personnel are aware of the consequences of lead and that parents are given the correct information. Those families of lower socioeconomic status are at greater risk for lead exposure (Raju & Kumar, 2017), and thus, it is critical for communities and governments to establish better prevention, identification, and treatment programs.

Awareness of the relationship between lead exposure and ADHD symptoms can help children be identified sooner who present with these symptoms after exposure and

aid in these children receiving the needed interventions earlier. Parents of children exposed to lead can also be preemptively provided education on ADHD symptoms and interventions to further ensure early identification and treatment. Early identification, even of those at risk, and appropriate interventions can result in better long term outcomes (Feil et al., 2016).

Conclusions

As I discussed throughout this dissertation, lead exposure continues to pose a significant public health risk despite increases in awareness and government regulations. There is a wealth of research supporting the negative impact of lead exposure on intellectual functioning (see Canfield et al., 2003; Beattle et al., 1975; Earl et al., 2016; Henn et al., 2012; Mohan et al., 2014; Rodrigues et al., 2016), and more recent research has begun to identify relationships between lead exposure and other cognitive and behavioral concerns, including lowered academic achievement and conduct problems (Marcus, Fulton, & Clarke, 2010; McCrindle et al., 2017; Strayhorn & Strayhorn, 2012).

The results of the present meta-analysis show a significant relationship between lead exposure and overall ADHD, as well as inattentive and hyperactive/impulsive symptoms. The estimated effect size for all three of these relationships was of medium strength. Although proving a causal relationship between lead exposure and ADHD symptoms is beyond the scope of this study, these results do support a significant relationship and suggest lead exposure should be considered a risk factor for ADHD. Additional research focusing on variables that may moderate or mediate this relationship, and clarify the dose response relationship, if any, is recommended.

The present study results can be used to continue to raise awareness for the public health concern lead exposure poses, and hopefully improve both prevention programs and treatment for the consequences of lead exposure. Early identification and treatment of all mental health concerns, including symptoms of ADHD, is imperative to improving the long term outcomes of those children with ADHD. Publication of this dissertation and conference presentations will hopefully bring these results to the attention of others in this field, and eventually result in improvement to public health.

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Appendix A: Letter to Researchers

DATE

ADDRESS

Dear RESEARCHER,

My name is Redacted and I am currently completed my Ph.D. in clinical psychology. I am completing my dissertation on the relationship between childhood lead exposure and ADHD symptoms. I am conducting a meta-analysis in this area, and am reaching out to researchers in this field who may have unpublished studies related to lead exposure and ADHD symptoms.

If you have any research in this area that has not been published and are willing to share with me I would greatly appreciate you reaching out to me. Below are my mailing address, email, and phone number. Please contact me in which way is most convenient for you.

Thank you for your time.

Sincerely,

Name redacted

Walden University

Phone number redacted

E-mail address redacted

Street address redacted

City, state, and zip code redacted

Appendix B: Coding Manual

1. Each study was first reviewed to determine if all inclusion criteria were met. The following information was extracted from each study and entered into a database:
    a) Type of statistic provided
    b) Sample size provided
    c) Measure of lead exposure
    d) Measure of overall, attention, and/or hyperactivity/impulsive symptoms
2. Once that was completed, a determination for each study was made regarding whether inclusion criteria were met. In order to be included a study had to include a type of statistic that could be converted to Cohen's d (correlation, ANOVA, t-test), the sample size(s) were provided if necessary, a measure of lead exposure was used, and measure of either overall, inattentive, and/or hyperactive/impulsive symptoms were used. For those studies that were deemed to meet inclusion criteria, the following information was then extracted from each study and entered into a database:
    a) Statistic
    b) P-value and/or significance
    c) Sample size
    d) When appropriate, group means
3. The following additional information was extracted from studies that met the inclusion criteria of having a measure of lead exposure and a measure of either

overall, inattentive, and/or hyperactive/impulsive symptoms, regardless of whether they were included in the meta-analysis.

a) Type of measure of lead exposure (blood, hair, teeth, urine)
b) Type of measure of overall, attention, and/or hyperactivity/impulsive symptoms
c) Significance of the results
d) Sample size and gender breakdown
e) Lead levels (mean, standard deviation, range)
f) Location
g) Inclusion/exclusion criteria
h) Covariates