EARLY LIFE LEAD EXPOSURE AS A RISK FACTOR FOR AGGRESSIVE AND VIOLENT BEHAVIOUR IN YOUNG ADULTS: A SYSTEMATIC REVIEW

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DEDICATION

To the memory of

Kehinde Funto Obamuyide

Friend, Wife, Mother and Angel

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ABSTRACT

Early life lead exposure as a risk factor for aggressive and violent behaviour in young adults: a systematic review

Henry A. Obamuyide

Under the supervision of Professor Richard Matzopoulos and Dr. Tamara Kredo

Over 1.3 million individuals die each year from preventable violence. Many of these violent acts are perpetrated by youths. Despite several initiatives, the prevalence of youth violence remains high. Early life lead exposure is a possible cause of aggressive and violent behaviour in young adults. Several aggregate-level and individual-level studies report an increase in risk of violent behaviour with increasing lead exposure. However, the evidence base for the role of lead in violence is conflicting as many other studies did not support this claim. No systematic synthesis of current evidence at the individual level exists to critically assess this association.

Therefore, we planned to conduct a systematic review and meta-analysis of studies examining the relationship between lead exposure in early life and the later development of aggressive and violent behaviour in young adulthood at the individual level. Extensive literature searches, including of grey literature, were performed to identify potentially relevant articles. Studies for inclusion were screened by two reviewers and selected using pilot-tested eligibility form. The two reviewers independently assessed risk of bias and carried out data extraction before analysis.

A systematic review and meta-analysis of currently available evidence was carried out. Searches were conducted between September 2019 and October 2019. We identified a total of 2182 reports, out of which six studies in 7 publications were eligible. All of the studies were conducted in high income countries, though a few recruited participants from low-income

communities. There were varying definitions of violence, ranging from very narrow to wide and the outcomes were measured as either a count or binary variable. Despite the diversity in study settings, the direction of findings was remarkably homogenous. For studies reporting dichotomous variable, the odds of being arrested or convicted for violent behaviour increases with increasing blood lead level (OR 1.13 to 1.16 with each 5µg/dl rise in blood lead) after controlling for other variables. For the studies reporting count outcome, blood lead may explain up to 63% of the variability in arrest or conviction rates after adjusting for co-variates (IRR for each 5µg/dl rise in blood lead level:1.1 to 1.13). Overall, using a random-effect model with restricted maximum likelihood estimation method, blood lead was associated with a higher risk of exhibiting violent behaviour (OR 1.16; 95% CI 1.10 – 1.23). There was insufficient data to perform sensitivity analyses based on study design, quality of studies or conduct a dose response meta-analysis.

We found that an increased exposure to lead in childhood is associated with a higher risk of being arrested or convicted for violent behaviour in young adulthood. In this context, environmental lead control may help to reduce the prevalence of aggressive and violent behaviour in young adults and should be integrated into violence prevention strategies. Despite the ubiquity of environmental lead, the importance of violence as a public health and social concern and the considerable debate their association has generated, we found very few good quality studies that reported enough methodological detail for evidence synthesis. More studies with better quality and from different settings need to be conducted.

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GLOSSARY OF TERMS

BLL: Blood Lead Level

COSMOS-E: Conducting Systematic Reviews and Meta-Analysis of Observational Studies of Etiology

GDP: Gross Domestic Product

HIC: High Income Country

HR: Hazard Ratio

IRR: Incidence Rate Ratio

IQ: Intelligent Quotient

LMIC: Low- and Middle-Income Country

MOOSE: Meta-analysis of Observational Studies in Epidemiology

MRI: Magnetic Resonance Imaging

OR: Odds Ratio

PRDBS: Parent-Report Pre-delinquent and Delinquent Behaviour Scores

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

PROSPERO: International Prospective Register of Systematic Reviews

RCTs: Randomised Controlled Trials

RR: Risk Ratio

SEM: Socio-Ecological Model

SES: Socio-Economic Status

SRDBS: Self-Report Delinquent Behaviour Scores

WHO: World Health Organization

ZAR: South African Rand

PART A: PROTOCOL

Early life lead exposure as a risk factor for aggressive and violent behaviour in young adults: A systematic review protocol

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Summary

Violence is responsible for the deaths of 1.3 to 1.6 million people annually. This is likely the tip of the iceberg, with the much larger and prevalent non-fatal injuries and psychological and social trauma hidden and unaccounted for. Two major contributors to these deaths are aggression and violence, human behaviours that have been linked to environmental exposure to lead, especially in early life. Because environmental lead is ubiquitous, up to 120 million individuals are exposed worldwide.

Previous studies have evaluated the relationship between lead exposure and aggressive and violent behaviour, but no study has synthesised the individual level evidence examining this association in young adulthood, the age group most responsible for aggression and violence.

This study therefore aims to systematically identify, appraise, analyse and synthesise all available evidence examining the association between early life lead exposure and the development of aggressive and violent behaviour in young adulthood.

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A.1. INTRODUCTION

A.1.1 Background

Annually, more than 1.3 million people worldwide die as a result of violence, accounting for 2.5% of global mortality (Butchart et al., 2015, GBD, 2017). Between the year 2000 and 2014, about 6 million people were killed in acts of interpersonal violence, an incidence rate of homicide higher than that from all wars (Butchart et al., 2015). From 2012 to 2016, it was estimated that for each year, between 475,000 to 453,700 people worldwide were victims of homicide (GBD, 2017). These are, however, the tip of the iceberg. Much more frequent are non-fatal violence which constitute the biggest part of the social and health burden of violence. These manifest as non-fatal physical injuries, mental and behavioural health problems, sexual and reproductive health challenges, chronic diseases and social effects (Butchart et al., 2015).

It has been estimated that tens of thousands of people around the world are victims of non-fatal violence every day: For every youth homicide, there are about 20-40 victims of non-fatal violence receiving hospital care (Butchart et al., 2015). For example, in the USA, 1,503,820 people were treated in emergency departments in 2015 for injuries sustained in an assault giving a crude rate of 467.87 per 100,000 population (CDC, 2015) compared to a homicide rate of 5 per 100,000 population for the same year (World Health Organization, 2015) while in Israel, the annual incidence of violent injuries receiving emergency room care in people under the age of 18 years was 196 per 100,000 population compared with youth homicide rates of 1.3 per 100,000 population for males and 0.4 per 100,000 population for females (Gofin et al., 2000).

Apart from lives lost, violence also places an economic toll on countries. For example, though the economic implication of violence depends on the method of measurement and the underlying burden of violence in each setting, in Colombia, the cost of violence was estimated

at 5% of the Gross Domestic Product (GDP) (Buvinic and Morrison, 1999); in the US the annual cost of violence averages 329.8 billion US dollars equivalent to 3.3% of the GDP (Miller et al., 2001) while in England and Wales homicides, wounding and sexual assault accounted for 40.2 billion US dollars in cost (Brand and Price, 2000).

In seeking to stem this human and economic cost, it is important to understand the factors that may be contributing to violence. A useful framework for understanding the risk factors for violence is the socio-ecological model (SEM) first introduced in the late 1970s (Bronfenbrenner, 1979) and adapted for violence prevention by the WHO in its report on violence and health (Krug et al., 2002). This model explores the interrelationship between individual and contextual factors in the causation of violence and considers violence as the result of multiple influences on behaviour (Figure A.1). These influences operate at individual, relationship, community, societal and structural levels (Krug et al., 2002).

The structural factors operate in the larger society, may extend beyond national boundaries, and help to create and sustain gaps and tensions between groups and nations. These include climate change, globalisation and policies in health, economic, educational, political and social sectors that ensure high levels of economic and social inequalities between groups. The societal level include factors that create an acceptable climate for violence or reduce inhibitions against violence such as cultural norms that support violence, give priority to parental rights over child welfare, entrench male dominance on women and children, support the use of excessive force by police and support political conflict (Krug et al., 2002).

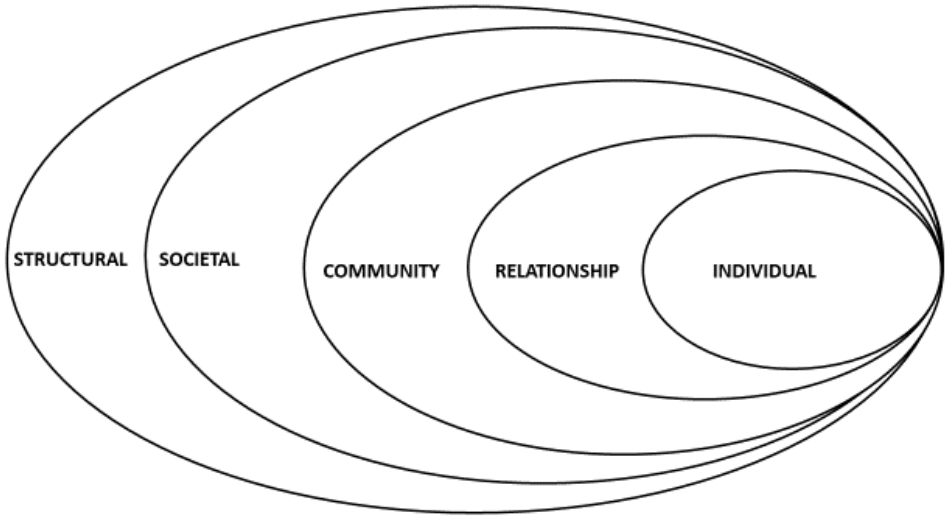

Figure A.1. The Socio-Ecological Model of Violence

The community levels refer to factors operating in contexts within which social relationships are embedded which promote the risk of being a victim or perpetrator of violence such as schools, workplaces and neighbourhood. These factors include high residential mobility, heterogeneity, high population density, drug trafficking and high rate of unemployment. The relationship level connotes the influence of proximal social relationships such as peer and family influence on behaviour (Krug et al., 2002).

Apart from these structural, societal, community and relational factors, some of the major risk factors for aggression and violence are individual factors. These include biological and personal history factors such as male sex, age, genetics, epigenetics, low educational attainment, substance and alcohol abuse, prior history of aggression or violence, prior history of abuse and psychological and personality disorders like impulsivity (Krug et al., 2002). These work through both anatomical and chemical pathways to influence violent behaviour.

The biological control of aggressive and violent behaviour has been linked to certain areas of the brain and neurotransmitter system. The prefrontal cortex, hypothalamus, amygdala, periaqueductal grey and the midbrain are important areas for the control of aggression (Kruk

et al., 1983, Potegal et al., 1996, Wang et al., 2016). Electrical stimulation of the hypothalamus and amygdala causes aggressive behaviours while reduced prefrontal cortical function, leading to reduced executive functioning has been associated with reduced self-control, impulsivity, inattention, low IQ and low educational attainments, factors which have all been correlated with aggression (Krug et al., 2002). Also, reduced serotonin (Schechter et al., 2017) and elevated levels of testosterone (Archer, 2006) have been associated with increased aggression.

Genetic and epigenetic factors are also important. Usually, a continuous phenotypic characteristic such as aggression reflect the interaction of several genes with each other and the environment. It is in this interaction of genes and the environment that a toxin like lead may influence the development of violent behaviour; at least one study has found an epigenetic change in the foetus associated with maternal aggression (Schechter et al., 2017) and environmental factors were found to account for 50% of the variance in aggression (Tuvblad and Baker, 2011). Over the last few decades, evidence has begun to accumulate about the possible role of early life exposure to environmental lead in the development of aggressive, violent and impulsive behaviours (Liu, 2011).

Lead is ubiquitous in the environment. An estimated 120 million persons in the world had a blood lead level (BLL) of between 5µg/dl and 10µg/dl in the year 2000 while approximately similar number had levels greater than 10µg/dl (Pruss-Ustun et al., 2004). Also, about 40% of children had blood lead levels above 5µg/dl and 20% had levels above 10µg/dl. Majority of these children, about 97% live in Low- and Middle Income Countries (LMICs) (Pruss-Ustun et al., 2004). Countries such as South Africa (Mathee, 2014), Romania (Nicolescu et al., 2010), Mexico (Kordas et al., 2007) and China (Wang et al., 2008) have high levels of environmental lead.

The first report of a possible association between lead exposure and aggressive behaviour was first made by Byers and Lord in 1943 in which they described 20 children who had 'recovered' from lead poisoning (Byers and Lord, 1943). Two of these children manifested aggressive behaviour including fighting with their teachers. Thereafter, many ecological studies have shown a link between lead exposure in childhood and the later development of violence. A study reported that between 1941 and 2003, the amount of gasoline lead exposure in the United States predicted violent crime rates roughly 20 years later (Nevin, 2000). A meta-analysis in 2010 examining the relationship between lead exposure and conduct problems, including aggressive and violent behaviours, found an association between lead exposure and conduct problems (Marcus et al., 2010). A cohort study in South Africa found an association between blood lead levels and the behaviour 'attacking people' in a Johannesburg cohort of adolescents (Naicker et al., 2013). Also, a study published in 2007 reported that a reduction in childhood lead exposure in the 1970s and 1980s accounted for greater than 50% of the decline in violent crime rate of the 1990s in the US (Reyes, 2007).

Using homicide data between 1989 and 1991, a US study found that counties with lead level equivalent to 0.17µg/m^3 had homicides rates that were four times the rates in counties with air lead level of 0µg/m^3 (Stretesky and Lynch, 2001). Drawing on lead pipe use in the late nineteenth century, another US study (Fegenbaum and Muller, 2016) estimated the effect of lead exposure from piped water on city-level homicide rates from 1921 to 1936 and found that cities that used lead pipe during that initial period had homicide rates that were 24% higher than the rate in cities that did not employ lead pipes. It was also found that a 1% increase in tonnage of air lead levels 22 years earlier increased a city's aggregate assault rate by 0.46% (95% CI 0.28-0.64) (Mielke and Zahran, 2012). And in comparing data from 8 countries, it was found that lead exposure in nation-specific regression models accounted for 63-95% of the temporal variation in arrests for violent crimes in those countries (Nevin, 2007). These findings

were supported by a cohort study that found a positive association between lead exposure and arrest for violent offences (Wright et al., 2008).

This association between lead and violence has been explained by the environmental hypothesis which holds that the "present period rates of adult violence are associated with spatial and temporal variation in childhood lead exposure, linked together by behavioural and cognitive mechanisms" (Mielke and Zahran, 2012). These behavioural and cognitive mechanisms include impulsivity, depressed intelligence quotient (IQ) and aggressivity. These are thought to be mediated by neurotoxicity in which lead exposure alters neurotransmitter and hormonal systems, thereby generating aggressive and violent behaviour (Stretesky and Lynch, 2004).

Apart from these chemical perturbations, structural changes have also been observed in the brain in the wake of lead exposure. Magnetic Resonance Imaging (MRI) studies show that adults who were exposed to lead during development have significantly lower grey matter volume compared to adults who were not (Cecil et al., 2008). And these volumetric grey matter losses are most prominent in the pre-frontal cortex and the anterior cingulate cortex, regions of the brain responsible for mood regulation, executive function and judgement (Brubaker et al., 2010). It is thought that early life blood lead impair formative brain development as the incomplete maturation of the blood brain barrier in foetuses and young children as well as the effect of lead itself on the barrier increases the ability of lead to enter the developing nervous system and thereby engender long term neuro-behavioural deficits (Needleman, 2004).

These nascent findings have been replicated in experimental animals. Predatory attack threshold in cats decreased significantly during initial lead exposure in 3 of 5 cats and increased after cessation of lead exposure in 4 of 5 cats (Li et al., 2003). Also, a study in golden hamsters

showed that lead exposed male hamsters were more likely to attack and bite their intruders than their corresponding unexposed ones (Delville, 1999).

A.1.2 Justification

Considering the ubiquity of environmental lead and its possible link to violence and aggression, it is important to explore this relationship by systematically examining the available literature. This is particularly relevant in the young adult population who are mostly responsible for acts of aggression and violence. Previous systematic reviews have tended to focus exclusively on children and adolescents (Marcus et al., 2010, Goodlad et al., 2013), , or confined itself to the association between lead exposure and intelligence (Pocock et al., 1994, Schwartz, 1994), attention deficit hyperactivity disorder (Goodlad et al., 2013) or broad, inclusive concepts like conduct problems which combine loosely related conditions like crime, delinquency, conduct disorder and anti-social disorders (Hall, 2013, Marcus et al., 2010). A systematic review of systematic reviews of explanatory risk factors for violence, offending and delinquency was published in 2017 evaluating underlying constructs contributing to violence, offending and delinquency but did not examine the relationship between lead and violence (Farrington et al., 2017).

Understanding the factors that may increase the risk of aggressive and violent behaviours in young adults is essential for developing effective prevention policies and programmes (Krug et al., 2002). Therefore, it is hoped that this evidence synthesis would ultimately be useful in estimating the burden of conditions, diseases and injuries attributable to environmental lead, for formulating policies to address the burden of environmental lead and in developing interventions to reduce the scourge of aggression and violence.

A.1.3 Description of the condition

Acts of aggression and violence involving young adults are a major problem worldwide. The definition of aggression and violence used in this review is that adopted by the World Health Organization (WHO) which defined violence as the "intentional use of physical force or power, threatened or actual, against oneself, another person, a group, a community that either results in or has a high likelihood of resulting into injury, death, psychological harm, mal-development or deprivation" (World Health Organization, 1996). This definition is complemented by the psycho-social definition wherein aggression is defined as "a behaviour that is intended to harm another person who is motivated to avoid that harm" while violence is defined as "an extreme form of aggression that has severe physical harm, for example, serious injury or death as its goal" (Allen and Anderson, 2015, Anderson and Bushman, 2002). Though the WHO definition includes suicide and other self-harm while the other definitions exclude these, common to both is the fact that violence is a ***behaviour*** that is ***intentional***. Thus, aggressive and violent behaviours are best considered as a continuum of severity in which minor acts of aggression (e.g., pushing) is at the lower end of the spectrum and violence (e.g., homicide) is at the upper end of the spectrum. So, all acts of violence would qualify as acts of aggression but not all acts of aggression would be considered as acts of violence.

The major perpetrators and victims of violence are young adults and youth violence is one of the most visible forms of violence (Reza et al., 2001). In 2000 alone, close to 200 000 youth homicides occurred worldwide, an average of 565 deaths of young people per day. Thus, violence by young people contribute significantly to the cost of health services, reduces a country's productivity and may undermine the fabric of society (Krug et al., 2002). Though for the purpose of the WHO report on world violence and health (Krug et al., 2002), youths were defined as "people between the ages of 10 and 29 years", that particular report recognised that high rates of offending and victimisation often extend up to the 30 – 35 years age bracket and

that this group needs to be taken into account in understanding and preventing youth violence. Also, a survey of homes in Johannesburg, South Africa, for example found that only 3.5% of victims of violence were 13 years old or younger while 74.2% were in the age range 14-35 years (Butchart et al., 1997). Recognising these peculiarities, this review will adopt the African Youth Charter definition of youths or young persons as people aged between 15 and 35 years (African Union Commission, 2006) in order to capture the full breath of this important population. Thus, aggression and violence by young adults in this review is taken as acts of aggression or violence committed by persons aged between 15 and 35 years of age.

There are a range of related terminologies and conditions which may be mediators or risk factors for aggressive or violent behaviours, but this review will not consider these as its primary outcome measures. These conditions include conduct disorders, antisocial disorders, psychopathy, juvenile delinquency, coercion, assertiveness, aggressive cognitions, aggressive affects or crimes without violence.

A.1.4 Description of the exposure

Lead, a non-biodegradable and non-corrosive heavy metal has been associated with toxicities for millennia (Needleman, 2004). The earliest victims of lead toxicity were lead workers and drinkers who took lead-seasoned wine as described by Mikander, a Greek physician of the second century BC (Needleman, 2004). However, the widespread use of lead began around the 1800s and it has now become a worldwide pervasive environmental pollutant present in water, earth crust and the atmosphere (Norman et al., 2007). Currently, exposure to lead occur via lead in petrol, paint, batteries, candles, crystal glass, cellular phones, computers, television sets, pottery, ammunitions, radiation protective clothing, fishing weights, wheel balancing weights, tobacco and traditional medicines and internalisation occur by ingestion, inhalation or dermal absorption (Norman et al., 2007).

Though elevated lead exposures, for example ≥60µg/dl, cause severe toxicities associated with lead poisoning which may manifest as anaemia, gastrointestinal effects, nephropathy, death or severe neurological sequelae like mental retardation, cerebral palsy and seizure disorder (Hubbs-Tait et al., 2005, Pruss-Ustun et al., 2004), low level exposure has been associated with a variety of negative psychological and developmental consequences (Needleman, 2009). There is no known safe threshold for lead exposure (Chiodo et al., 2004, Gavaghan, 2002).

Exposure to lead is harmful across the life span, interfering with the development of the central nervous system and is particularly potent during childhood and early adolescence, the critical period of brain development (Canfield et al., 2003). This suggests that the influence of lead exposure on aggression and violence may follow the critical period model with later effect modifiers as described in the life course approach to epidemiology (Ben-Shlomo and Kuh, 2002).

Environmental exposure to lead can be quantified at the aggregate or individual level. Examples of the first are air lead concentration for an area (Reyes, 2007), gasoline lead content in a jurisdiction (Reyes, 2007), water lead contamination (Fegenbaum and Muller, 2016) and city burden of lead (Mielke and Zahran, 2012). These measures use aggregate exposure and has the disadvantage that it uses a single aggregate measurement to represent exposure for people over a particular geographic area. The second include individual's blood lead levels (Wright et al., 2008), bone lead levels (Needleman et al., 1996), dentine lead levels (Fergusson et al., 2008) and hair lead levels (Marlowe and Bliss, 1993). These later measures are generally presumed to be better as they reflect the actual individual exposure, as someone might have been born in an area, move out and return and be assigned a particular aggregate lead level that may bear little relation to his actual level of exposure. The biomarker level in an individual thus reflects the person's exposure, absorption, kinetics and metabolism.

A.1.5 Peculiarities of investigating environmental exposures

Environmental exposures have certain peculiarities that are important to bear in mind in evaluating their association with health outcomes. For example, the dose-response curve for the relationship between exposure and outcome may not be linear; the strength of association may be relatively small and the risks of the outcome from environmental exposure may be small in individuals, but because the exposure occurs over a large area and population, it may generate a considerable burden and cost to public health.

As described by a classic epidemiology paper (Rose, 2001), the causes of incidence in the population are different from the causes of cases in individuals. To determine the causes of incidence and prevalence, we may need to study characteristics of populations, not just characteristics of individuals. While studies of individuals may help to answer the question "why are some individuals more likely to exhibit certain outcomes than others?", this may miss the more important public health point, which is: why is the outcome higher in one population compared to another? This is because if exposure is locally uniform, as it is for environmental toxins, it is unlikely to be identifiable as a risk factor for individuals because the traditional methods of investigating association using case control and cohort studies require heterogeneity between individuals for the identification of risk factors (Rose, 2001). Notably, environmental risk factors have greater heterogeneity between populations separated geographically or by time periods than between individuals within the same population.

Therefore, identifying causal agents by the traditional case control and cohort studies may be unsuccessful if there are not sufficient differences in exposures within the study population at the time of the study. In these instances what these traditional methods may achieve is to identify as risk factors markers of individual susceptibility and not the exposure that is common to all in the population. Thus, it is important to bear in mind that investigating environmental

risk factors such as the link between lead and violence may reveal differences only in ecological studies (Fegenbaum and Muller, 2016, Mielke and Zahran, 2012, Nevin, 2007, Nevin, 2000, Stretesky and Lynch, 2001) and not in other epidemiological studies. It is thus conceivable that significant associations may be found in ecological studies while no or insignificant relationships may be found at the individual level (Schwatz, 1994, Pearce, 2000).

However, since structural factors are associated with both lead and violence, the exposure and outcome variables in this review, deciphering the complex interactive relationship between biological factors and violence may be difficult due to the effects of third variables; and this difficulty is more pronounced with ecological studies than individual-level studies. This may account for the conflicting results of various studies on the subject. Therefore, because investigating causation requires the establishment of a direct relationship and confounders can be better controlled for at the individual level than at the aggregate level, this review will focus on individual level studies.

It is also recognised that publications on this topic may not be limited to English language. For instance, a study which described their method for conducting a systematic review of risk factors for conduct problems and youth violence in LMICs found that 85% of eligible studies were in English language while the remaining 15% were in Chinese, Spanish, Portuguese, Russian and French languages. Of the 15% in languages other than English, two-thirds were identifiable only by regional databases (Shenderovich et al., 2016).

It is therefore hypothesised that the effect of lead exposure on the development of aggressive and violent behaviour follows the critical period model, with a latency period of 10 to 20 years. The critical period is hypothesised as being early life, from gestation to age 12 years. Thus, exposure to subclinical lead at early life period is expected to be associated with the development of aggression and violence in later years.

A.1.6 Review question

This review will examine the following question: In young adults between ages 15 and 35 years, is early life exposure to environmental lead, defined as prenatal and childhood lead exposure up to the age of 12 years, a risk factor for the development of aggressive and violent behaviour?

A.1.7 Aim and objectives

This review aims to investigate the association between early life environmental lead exposure and later development of aggressive and violent behaviours in young adulthood.

Specific objectives include:

- To synthesise available evidence linking lead exposure and aggressive or violent behaviour
- To assess the consistency of the association of early life lead exposure and aggressive or violent behaviour
- To estimate the strength of association between early life lead exposure and aggressive or violent behaviour in young adulthood
- To investigate any dose response relationship between early life lead exposure and aggressive and violent behaviour in young adults
- To identify gaps in the evidence for the association of lead and aggressive or violent behaviour

A.2. METHODS

A.2.1 Review design and study types

This is a systematic review and meta-analysis of observational studies of aetiology, investigating the association between early life environmental lead exposure and aggressive and violent behaviour in young adulthood. Studies investigating temporal relationship between the exposure and outcomes would be included. Though a randomised controlled trial (RCT) is considered the gold standard in investigating causation, this is not feasible in this context. This review will thus include the following type of studies: Cohort studies and Case Control studies-traditional, case-cohort and nested case control

A.2.2 Population

For this review, the population of interest would be young adults between the ages of 15 and 35 years who must have been exposed to lead either in prenatal life or in childhood up to the age of 12 years.

A.2.3 Measures of outcome

The primary outcomes to be considered will include binary outcomes (presence versus absence) and/or counts of aggressive/violent behaviours such as violent crimes (murder, homicide, rape, simple and aggravated robbery and assault). Secondary outcomes would include scores on aggression or violence rating scales.

A.2.4 Measures of exposure

The following measures of exposure would be considered: blood, bone, teeth and dentine lead levels. These could have been determined prenatally using mother's blood samples, at birth using cord blood or thereafter up to the age of 12 years by using any of the previously mentioned tissues.

A.2.5 Measures of Effect

Risk Ratios (RR), Incidence Rate Ratios (IRR), Odds Ratios (OR) and Hazard Ratios (HR) would be considered the primary measures of association. Where indicated, Odds Ratios (OR) would be adjusted by the Zhang and Yu method (Zhang and Yu, 1998). Scores, mean difference, standardised mean difference (SMD) or correlation coefficients (*r*) would be considered as the measure of association for secondary outcome.

A.2.6 Inclusion and exclusion criteria

Studies with the following characteristics, without language restriction, will be included:

i. Examining relationship of early life lead exposure and young adults' aggressive or violent behaviour
ii. In populations aged 15 to 35 years
iii. With exposure determined before and up to the age of 12 years

The following studies will be excluded:

i. Cross-sectional studies
ii. Ecological studies
iii. Studies with age of exposure greater than 12 years
iv. Studies with outcome population age younger than 15 years or older than 35 years

A.2.7 Search methods for identification of studies

Sensitive searches using both keywords and MESH terms will be conducted with the help of a University of Cape Town librarian to identify eligible studies and the resulting citations documented (Appendix 7.1). The following worldwide electronic databases will be searched: PubMed, SCOPUS, Web of Science, Google Scholar, Cochrane collaboration, Campbell collaboration, Academic Search Premier, Cumulative Index to Nursing and Allied Health

Literature (CINAHL), PsycArticles and PsycINFO. Regional databases to be searched include: Scientific Electronic Library Online (SciELO), LILACS (Latin America and Caribbean) , Wanfang (China), China National Knowledge Infrastructure (CNKI), Western Pacific Region Index Medicus (WPRIM), Index Medicus for the Eastern Mediterranean Region (IMEMR), Index Medicus for the South-East Asian Region (IMSEAR) and Africa Wide Information . Grey literature, trial registers, conference proceedings and reference list of narrative and systematic reviews as well as primary studies will be hand-searched for relevant studies. Appendix A shows the search strategy to be applied to identify eligible studies, modified as necessary for each database. Data will also be requested from identified authors where the published article is incomplete, with a time limit of one month given for response.

A.2.8 Study selection

This review will employ a screening guide formulated specifically for the purpose to ensure fidelity to inclusion criteria (Appendix B). Two reviewers will independently go through the titles and abstracts of studies identified through the literature search to determine if they meet eligibility criteria. Thereafter, the full texts of eligible studies will be obtained and each will be independently assessed by two reviewers for final inclusion and the results compared. Disagreements will be resolved by discussion and consensus or by consultation with the supervisor. The reasons for exclusion of all studies on the exposure and outcome will be documented.

Included studies will be imported into a reference manager software (Endnote X7) and duplicate copies will be removed.

A.2.9 Data extraction and management

Two reviewers will independently extract data from each eligible article using a standardised, pilot-tested form (Appendix B). Any disagreements will be resolved by discussion and

consensus as well as consultation with the supervisor if necessary. The following data points will be extracted:

- Study author, year, period, country, design
- Objectives and inclusion criteria
- Study population, exposure and outcome data
- Measure of association and risk estimates
- Confounder adjustment and length of follow-up

The resulting data will be entered into an Excel spreadsheet (Microsoft Corporation, 2017). Data cleaning and cross-checking will be done to prevent data entry errors.

A.2.10 Assessment of risk of bias

Two reviewers will independently assess the quality of all included studies using a modified version of the Newcastle-Ottawa scale for both cohort and case-control studies. This instrument assesses seven questions under the following three domains: selection, comparability and outcome ascertainment.

A.2.11 Data synthesis

A.2.11.1 Statistical software All analyses will be conducted with Stata 16 statistical software (StataCorp, College Station, Texas, US).

A.2.11.2 Dealing with missing data In situations in which included studies have missing data deemed relevant, the authors would be contacted. If this data is not obtainable, then we will describe it and examine the influence of the missing data on the results.

A.2.11.3 Heterogeneity The included studies will be assessed for heterogeneity which would be quantified with Higgins I^2 statistics. Where there is significant heterogeneity ($I^2 > 50\%$), the studies will not be pooled, and the synthesis will be presented in a narrative format.

However, where heterogeneity is mild to moderate, the results will be pooled using random effects model and sources of heterogeneity investigated.

A.2.11.4 Assessment of reporting bias Small study effects including publication bias will be assessed with the aid of funnel plots.

A.2.11.5 Pooling Aggregate data from qualified individual studies will be pooled, if appropriate. Meta-regression may be carried out to assess the influence of confounders on the pooled estimate if the number of eligible studies is found sufficient for such analysis.

A.2.11.6 Sub-group analyses Sub-group analyses would be carried out based on study design, method of exposure measurement, types of outcome measures and the quality of included studies.

A.2.11.6 Sensitivity analyses Multiple sensitivity analyses would be done. The influence of study design, how the outcome is defined and the method of exposure assessment on results would be evaluated. Also, we would investigate the effect of excluding studies with poor quality and high risk of bias.

A.2.12 Reporting of the review

The findings of this review will be summarised with the aid of a PRISMA flow diagram (Moher et al., 2010) and reported according to the MOOSE guideline (Stroup et al., 2000).

A.3. ETHICAL CONSIDERATION

A formal institutional ethics review board clearance is not needed for this systematic review as it utilizes publicly available data. However, departmental approval would be sought from the School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa (Appendix 2).

A.4. LOGISTICS

A.4.1 Timetable

The timetable for this review is as outlined in Table A.4.1 below. The review process is expected to span between July 2018 and December 2020.

2018-2019	Jul-Sep 2018	Oct-Dec 2018	Jan-Mar 2019	Apr-Jun 2019	Jul-Sep 2019	Oct-Dec 2019	Jan-Mar 2020	Apr-Jun 2020	Jul-Sep 2020	Oct-Dec 2020
Departmental approval										
PROSPERO Registration										
Literature Search										
Data extraction										
Author correspondence										
Data analysis										
Write-up										
Submission										
Dissemination										

Table A.4.1. A Gantt chart of timeline for review

A.4.2 Budget

The proposed budget for this review is as detailed in Table 4.2 below. This cost would be covered by the research student as no specific funding was obtained for the review.

Items	Cost per Unit	Number of Units	Total Cost
Photocopies/Printing	ZAR 0.36/page	1000	360.00
Surface mails-international	ZAR 500/copy	2	1,000.00
Book purchase	ZAR 2000/copy	1	2000.00
Article purchase	ZAR 400/copy	3	1200.00
Software license	ZAR 500/copy	3	1500.00
Total (ZAR)			6060.00

Table A.4.2 Proposed budget for the review

A.5. DISSEMINATION

The potential users of the results of this review would be other researchers, governmental and non-governmental agencies and communities that are impacted by high burden of lead. The protocol for this review will be registered on PROSPERO and the final review will be submitted to the University of Cape Town School of Public Health and Family Medicine. In addition to dissemination at local and international meetings, the findings will also be published in a peer-reviewed journal.

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A.7 APPENDICES

Appendix 1: Search Strategy and Results

WORLDWIDE DATABASES

PubMed (Medline)

Result: 941 citations

(((((((lead[MeSH Terms]) OR lead poisoning[MeSH Terms]) OR blood lead levels) OR blood lead concentrations) OR lead exposure) OR lead poisoning)) AND ((((((((((((((((((((crime[MeSH Terms]) OR aggression[MeSH Terms]) OR social behavior disorders[MeSH Terms]) OR conduct disorder[MeSH Terms]) OR violence[MeSH Terms]) OR violent) OR violence) OR aggression) OR aggressive) OR rage) OR antisocial behavior) OR delinquent behavior) OR delinquency) OR conduct disorder) OR criminal arrest) OR criminal behavior) OR offending) OR violent crime) OR homicide) OR assault) OR rape) OR crime**):** Filter: Human

EBSco (Academic Search Complete; CINAHL; Violence & Abuse Abstracts; Criminal Justice Abstracts)

Result: 476 citations

blood lead levels OR blood lead concentrations OR lead exposure OR lead poisoning AND crime OR violen* OR aggress* OR rage OR assault OR homicide OR rape OR antisocial behavior OR delinquent behavior OR delinquency OR conduct disorder: Filter: 1962-2019

SCOPUS

Result: 1007 citations

("lead levels" OR "blood lead levels" OR "dentine lead levels" OR "hair lead levels" OR "bone lead levels" OR "blood lead concentrations" OR "lead exposure" OR "lead poisoning") AND ((TITLE-ABS-KEY (crime) OR TITLE-ABS-

KEY (violen*) OR TITLE-ABS-KEY (aggress*) OR TITLE-ABS-KEY (assault) OR TITLE-ABS-KEY (homicide) OR TITLE-ABS-KEY (rape) OR TITLE-ABS-KEY (offending) OR TITLE-ABS-KEY ("antisocial behavior") OR TITLE-ABS-KEY ("conduct disorder") OR TITLE-ABS-KEY (delinquency) OR TITLE-ABS-KEY ("delinquent behavior")))

Proquest Dissertation and Thesis Global

Result: 14 citations

noft("lead levels") OR noft("blood lead levels") OR noft("blood lead concentrations") OR noft("dentine lead levels") OR noft("hair lead levels") OR noft("bone lead levels") OR noft("lead exposure") OR noft("lead poisoning") AND noft(crime) OR noft(violence) OR noft(aggression) OR noft(rage) OR noft(assault) OR noft(homicide) OR noft(rape) OR noft(offending): Filter: 1913-2020

PsychINFO

Result: 62 citations

24/09/1919 – 18/06/2019

("blood lead levels" or "blood lead concentrations" or "lead exposure" or "lead poisoning" or "dentine lead levels" or "hair lead levels" or "bone lead levels").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] AND (crime or violen* or aggress* or rage or assault or homicide or rape or "antisocial behavior" or "delinquent behavior" or delinquency or "conduct disorder").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]

PsychArticles

("blood lead levels" or "blood lead concentrations" or "lead exposure" or "lead poisoning" or "dentine lead levels" or "hair lead levels" or "bone lead levels").mp. [mp=title, abstract, full text, caption text]

AND (crime or violen* or aggress* or rage or assault or homicide or rape or "antisocial behavior" or "delinquent behavior" or delinquency or "conduct disorder").mp. [mp=title, abstract, full text, caption text]

Web of Science CORE collection

(Science Citation Index Expanded (SCI-EXPANDED) --1900-present; Social Sciences Citation Index (SSCI) --1956-present; Arts & Humanities Citation Index (A&HCI) --1975-present; Conference Proceedings Citation Index- Science (CPCI-S) --1990-present; Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH) --1990-present; Book Citation Index– Science (BKCI-S) --2005-present; Book Citation Index– Social Sciences & Humanities (BKCI-SSH) --2005-present; Emerging Sources Citation Index (ESCI) --2015-present)

Result: 185 citations

TS=("blood lead levels" or "blood lead concentrations" or "lead exposure" or "lead poisoning" or "dentine lead levels" or "hair lead levels" or "bone lead levels")

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years AND TS=(crime or violen* or aggress* or rage or assault or homicide or rape or "antisocial behavior" or "delinquent behavior" or delinquency or "conduct disorder") , *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*

SciELO (Through Web of Science)

Result: 5 citations

TS=("blood lead levels" or "blood lead concentrations" or "lead exposure" or "lead poisoning" or "dentine lead levels" or "hair lead levels" or "bone lead levels") *Indexes=SCIELO Timespan=All years* AND TS=(crime or violen* or aggress* or rage or assault or homicide or rape or "antisocial behavior" or "delinquent behavior" or delinquency or "conduct disorder")

Indexes=SCIELO Timespan=All years

Cochrane Library

Result: 2 citations

"Lead levels"):ti,ab,kw OR ("lead concentrations"):ti,ab,kw OR ("lead exposure"):ti,ab,kw OR ("lead poisoning"):ti,ab,kw AND violence):ti,ab,kw OR (aggression):ti,ab,kw OR (crime):ti,ab,kw OR (assault):ti,ab,kw OR ("antisocial disorder"):ti,ab,kw

Campbell Collaboration

Result: 0 citations

Lead levels AND violence

REGIONAL DATABASES

LILACS

Result:156 citations

tw:((tw:("blood lead levels" OR "blood lead concentrations" OR "lead exposure" OR "lead poisoning" OR "dentine lead levels" OR "hair lead levels" OR "bone lead levels")) AND (tw:(crime OR violence OR aggression OR rage OR assault OR homicide OR rape OR "antisocial behavior" OR "delinquent behavior" OR delinquency OR "conduct disorder")))

Wanfang (China)

Result: 6 citations

Lead AND Violence **(铅金属 暴力）**

CNKI (China)

Result: 2 citations

Lead AND Violence

WPRIM (Western Pacific)

Result: 3

Abstract: violence OR Abstract: aggression AND Abstract: lead level

IMER

Result: 6 citations

violence [KeyWords] or aggression [KeyWords] and lead [KeyWords]

IMSEAR

Result: 7 citations

violence aggression AND "lead level

Africa Wide Information via EBSCOhost

Result:4 citations

AB "lead levels" AND AB violence OR AB aggression

Appendix 2. Departmental Approval

D1 + D3 - Approval of Study Proposal / Supervisor/s – amended April 2017

University of Cape Town

Faculty of Health Sciences

Form D1: Approval of Study Proposal

(incorporating Supervisor Approval)

SUBMISSION OF STUDY PROPOSAL FOR A MASTER'S OR DOCTORAL DEGREE *AFTER ETHICAL APPROVAL*

PLEASE NOTE: This form must not be sent to Ethics

I would like to submit the attached proposal and supporting documentation for consideration by the Dissertations Committee (after Ethics approval).

Signature (Candidate): Signature Removed Date 12 June 2018

SURNAME OF CANDIDATE	OBAMUYIDE	**FIRST NAMES**	HENRY
STUDENT NUMBER	OBMHEN001	PEOPLESOFT ID See stucent card	1 5 9 9 9 3 9
UCT STUDENT EMAIL ADDRESS	OBMHEN001@MYUCT.AC.ZA		
QUALIFICATIONS	MB;BS		
TITLE OF PROPOSED PROJECT **(Proposal attached)**	Early life lead exposure as a risk factor for aggressive and violent behaviours in young adults: a systematic review and meta-analysis protocol		
DEPARTMENT	School of Public Health and Family Medicine		
DEGREE NAME (e.g MSc (MED) IN HUMAN GENETICS)	MPH (Epidemiology and Biostatistics)	DEGREE CODE	M M 0 1 2
PROPOSAL APPROVED BY (Delete any one if not applicable) Human Ethics Committee, ERC No: Animal Ethics Committee, ERC No:	**If ethics approval is not required please motivate why not and provide the signature and name of Dept. Research Chair below** It is a systematic review and possible meta-analysis of already published data Prof Jill Olivier Signature Removed		
APPROVAL BY **SUPERVISOR** *For specialty/subspecialty master's degrees, this signature confirms that I am satisfied that the proposal meets the requirements of form D1a*	**Name:** RICHARD MATZOPOULOS **Signature:** Signature Removed		
NAME(S) OF CO-SUPERVISOR(S)	1. (Staff No:) 2. (Staff No:) 3. (Staff No:)		
FINAL SUBMISSION APPROVED BY HEAD OF DIVISION/OR DEPARTMENT	**Name:** Prof Willie London **Signature** Signature Removed		

Together with this form you must submit:

A copy of the ethics approval letter (if relevant); a copy of the department/ethics-approved study proposal; for specialty/subspecialty masters degrees a signed form D1a must also be submitted

For office use:

Received by:	Name:	Date:	
Captured on PSoft / Database	Name:	Date:	
Entered in DC	Name:	DC no: PG-Med	Date:

PART B: JOURNAL MANUSCRIPT[1]

Early life lead exposure as a risk factor for aggressive and violent behaviour in young adults: A systematic review

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South Africa

[1] Formatted for the journal: *Aggression and Violent Behaviour.*

ABSTRACT

Introduction

This review aims to synthesise individual level evidence on the association between early life lead exposure and aggressive or violent behaviour in young adults.

Methods

We conducted comprehensive searches in 17 electronic databases between September 19th and October 30th, 2019. Two reviewers independently screened all records and full texts, extracted data from included studies, and assessed risk of bias using the Newcastle Ottawa tool. Results were pooled by random effects meta-analysis. Relevant subgroup and sensitivity analyses were carried out.

Results

Six out of 2182 studies were found eligible. All were conducted in high income countries and were of moderate to good quality. The definition of violence varied across studies. Blood lead level was associated with an increased risk of arrest or conviction for violent crime (pooled OR: 1.16; 95% CI: 1.10 – 1.23 for each 5µg/dl). There was insufficient data to conduct a dose response meta-analysis.

Conclusion

Despite heterogeneity in study designs, settings and definitions, studies consistently reported an association between lead exposure in childhood and violent behaviour in young adulthood. Better reported studies, particularly from lower resourced settings, are needed to confirm these results. Environmental lead control may help to reduce aggressive and violent behaviour in young adults.

Keywords: Systematic Review, Lead, Violence, Aggression, Youth

Table of Contents

B.1 INTRODUCTION

Each year, over 1.3 million persons lose their lives as a result of violence (GBD, 2017). In addition, violence results in non-fatal injuries (Butchart et al., 2014), psychological trauma and social displacement (Lee, 2015a). The morbidities associated with violence include effects on mental, behavioural, sexual, reproductive and social health (Butchart et al., 2014). Therefore, more than just lives lost, violence places a huge economic burden on societies, ranging in estimates from 3.3% to 5% of a country's Gross Domestic Product (GDP) (Buvinic and Morrison, 1999, Miller et al., 2001).

While aggression is a behaviour with the immediate aim to harm that is directed at another person who does not consent to be harmed (Anderson and Bushman, 2002), violence is the "intentional use of physical force or power, threatened or actual, that results in or has a high likelihood of resulting in injury, death, psychological harm, maldevelopment or deprivation" (Krug et al., 2002).

The aetiology of violence and aggression is multi-factorial. A useful framework for understanding the causation of violence is the Socio-Economic Model (SEM), adapted for violence prevention by the World Health Organisation in its report on violence and health (Bronfenbrenner, 1979, Krug et al., 2002). These influences operate at the individual, relationship, community, societal and structural levels; they interact and create a nexus for violence and aggression. For instance, in addition to age and gender, various other individual factors like genetics, mental disorder, substance and alcohol abuse, low educational attainment, personality disorders, psychological traits like impulsivity, prior histories of aggression and violence and exposure to lead contribute to the tendency towards aggression and violence (Lee, 2015b).

Lead exposure is common as lead is ubiquitous in the environment. An estimated 120 million persons worldwide had a blood lead level of 5µg/dl and 10µg/dl in the year 2000 and majority of these live in Low- and Middle- Income Countries (LMIC) (Pruss-Ustun et al., 2004). Exposure to lead occurs via ingestion, inhalation or dermal absorption of lead in gasoline, soil, paint, batteries, candles, crystal glass, cellular phones, fishing weights, wheel balancing weights, tobacco, traditional medicines and living near old smelter plants (Norman et al., 2007). As lead level in the environment is eminently controllable, it is thus conceivable that environmental lead exposure could be one of the preventable causes of aggression and violence.

Exposure to lead is harmful across the lifespan but it is especially potent during critical brain development that takes place in the interval between birth and early adolescence (Canfield et al., 2003). This suggests a critical period model with later effect modifiers as described in the life course approach to epidemiology (Ben-Shlomo and Kuh, 2002). Environmental toxins like lead act through epigenetic mechanisms (Lee, 2015b). It is postulated that early lead exposure leads to neurotoxicity by altering neurotransmitter and hormonal systems (Stretesky and Lynch, 2004, Martinez-Lazcano et al., 2018) and by causing structural changes in the developing brain such as lower grey matter volume in the pre-frontal cortex and the anterior cingulate cortex, areas of the brain responsible for mood regulation, executive function and judgement (Cecil et al., 2008, Brubaker et al., 2010), thereby generating aggressive and violent behaviour.

B.1.1 Lead and Violence

The first report of a possible association between lead exposure and aggressive behaviour was made by Byers and Lord in 1943 in which they described 20 children who had ‘recovered’ from lead poisoning; two of these children manifested aggressive behaviour including fighting with their teachers (Byers and Lord, 1943). Since then multiple studies have been published

implicating lead in the possible causation of aggression and violence. For instance, in animals, a study in golden hamsters showed that lead-exposed male hamsters were more likely to attack and bite their intruders than their corresponding unexposed ones (Delville, 1999) and a study in cats found that predatory attack threshold decreased significantly during initial lead exposure in 3 of 5 cats and increased after cessation of lead exposure in 4 of 5 cats (Li et al., 2003).

Many human ecological studies, across multiple levels, have shown a link between lead exposure in childhood and the later development of violence. In a study comparing data across 8 countries, Nevin found that lead exposure accounted for 63-95% of the variation for arrests for violent crimes (Nevin, 2007). An econometric analysis of US national data looking at different states found that childhood lead exposure was associated with rates of violent crimes 20 years later when children exposed to lead reach peak age for criminal activities (Reyes, 2007). Using homicide data between 1989 and 1991, another US study found that counties with lead equivalent to 0.17µg/m^3 had homicides rates that were four times the homicides rates in counties with air lead levels of 0µg/m^3 (Stretesky and Lynch, 2001). This relationship has also been documented by several other aggregate level studies (Feigenbaum and Muller, 2016, Mielke and Zahran, 2012, Taylor et al., 2016, Nevin, 2000, Boutwell et al., 2016, Boutwell et al., 2017).

In addition to ecological findings, many individual level studies have shown similar correlation. In South Africa, association were found between blood lead levels and violent behaviours in a Johannesburg cohort of adolescents (Naicker et al., 2012, Nkomo et al., 2017). Also, in the United States, Wright and co-workers found a positive association between lead exposure and arrest for violent offenses (Wright et al., 2008) while Needleman et al found that adjudicated delinquents were four times more likely to have bone lead levels > 25ppm than controls after adjusting for confounders in a case control study (Needleman et al., 2002a).

However, these findings have been challenged. McCall and Land, using the same data as Nevin (Nevin, 2000) re-examined Nevin's hypothesis using a different analytic approach. Employing Age-Period-Cohort analysis, they were unable to find an association between lead levels and youth troubled behaviours, including murder rates (McCall and Land, 2004). Also, the importance of which data were chosen for conducting these ecological studies have been highlighted by Lauritsen et al who found significant differences in rates and correlations for different crimes based on the definitions used in the different databases (Lauritsen et al., 2016). Furthermore, Fergusson et al found that lead exposure accounted for less than 1% in the variation in arrests for violent crimes after controlling for other covariates while Beckley could not demonstrate a statistically significant association between blood lead and violent crime (Fergusson et al., 2008, Beckley et al., 2018).

A narrative review had sought to examine if reduction in lead exposure was responsible for reduced crime rate in the US (Hall, 2013), but it combined both aggregate and individual level data and was not systematic while a previous systematic review had focused on the effects of lead on conduct problems (Marcus et al., 2010). Considering the ubiquity of lead in the environment, the heavy tolls of violence and the variation in study results, it is important to explore this relationship in a systematic way. However, as structural factors are associated with both lead exposure and violence, deciphering the complex relationship between biological factors such as lead and violence may be challenging (Lee, 2015b, Wilson, 2016). Therefore, considering that these challenges are greater with ecological studies, this review will focus on individual level studies.

B.1.2 The Present Study

This review sought to find out in a systematic way, using all available individual level data where exposure could be ascertained to have occurred before the index behaviour, whether in young adults an early life exposure to lead is a risk factor for the development of aggressive

and violent behaviour. Specifically, it sought to synthesize all the available individual-level data linking lead exposure to aggressive and violent behaviour, assess the consistency and estimate the strength of this association, examine for dose-response relationship and identify relevant gaps in the literature.

For this review, a young adult is defined as a person between the ages of 15 and 35 years in keeping with the African Youth Charter (African Union Commission, 2006), recognising that offending and victimisation occur most commonly within this age bracket (Butchart et al., 1997). Studies were included if they assessed aggression or violence in young adults aged 15 to 35 years, with lead exposure level determined from *in utero* up to age 12 years and were cohort or case control studies with individual-level data. Studies were excluded if based on aggregate data. This report follows the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting recommendations (Appendix E) (Stroup et al., 2000).

B.2 METHODS

B.2.1 Search and Study Selection

Studies investigating temporal relationship between lead and aggression/violence using individual-level data were included. Because randomised controlled trials (RCTs) are not ethical for the investigation of this association this review considered only cohort studies and case control studies. The population of interest was young adults and youths between the ages of 15 and 35 years who had assessment for aggression and/or violence behaviour and had a documented lead exposure assessment carried out before age 13 years, using blood, bone, teeth or hair lead. Primary outcome was counts of violent behaviour, including violent crimes such as murder, homicide, rape, common and aggravated robbery and assault. Secondary outcomes included aggression and violence scores on tests. Various measures of relative risks, such as Risk Ratios (RR), Incidence Rate Ratios (IRR), Odds Ratios (OR) and Hazard Ratios (HR)

were considered. No language or time restrictions were applied. Ecological studies, cross-sectional studies and studies not meeting age criteria for the outcome and exposure were excluded.

This systematic review and meta-analysis was conducted in accordance with the Joanna Briggs Institute and COSMOS-E guidance documents (Moola, 2015, Dekkers, 2019). The team consisted of the primary investigator aided by a University of Cape Town librarian and experts in violence research, lead research, systematic review methodology and a statistical consultant.

The search plan consisted of sensitive searches using both keywords and MESH terms in many databases to identify eligible studies. Appendix A shows the search strategy for PubMed and this was modified as appropriate for each database. The following worldwide databases were searched: PubMed, SCOPUS, Web of Science, Cochrane Collaboration, Campbell Collaboration, Academic Search Premier, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsychArticles and PsychINFO. In addition, the following regional databases were searched: Scientific Electronic Library Online (SciELO), Latin America and Caribbean (LILACS), Wanfang, China National Knowledge Infrastructure (CNKI), Western Pacific Region Index Medicus (WPRIM), Index Medicus for the Eastern Mediterranean Region (IMEMR), Index Medicus for the South-East Asian Region (IMSEAR) and Africa Wide Information. Grey literature as well as reference list of narrative and systematic reviews and primary studies were also searched. Title and abstracts in non-English articles were translated for screening.

This review utilised a screening guide formulated specifically for this purpose (Appendix B). Search results were imported into a reference manager software (EndNote X7) for screening and duplicate copies removed. Two reviewers independently screened the titles and abstracts of the articles and potentially eligible publications were then assessed independently by both

reviewers for inclusion. Disagreements were resolved during discussions to reach consensus. Reasons for exclusion of each full article assessed were documented.

B.2.2 Data Extraction and Management

Two reviewers independently extracted data from each eligible study using a standardised and pilot tested form (Appendix B). Disagreements were resolved by discussion and consensus. The following datapoint were extracted: study author, year of publication, country of study, study design, aim, study population, exposure and outcome data, measure of association, confounders and duration of study. These were then entered into an Excel spreadsheet (Microsoft Corporation), cleaned and cross-checked for errors before analysis. A modified version of the Newcastle-Ottawa Scale (Wells et al.) was used independently by two reviewers to assess the risk of bias of each eligible study (Appendix C).

B.2.3 Ethics and Protocol Registration

A formal ethics approval was not obtained as the review utilized already published data. A protocol registration data for this review is available at the PROSPERO site: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019145031.

B.2.4 Data Synthesis

All statistical analyses were conducted using Stata 16 IC (StataCorp, College Station, Texas 2019). Statistical heterogeneity was quantified with Higgins I^2 statistics. Small study effects were examined with a Funnel plot. Meta-analysis was conducted with a random effects model with restricted maximum estimation method. As all studies were analysed with regression methods giving measures of association in relation to different weight of increase in lead levels, a uniform increase of 5µg/dl was chosen for this analysis. A sub-group analysis based on method of outcome assessment, counts versus dichotomous variable, was performed. Also, sensitivity analyses, examining the effect of including the only study utilizing dentine lead level as exposure variable or the exclusion of the study with the greatest weight were carried out.

B.2.5 Justification for Meta-Analysis

Being a systematic review of epidemiological study of environmental exposure and a behavioural outcome with health implications, some variability in exposure and outcome assessments was expected. Therefore, as four of the included studies had clinical, methodological and statistical homogeneity, a meta-analysis was considered justifiable. Essentially, these studies examined the relationship of blood lead levels determined in children up to age 12 years with violent crime arrest or conviction when they were between the ages of 15 to 35 years.

B.3 RESULTS

B.3.1 Study Selection

A total of 2951 citations were identified through literature search between September 19th and October 30th, 2019 (Figure B.1). Two additional papers were identified through hand-searching. After duplicates were removed, a total of 2182 articles remained, out of which 15 potentially relevant studies were identified. The full papers of these studies were then procured and reviewed by the two reviewers for inclusion. Out of these, 7 papers representing reports of 6 studies met inclusion criteria and were included in the analysis. Eight studies were excluded for various reasons, including outcomes not satisfying inclusion criteria, difficulty in ascertaining exposure time and using predicted exposure variable (Appendix D).

Two publications were an initial and a follow-up report of the same study; only the more recent study (Wright et al., 2008) was included in the final analysis while the earlier study (Dietrich et al., 2001) provided additional background data. Two studies contributed to the narrative synthesis but were not included in the meta-analysis because one lacked usable data (Denno, 1990) and the other had a different method of exposure assessment (Fergusson et al., 2008).

B.3.2 Narrative Synthesis

B.3.2.1 Study characteristics

Table B.1 provides a summary of the study characteristics. One study was split across two publications: one publication reported the relationship between lead exposure and anti-social/delinquent behaviours (including violence against others) when the cohort was aged 15 - 17 years (Dietrich et al., 2001) while the other reported the relationship between lead exposure and violent acts at age 19 – 24 years (Wright et al., 2008). The number of studies was equally split between retrospective and prospective cohort design. The studies were conducted exclusively in High Income Countries (HIC): four in the United States and two in New Zealand. Participants for the studies were recruited between 1959 and 1997. Five of the studies came out in the decade between 2008 and 2018 while one study was published ten years earlier in 1990. Four were published peer reviewed articles, one was a book and the other a PhD thesis.

There were varying but overlapping definitions of what constituted violent crime as described in Table B.1: it ranged from firearm homicide or victimisation (Emer, 2017) to murder, simple assault, assault with intent to kill, rape, robbery with injury and any offense resulting in injury to victim (Denno, 1990). While one study was very narrow in its definition (Emer, 2017), the others employed a broader definition of violent crime. None of the studies reported aggression specifically. The outcome was assessed as counts in four studies and as binary variable in two. All published studies included sponsorship information except the unpublished thesis (Emer, 2017).

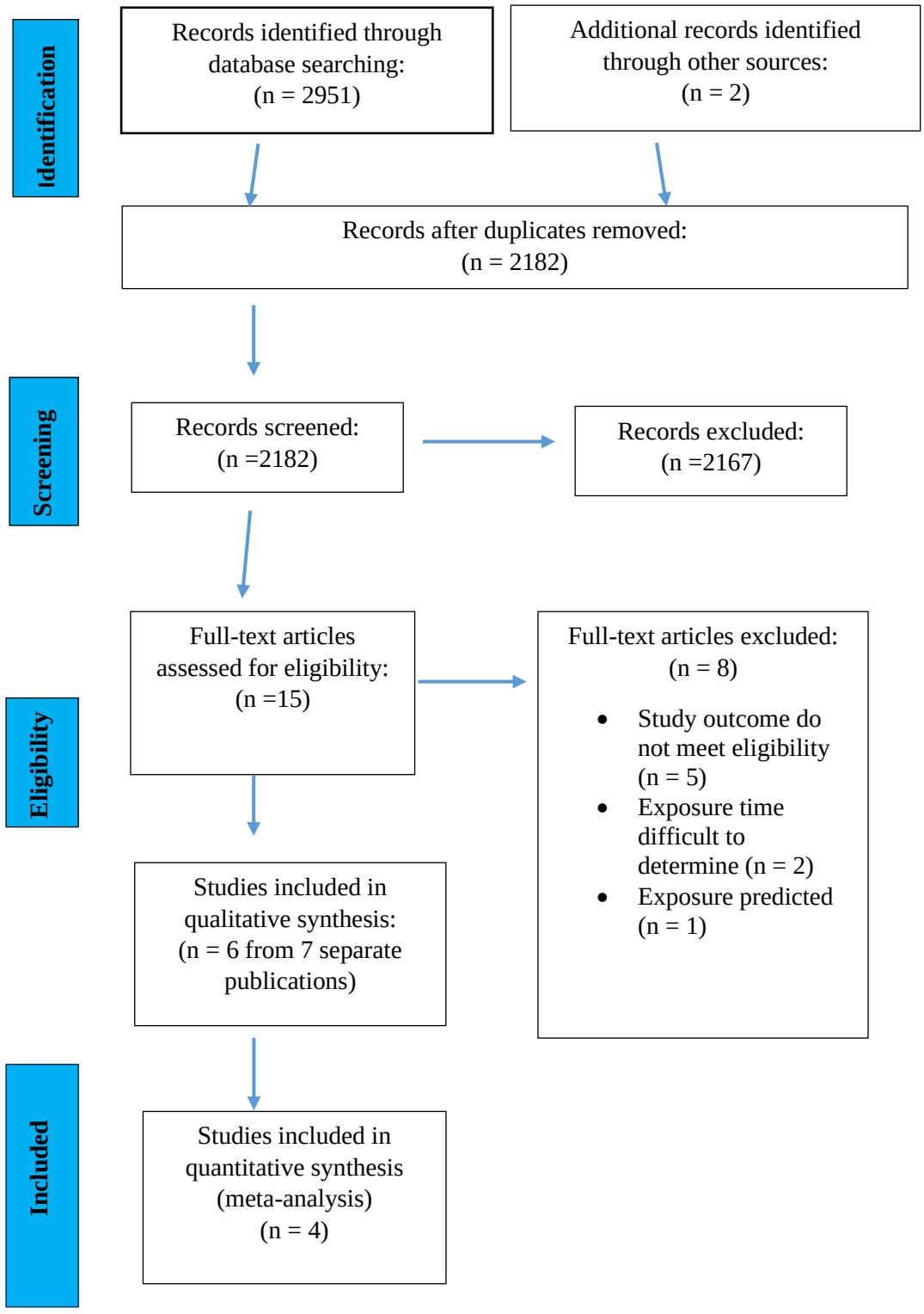

Figure B.1. PRISMA Flow Diagram

B.3.2.2 Participant characteristics

A description of participants details is shown in Table B.2. Half of the studies assessed exposure to lead up to age six while the other half assessed lead exposure at between age 7 and 11 years. However, age at outcome assessment range from 16 to 38 years. Proportion of participants that were male range from 46% to 51%. In only one of the studies (Beckley et al., 2018), is the sample representative of the source population. The American studies included mainly racial minorities. One study represented the full range of socio-economic status (SES), one under-represented individuals from low SES while the others consisted mainly of individuals from low SES. The mean childhood blood lead level ranges from 6.2 ug/dl to 13.4 ug/dl.

B.3.2.3 Included Studies

While some of the studies examined violent crime as a binary outcome - (present or absent), most studies (n = 4) reported it as a count variable, measuring the number of occurrences of violent acts. The sample sizes range from 250 to 89,129. Table B.3 presents a summary of the results of the individual studies.

B.3.2.3.1 Violent crime as binary outcome

The two studies reporting violence and violent crimes as a binary outcome found a higher odds of being arrested for or perpetrating violent crime with increasing blood lead levels (BLL), with an OR (95% CI) of 1.13 (0.82 – 1.55) for each 5µg/dl increase in BLL and 1.03 (1.02 - 1.03) for each 1µg/dl increase in BLL respectively (Beckley et al., 2018, Emer, 2017). Though both studies consistently report an increased odd of violent crime with increasing BLL, the first study was not statistically significant while the second study reached statistical significance. Thus, Beckley et al could not demonstrate an association between BLL and violent crime while Emer did.

Study	Study Design/Country	Recruitment years	Violence/Aggression	Nature of Outcome	Publication type	Aim/Objectives	Sponsorship
Beckley (2017)	Retrospective cohort/ Dunedin, New Zealand	1975 - 1976	Simple and aggravated assault, gang fighting, robbery, arson and forced sex	Binary: Conviction vs No Conviction	Full text	Effect of lead on crime. -association with crime conviction -association with recidivism - association with violent offending# -association with self-reported offending	New Zealand Health Research Council, New Zealand Ministry of Business, Innovation, and Employment, US National Institute of Aging, UK Medical Research Council, Economic and Social Research Council, Jacobs Foundation, Avielle Foundation, Seventh Framework Programme
Denno (1990)	Prospective cohort/ Philadelphia, United States	1959-1962	Murder, Assault with intent to kill, Simple assault, Rape, Robbery with injury, any offense resulting in injury to victim	Counts: Number of offenses	Book	Examine various influences on crime	National Institutes of Justice, US Department of Justice
Emer (2017)	Retrospective cohort/ Milwaukee, United States	Linked data queried for individuals born between June 1986 – December 2003 with BLL and police data	Firearm victimization and Homicide, Firearm Victimization (Suspect, arrestee or person of interest)	Binary: Victimization vs No-Victimization	Thesis	Is lead exposure in childhood associated with - firearm victimization - firearm perpetration Is there a specific association between BLL and argument-related firearm violence compared to other types of firearm violence?	Not stated
Ferguson (2008)	Prospective cohort/ Christchurch, New Zealand	Birth cohort born in 1977	Assault, Fighting, Robbery, use of Weapon, threats of Violence against a person	Counts: Mean number of convictions	Full text	Determine if lead exposure is associated with increased criminal behaviour	Health Research Foundation of New Zealand, National Child Health Research Foundation, Canterbury

						Estimate the extent to which lead exposure is responsible for increases in criminal behaviour	Medical Research Foundation, New Zealand Lottery Grants Board
Sampson (2018)	Retrospective cohort, Chicago, United States	1995 - 1997	Violent arrest not specifically defined	Counts: Number of arrests	Full Text	Investigate the effect of childhood lead poisoning on delinquency and official criminal histories	Ford Foundation, Hutchins Family Foundation, Hymen Milgrom Supporting organization
Wright (2008)	Prospective cohort/ Cincinnati, United States	Recruited between 1979-1984	Murder, rape, domestic violence, assault, robbery, or possession of a weapon	Counts: Number of arrests	Full Text	Determine if prenatal and childhood lead exposure are associated with arrests for criminal offenses	National Institutes of Environmental Health Sciences; US Environmental protection Agency
Dietrich (2001)*	Prospective cohort/ Cincinnati, United States	Cincinnati Lead Study recruited 1979-1985	Not defined. Included because results stated "Females and males were equally likely to self-report antisocial/delinquent behavioural events (including violence against others)…"	Continuous: Scores on SRDB and PRDB	Full Text	Appraise the relationship between early lead exposure and neuropsychologic and social functioning in middle adolescence	National institutes of Environmental Health Sciences. National institute of Health

* Same cohort as Wright (2008). SRDB: Self-Report Delinquency Behaviour. PRDB: Parent-Report Pre-delinquent and Delinquent Behaviour

Table B.1. Study Characteristics

B.3.2.3.2 Violent crime as count outcome

Four studies reported violence in the form of violent crime as count variables, with three of them using negative binomial regression for the main analysis, except Denno which used structural equation modelling. While three of the studies used BLL as the exposure variable, one (Fergusson et al., 2008) used dentine lead levels obtained from deciduous teeth. Both Fergusson et al and Wright et al found a positive association between lead and violent crime, with a 63% higher rate of official conviction for each 1µg/g increase in dentine lead, and a 30% higher rate of arrest for violent crime per each 5µg/dl increase in BLL respectively (Fergusson et al., 2008, Wright et al., 2008). There was no significant association between BLL and number of arrests in the Sampson et al study (Sampson and Winter, 2018). Denno did not report a direct relationship between blood lead concentration and number of official convictions between ages 18-22 in males, but reported a derived estimate through a reduced form equation that took into consideration the influence of lead on two intermediate variables – delinquency and disciplinary problems (Denno, 1990).

Study	Exposure Age	Outcome Age	Male: Number (%)	Ethnicity	Socioeconomic status	Mean Lead level
Beckley (2017)	11	Self-report:15 – 38. Police record: 21 - 38	255 (46.11)	Primarily White (Representative of general population, % not stated)	Full range of SES	11.01µ/dl (Blood)
Denno (1990)	7	Delinquency: 7-17 Young Adult Crime: 18-22	487 (49.34)	Mainly Black – 100% Not representative of general population	Low: One Decile below US general population	Not stated
Emer (2017)	Birth - 6	Victim: 13 – 30 Older than 20: 93% Perpetrator: 12- 27	45,774 (51%)	Black – 63%, White – 27%, Others – 10% (Not representative of general population)	Mainly low: 74 % low SES, 20 Middle, 4% in Upper and 3% in Other	7.6 µg/dl (Blood) (for source population)
Fergusson (2008)	6 - 8	14 - 21	635(50.20%) for the total cohort	Non-Maori and Maori. Proportion not stated.	Sample under-represented individuals from low SES	6.2µg/g (Dentine)
Sampson (2018)	Birth - 5	16 – 18 (CBCL) > 21 for official arrest	100 (47%)	Black 49%, White 12% Hispanic 34%, Others 5%	Low SES (Receives TANF: 45%).	6.20µg/dl (Blood)
Wright (2008)	Prenatal – 6.5	19 - 24	125 (50%)	Black 90% (Not representative of general population)	Mainly low SES	13.4µg/dl (Blood)
Dietrich (2001)	Prenatal – 6.5	15 -17	53%	Black 92% (Not representative of general population)	Mainly low SES	Not stated

CBCL: Child Behaviour Checklist| TANF: Temporary Assistance for Needy Family| SES: Socio-Economic Status

Table B.2. Participants Characteristics

Study	Number Analytic /Violent	Exposure Assessment – Lead Measure	Outcome Assessment – Violence/Aggression Measure	Statistical analysis method - Specific	Confounders adjusted for	Measure	Effect Size
Beckley (2017)	553/53	Blood lead – venous. Graphite furnace atomic absorption spectrophotometry	Official conviction records from age 14 to 38 (1– conviction; 0 – no conviction) (one-time vs recidivated offender) **(**non-violent vs violent crime) Self-reported offending from age 15 – 38, converted to a variety score for offense type calculated by summing 1 point for every 'yes' to each type of offense but Winsorized at 10	# Logistic regression (conviction vs no-conviction) *Multinomial logistic regression (one-time vs recidivating vs non-offender) (nonviolent vs violent vs nonoffender) *OLS regression *Accuracy of BLL to discriminate between conviction and no-conviction tested by ROC curves and AUC	Sex (Male) *SES and Ethnicity corrected for by restriction*	OR for each 5µg/dl increase	1.13 (0.82-1.55) p = 0.45
Denno (1990)	487/36	Blood lead Exact lab method not stated	Official police records: violent, property and non-index offenses	Structural Equation Modelling with forward selection	Family income, Family size. This analysis restricted to male sample	NS	0.080[&] (Male)
Emer (2017)	89129/ 554 [$]	Mean childhood blood lead – venous and capillary Exact lab method not stated. *Peak lead also used for analysis in study*	Official police records of firearm perpetration or victimization (Yes or No)	#Logistic regression *Multinomial logistic regression	Sex, Race, SES, Year of Birth	OR (for each 1µg/dl increase)	1.03 (1.02-1.04)
Fergusson (2008)	984/853	Dentine lead levels Flameless atomic absorption spectrophotometry	Official conviction records – mean number of violent or property conviction from 14-21 years Self-report –offending ages 14-21 (Self-report Early	#Negative Binomial Regression (After adjustments, Lead accounted for < 1% of the variance in conviction).	Maternal education, SES, Ethnicity, Family conflict, maternal smoking during pregnancy, childhood physical abuse, parental alcohol problems, parental offending	B (for each 1µg/g) increase	0.49 (0.17 SE) p = 0.005

			Delinquency Scale and Self-report delinquency Inventory)				
Sampson (2018)	254/212	Average blood lead level before age 6 – venous, some capillary Exact laboratory method not stated	Number of arrests from official record – at 21+ Antisocial behaviour scale part of Child Behaviour Checklist-ages 16-18	# Negative Binomial Regression for arrests *Ordinary Least Squares regression for standardized antisocial scores	Age, Ethnicity, Sex, immigrant generational status, parental educational level, SES (TANF), caregivers' marital status	B (for each 1µg/dl increase)	0.02 (-0.07 – 0.11)
Wright (2008)	250/NS-14%	Prenatal, average childhood and age 6.5 years BLL Exact laboratory method not stated	Official arrest data – number of violent crimes and total criminal arrest since turning 18 (108 of 800 arrests were for violent crime)	Negative Binomial Regression	Sex, SES score, Maternal IQ and Maternal Education.	RR[c] (For each 5µg/dl increase)	Prenatal BLL: 1.34 (0.88-2.03) Mean childhood BLL: 1.30 ?1.48 (1.03 – 1.64)
Dietrich (2001)	195/157[a]/ 186[b]	Prenatal, Mean childhood and age 6.5 years BLL Exact laboratory method not stated	Self-Report Delinquent Behaviour questionnaire (SRDB) score at age 15 - 17 Parent Report of Pre-delinquent and Delinquent Behaviour (PRDB) score at age 15 - 17	#Multiple Linear Regression *ANCOVA	Birth weight, HOME score, SES, and parental IQ	B	PRDB Scores Prenatal: 0.194 (SE 0.089) Average: 0.090 (SE 0.056) SRDB Scores Prenatal: 0.192 (SE 0.076) Average: 0.101 (SE 0.047)

TANF: Temporary Assistance for Needy Families| SES: Socio-Economic Status | SRDB: Self-Report Delinquent Behaviour Score | PRDB: Parent-Report Pre-delinquent and Delinquent Behaviour Score| HOME Score: Home Observation for Measurement of the Environment |BLL: Blood Lead Level |OR: Odds Ratio | RR: Rate Ratio | B: B coefficient| [$]: Perpetrators |a = Prenatal |b = Postnatal| c = Rate Ratio|1°: Primary |2°: Secondary| NS: Not Stated|[&]: Not a direct Coefficient |SE: Standard Error. Where available, adjusted estimates are used. Dietrich provided data on dose-response.

Table B.3. Study Results

B.3.3 Quality Assessment

The quality rating of included studies ranges from five to six out of seven points, using a modified Newcastle Ottawa scale, with a median of six (Table B.4). This is a narrow range of quality scores indicating that the studies are of similar quality.

Indicators/Studies	**Beckley**	**Denno**	**Emer**	**Ferguson**	**Sampson**	**Wright**	**#Dietrich**
SELECTION							
1. Representativeness of the exposed cohort	*	o	*	*	*	o	o
2. Selection of the non-exposed cohort	*	*	*	*	*	*	*
3. Ascertainment of exposure	*	*	*	*	*	*	*
COMPARABILITY							
1. Comparability of cohorts on the basis of design or analysis	*	*	*	*	**	**	**
OUTCOME							
1. Assessment of outcome	*	*	*	*	*	*	o
2. Adequacy of follow-up of cohorts	*	*	*	o	o	*	o
TOTAL SCORE	******	*****	******	*****	******	******	****

* one star earned | º no point earned | # Same data as Wright et al | ± This is modified because item 4 of Selection (demonstration that outcome of interest was not present at start of study) and item 2 of Outcome (was follow-up long enough for outcomes to occur?) were removed as they are not applicable this review. Outcome (young adult violence) cannot be present in childhood and also studies with inadequate period between exposure and outcome were excluded a priori.

Table B.4. Modified± Newcastle-Ottawa Scale

B.3.4 Meta-analysis

B.3.4.1 Main findings

The four included studies that reported this outcome had an association between blood lead levels and the odds of committing or being arrested and convicted for a violent crime, with OR ranging from 1.16 to 1.30 for each 5ug/dl rise in childhood blood lead levels. The summary

Odds Ratio (95% Confidence Interval) was 1.16 (1.10 – 1.23) for each 5ug/dl increase in blood lead. One study, Emer dominated the studies with a weighting of over 90%. A forest plot is shown in Figure B.2.

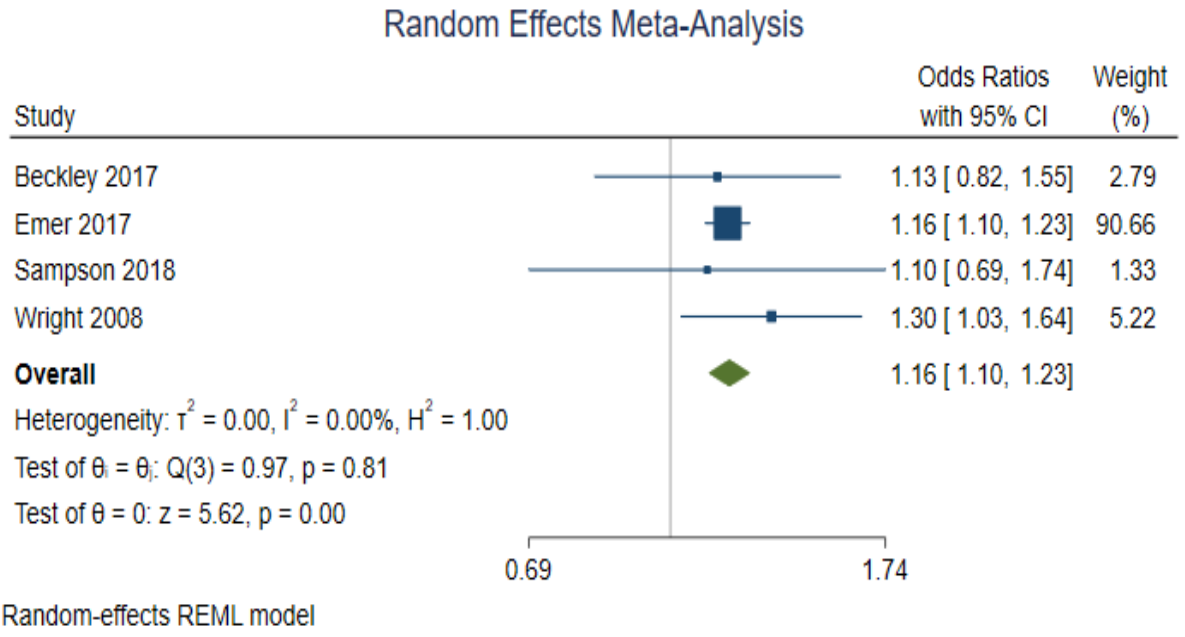

Figure B.2. Forest plot, with a vertical line indicating the point of no risk (OR = 1.00). Effect sizes is OR for each 5µg/dl change in blood lead.

B.3.4.2 Heterogeneity

There was considerable overlap in the confidence intervals of the effect sizes derived from each study. The I^2 was 0.00, suggesting lack of statistical heterogeneity. Thus, the variance of the effect size reflects mainly the influence of within-study sampling error with limited between-study heterogeneity.

B.3.4.3 Sub-group and Sensitivity analyses

With the significant homogeneity of the results, a sub-group analysis was not strictly warranted but because some studies measured the outcome as a dichotomous variable while others measured the outcome as a count variable, a subgroup analysis based on the measure of association (Rate Ratio versus Odds Ratio) was carried out and is shown in Figure B.3.

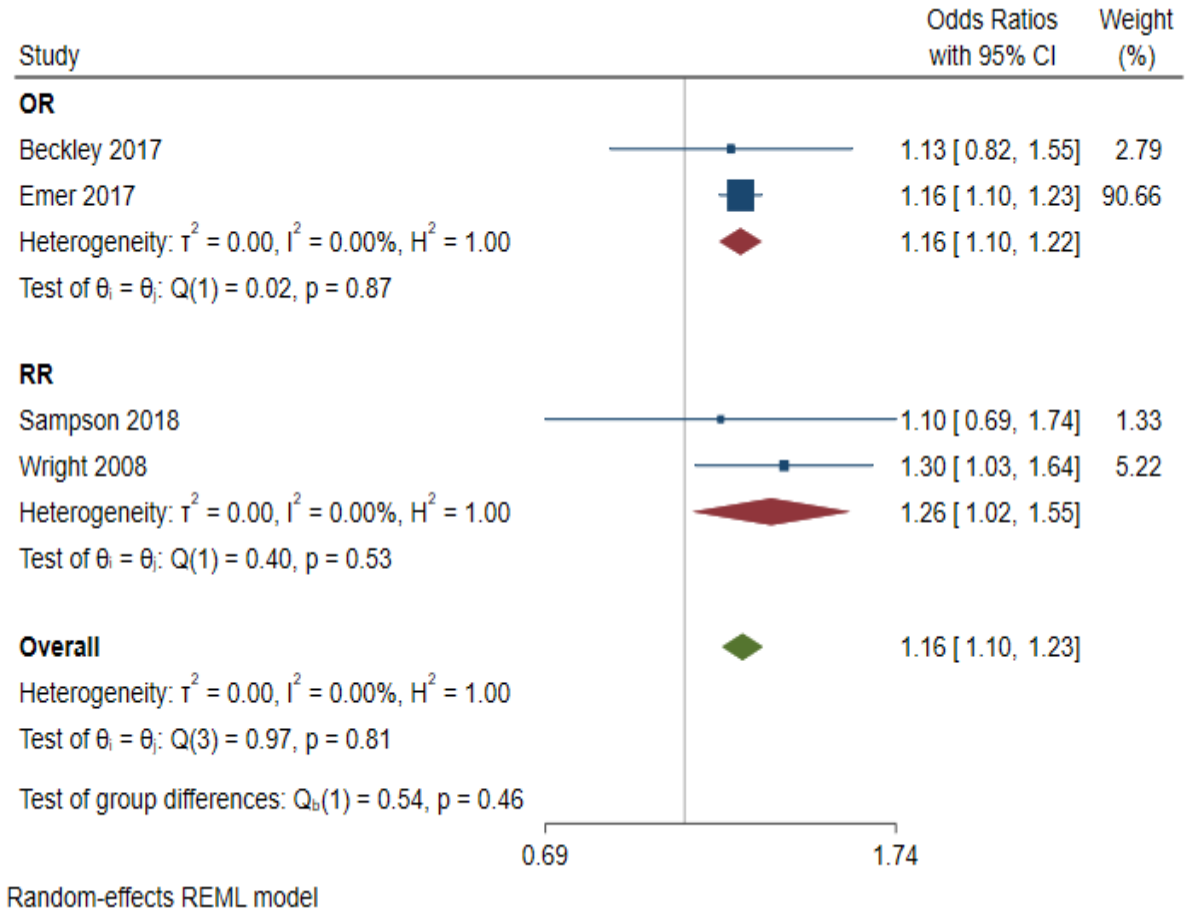

Figure B.3. Sub-group analysis with a vertical line indicating the point of null effect (OR: 1.00).

Both subgroups had a statistically significant association between blood leads level and the odds of being arrested or committing a violent crime with an OR of 1.16 (1.10 – 1.22) as well as the number of violent acts arrested for with a RR of 1.26 (1.02 – 1.55).

Planned sensitivity analyses were constrained by limited data. In sensitivity analyses, adding the study utilizing dentine lead levels did not substantially change the summary estimate. The summary OR obtained was 1.17 with a 95% confidence interval of 1.11 – 1.23 for each 5µg/dl increase in lead level. Furthermore, with the exclusion of the study by Emer, which employed a very narrow definition of violence and constituting almost 91% of the study weights, the resulting OR (95% CI) was 1.22 (1.02 – 1.45).

B.3.4.4 Small Study Effect

Figure B.4 is a Funnel plot of the included studies. The small number of eligible studies complicates the interpretation of this chart.

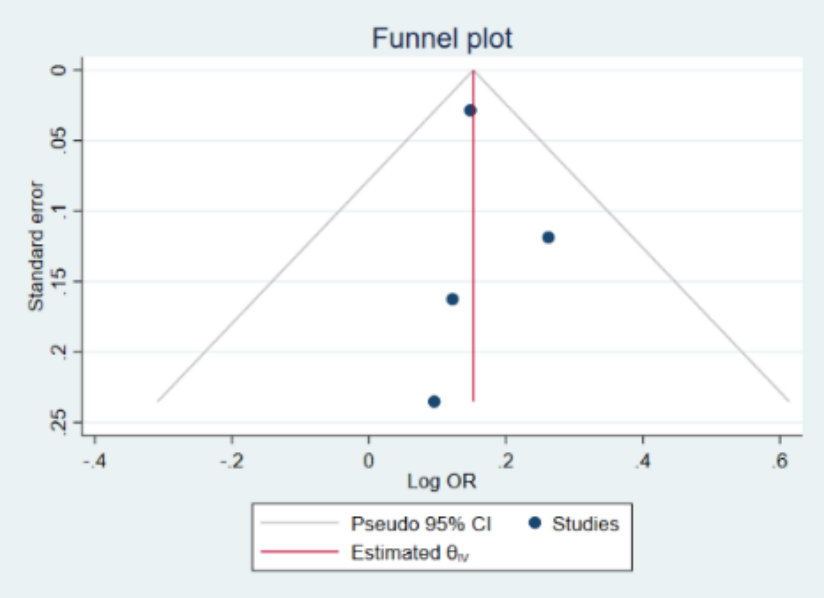

Figure B.4. Funnel Plot showing small study effects

B.3.5 Dose Response relationship

There is inadequate data to conduct a dose-response meta-analysis from this review. While three studies provided some dose response data (Table B.5), only one study presented them in a usable form (Emer, 2017). Generally, there was an upward trend for violent acts with increasing blood lead levels.

Study	Lead Dose Categories	Response Values
Emer 2017	Mean Childhood BLL (µg/dl)	Odds Ratio
	0-4	1(Reference)
	5-9	2.3 (1.6-3.3)
	10-19	2.6 (1.8-3.8)
	≥ 20	3.0 (1.9-4.5)
Fergusson 2008	Dentine lead (µg/g)	Mean number of violent convictions
	0-2	0.24
	3-5	0.39
	6-8	0.63
	9-11	1.03
Dietrich 2001	Mean Childhood Blood lead (µg/dl)	Total SRDS
	≤ 10	3.4
	10-15	2.6
	16-20	4.7
	>20	4.6

SRDBS: Self Report Delinquency Behaviour Scores

Table B.5. Dose Response Data

B.4 DISCUSSION

B.4.1 Summary of findings

We found six studies at the individual level assessing the relationship between exposure to lead in childhood and the development of violence in young adulthood. An increasing risk of committing, being arrested or convicted for violence offense in youth was associated with increasing level of blood lead in childhood, with a pooled OR of 1.16 (1.10 – 1.23). This increased risk was a consistent finding across studies conducted in divergent contexts. This review was able to synthesize all available and relevant individual-level evidence on the association of lead exposure in childhood with later development of violence where the exposure pre-dates the outcome. However, contrary to expectations, we found relatively few studies addressing this important such that there was not enough data to perform either a dose response meta-analysis or planned sensitivity analyses and lacunae in the current literature were identified. To our knowledge, this review is the first to provide a systematic summary of

studies looking at the association of lead and violence using individual level data in which the exposure was definitely established before the outcome assessment.

B.4.2 Context from Literature

Though the influence of unmeasured and residual confounding cannot be excluded due to the impossibility of conducting a randomised controlled trial (RCT) on this topic, this review found an increased risk of violent offenses in young adults who were exposed to lead in childhood. Because of the relatively good quality of included studies and the low statistical heterogeneity, the main result is likely to be a reasonably valid estimate of the risk of youth violence associated with childhood lead exposure. This is in line with multiple earlier ecological and individual-level studies which have suggested the putative role of lead in the causation of violence.

For example, Reyes et al found a close relationship between the decline in lead exposure and the reduction in violent crime in the United States if a 20-year-lag period representing the time for children to reach young adulthood, is allowed. In addition, the largest declines in violent crime rates were found in states with the largest reduction in lead exposure (Reyes, 2007). A similar pattern has been reported by several other ecological studies (Feigenbaum and Muller, 2016, Mielke and Zahran, 2012, Stretesky and Lynch, 2001, Gronqvist et al., 2014, Boutwell et al., 2016, Nevin, 2000, Stretesky and Lynch, 2004). Though the study by Fergusson found a positive association between dentine lead in childhood and conviction rate in young adulthood, lead was said to account for less than 1% of the variance in conviction after adjusting for a covariate, educational under-achievement, a mediator of the role of lead in the causation of violent crime (Fergusson et al., 2008). In effect, the possible effect of lead was downplayed in that study as controlling for a mediator would ordinarily remove all association and thus the 1% left after was probably due to residual or unmeasured confounding. In fact, this particular study reported the highest measure of association between lead and violence at the individual level.

Other individual-level studies have also shown an association between lead exposure and violence. For instance, Needleman et al in adjudicated delinquents found that bone lead was associated with elevated risk of adjudicated delinquency (Needleman et al., 2002b). Similar findings have been reported by other workers (Pihl and Ervin, 1990, Naicker et al., 2012). Combined with ecological and laboratory-animal studies, this review deepens the evidence base for the role of lead exposure in violence and offers another triangulation point for the elucidation of the causative role of lead in violence.

B.4.3 Strengths and Limitations of Included Studies

Most of the included studies were of moderate to good quality, despite challenges of studying exposure to heavy metals. The studies adopted slightly different but overlapping definitions of violence. Notably, the study with the greatest weight (Emer, 2017) only evaluated firearm victimization or perpetration and is not yet published in a peer-reviewed journal. The majority of this study sample did not exhibit firearm violence but may have been involved in other violent acts not captured by the study. This may have important ramifications for the size and direction of estimated effect size.

The only study with a significantly different result used dentine lead level as its exposure method; despite this, the direction of association was still the same, yielding a higher risk of association (Fergusson et al., 2008). Method of assessing lead burden is a recognised cause of heterogeneity (Marcus et al., 2010). While BLL reflects recent lead exposure, shed teeth mirror cumulative exposure from around birth to the time of shedding and although any lead estimation method may be subject to error from contamination, this risk is greater with tooth lead analysis (National Research Council (US) Committee on Measuring Lead in Critical Populations, 1993). Thus, the higher level of risk as reported by Fergusson et al could therefore have been due to unmeasured or residual confounding or to the fact that dentine lead levels were used for exposure assessment.

Many of the included studies reported regression coefficients associated with different weight of increase in lead levels. For ease of comparability and for interpretation, a uniform weight of increase, 5µg/dl was chosen. Also, since there is no known safe level for lead and an RCT cannot be conducted, none of the studies compared 'exposed' to 'non-exposed' groups. This limited the application of alternative meta-analytic techniques.

Notably, none of the studies was conducted in LMIC, where regulatory environment for heavy metal exposure is likely to be poorer. Despite this fact a few of the studies sampled individuals from low-income communities within these high-income countries. Since lead exposure is generally higher in LMIC, the estimate provided by this review might represent the lower end of the risk of violence associated with environmental lead.

B.4.4 Strengths and Limitations of the Review Process

Perhaps, the most striking aspect of this meta-analysis was the consistency of results across studies, despite the variability in the exact definition of violence used, the socio-economic and ethnic distribution of the participants and the countries of study. The review process adhered to the requirements for reporting of systematic reviews of observational studies (MOOSE). The search was comprehensive with no language restrictions and inclusion of grey literature. Screening, selection and quality assessments were done by two independent reviewers. However, as common with non-experimental designs, unmeasured and residual confounding and bias in the original studies cannot be overcome by pooling.

Having a single predominant study account for 90% of the combined weight is a major limitation (Emer, 2017), but despite this, we believe the results of this review represent the best available evidence as excluding this study from analysis results in a higher odds of the violent behaviour. Also, the seeming lack of heterogeneity may have been due to the limited number of studies included in the review as this affects the estimate of the between-study variance. Finally, conducting a systematic review of observational studies, particularly examining

health-related conditions in contrast to disease conditions that are well defined requires iterative methodology, unlike when reviewing RCTs (Dekkers, 2019).

Considering the considerable debate and the importance of this subject, not nearly enough usable evidence was available after all the searches. In some instances there were multiple reports from the same cohort. For example, Wright et al is based on the same study and sample as Dietrich et al. Thus the latest study and the one with the more appropriate outcome was included in the analysis, though Dietrich et al provided some dose response data and useful background information (Dietrich et al., 2001, Wright et al., 2008). The small number of studies limited confidence in the interpretation of assessment of heterogeneity and small study effects. The review was unable to describe a pooled dose-response curve as only one study provided dose categories and their associated relative risks (Emer, 2017). The other studies with dose response data provided only dose categories and predicted counts and scores estimated from regression of continuous data.

B.4.5 Implications and Conclusions

Our systematic review identified six cohort studies and the results suggest that childhood exposure to lead is a risk factor for the development of violence in young adulthood and may be responsible for a small to medium increase in incidence of violent behaviour by youths. The ubiquity of lead and its consistent effects across multiple diverse settings make this finding of particular significance. Therefore, measures to reduce environmental lead, especially in LMICs where lead exposure is still relatively high are needed in order to contribute to violence mitigation.

Further research needs to consider the reporting shortcomings of the current studies and follow recommended guidelines to aid their eventual inclusion in future synthesis. Improved studies with pre-defined hypothesis relating lead to violence with sufficient follow up and incorporating participants from different ethnic and socio-economic backgrounds, particularly

from LMICs, need to be conducted. Dose-response data should be analysed and reported in useful format. Further confirmation of these findings would serve to elucidate the role of environmental lead in the aetiology of violence and help in strengthening the development of mitigation efforts in violence prevention, especially in regions with higher environmental burden of lead.

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PART C: APPENDIX

Appendix A. Search Strategy for Medline (PubMed)

Search	Query
#1	(((((lead[MeSH Terms]) OR lead poisoning[MeSH Terms]) OR blood lead levels) OR blood lead concentrations) OR lead exposure) OR lead poisoning
#2	((((((((((((((((((((crime[MeSH Terms]) OR aggression[MeSH Terms]) OR social behavior disorders[MeSH Terms]) OR conduct disorder[MeSH Terms]) OR violence[MeSH Terms]) OR violent) OR violence) OR aggression) OR aggressive) OR rage) OR antisocial behavior) OR delinquent behavior) OR delinquency) OR conduct disorder) OR criminal arrest) OR criminal behavior) OR offending) OR violent crime) OR homicide) OR assault) OR rape) OR crime
#3	(((((((lead[MeSH Terms]) OR lead poisoning[MeSH Terms]) OR blood lead levels) OR blood lead concentrations) OR lead exposure) OR lead poisoning)) AND ((((((((((((((((((((crime[MeSH Terms]) OR aggression[MeSH Terms]) OR social behavior disorders[MeSH Terms]) OR conduct disorder[MeSH Terms]) OR violence[MeSH Terms]) OR violent) OR violence) OR aggression) OR aggressive) OR rage) OR antisocial behavior) OR delinquent behavior) OR delinquency) OR conduct disorder) OR criminal arrest) OR criminal behavior) OR offending) OR violent crime) OR homicide) OR assault) OR rape) OR crime)
#4	(((((((lead[MeSH Terms]) OR lead poisoning[MeSH Terms]) OR blood lead levels) OR blood lead concentrations) OR lead exposure) OR lead poisoning)) AND ((((((((((((((((((((crime[MeSH Terms]) OR aggression[MeSH Terms]) OR social behavior disorders[MeSH Terms]) OR conduct disorder[MeSH Terms]) OR violence[MeSH Terms]) OR violent) OR violence) OR aggression) OR aggressive) OR rage) OR antisocial behavior) OR delinquent behavior) OR delinquency) OR conduct disorder) OR criminal arrest) OR criminal behavior) OR offending) OR violent crime) OR homicide) OR assault) OR rape) OR crime) Filters: Humans

MeSH: Medical Subject Headings

Appendix B. Data Eligibility and Extraction Form

Early life environmental lead exposure as a risk factor for aggressive and violent behaviour in young adults: a systematic review protocol

A. SOURCE

General Information	
Reviewer ID	
Study ID (Author, Year)	
Study country	
Date of data extraction	
Title of Article	
Author contact details	
Publication type	Full text: □ Abstract: □ Book Chapter: □ Others: □ Specify…….
Published	Yes: □ No: □
Full citation	
Journal/Source	

B. STUDY ELIGIBILITY FORM

Factors	**Assessment**			**Comments**
Study design				
Cohort Study	Yes: □ Unclear: □ No: □			
Case Control Study	Yes: □ Unclear: □ No: □			
Case Cohort Study	Yes: □ Unclear: □ No: □			
Nested Case Control Study	Yes: □ Unclear: □ No: □			
Population				
Outcome: Age 15–35 years	Yes: □ Unclear: □ No: □			
Exposure: Prenatal to ≤ 12 years	Yes: □ Unclear: □ No: □			
Exposure				
Blood lead	Yes: □ Unclear: □ No: □			
Bone lead	Yes: □ Unclear: □ No: □			
Dentine lead	Yes: □ Unclear: □ No: □			
Outcome				
Aggression	Yes: □ Unclear: □ No: □			
Violence	Yes: □ Unclear: □ No: □			
Homicide	Yes: □ Unclear: □ No: □			
Aggravated assault	Yes: □ Unclear: □ No: □			
Violent crime	Yes: □ Unclear: □ No: □			
Forcible rape	Yes: □ Unclear: □ No: □			
Verdict	Include □	Unclear □	Exclude □	
Reason for verdict				
Do not proceed if study is excluded from review				

C. STUDY DETAILS

Information	**Specifics**
Country of study	
Aim/Objectives	
Ethics approval obtained?	
Funding source(s)	
Conflict of interest declared?	

D. STUDY METHODS

Methods	Details
Study design	
Sample/Cohort description	
Follow -up	
How long is follow-up?	
How frequent was follow-up?	
Population	
Population of exposure group	
Population of outcome group	
Exposure	
Unit (exposure)	
Laboratory method(exposure)	
Outcome(s)	
Unit (Outcome)	
Method (Outcome)	
Analysis type	

	State Specific Method (e.g. Simple logistic regression, Negative binomial regression)
Univariable	
Multivariable	
Outcome assessed as	Dichotomous: □ Continuous: □ Count: □
Variables/Confounders adjusted or controlled for in design and analysis	
Measure of association *(Give details e.g. OR, HR, Standardized Mean Difference)*	

E. STUDY RESULTS

I. General cohort characteristics

Baseline characteristics of participants	
Total Number	
Number involved in aggression/Violence	
Age	
Gender	
Ethnicity	
Socioeconomic status	
Range of lead level	
Mean lead level	

II. Group differences

Group characteristics		
	Non-violent group	Violent group
Age		
Gender		
Ethnicity		
Socioeconomic status		
Range of lead level		
Mean lead level		

III. Effect size

Measure of association	
Name (e.g. OR/β coefficient)	
Unadjusted	
Adjusted	
Weighting of lead increase for coefficient (e.g. 1µg.dl or 5µg/dl)	

IV. Dose response data

Dose Response	
Available?	Yes: □ No: □
Dose Category	Association (indicate reference category)
1).	
2).	
3).	
4).	

Appendix C. Modified Newcastle Ottawa Scale for Cohort Studies

Criteria	Maximum of one star per numbered item except 'comparability' where 2 stars can be awarded.
SELECTION	1. Representativeness of the exposed cohort a) Truly representative of the average child in the community* b) Somewhat representative of the average child in the community* c) Selected group of kids d) No description of the derivation of cohort 2. Selection of the non-exposed cohort a) Drawn from the same community as the exposed* b) Drawn from a different source c) No description of the derivation of the non-exposed cohort 3. Ascertainment of exposure a) Secure record e.g. lab results* b) Structured interview* c) No description
COMPARABILITY	1. Comparability of cohorts on the basis of design or analysis a) Study controls for at least three of b) Study controls for at least four of the following in addition
OUTCOME	1. Assessment of outcome a) Independent blind assessment* b) Record linkage e.g. government records* c) Self-report d) No description 2. Adequacy of follow-up of cohorts a) Complete follow-up- all subjects accounted for* b) Subjects lost to follow-up unlikely to introduce bias (>80% follow-up)* c) Follow-up rate < 80% and no description of those lost d) No statement

Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Available from: URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm

Appendix D. Excluded Studies

Study	Reason for Exclusion
Aizer 2019	Outcome does not meet eligibility
Hill-Hornby 1998	Outcome does not meet eligibility
Lob 1976	Outcome does not meet eligibility
Needleman 1996	Outcome does not meet eligibility
Needleman 2002	Period of exposure unclear
Pihl 1990	Period of exposure unclear
Reyes 2015	Lead levels are predicted from a different sample
Wright 2009	Outcome does not meet eligibility

Appendix E. MOOSE Checklist

Item	Topic	Page Number
Title	Identify the study as a meta-analysis (or systematic review)	0
Abstract	Use the journal's structured format	i
Introduction	The clinical problem	1
	The hypothesis	4
	A statement of objectives that includes the study population, the condition of interest, the exposure or intervention, and the outcome(s) considered	5
Sources	Qualifications of searchers (e.g., librarians and investigators)	6
	Search strategy, including time period included in the synthesis and keywords	6 Appendix A
	Effort to include all available studies, including contact with authors	6
	Databases and registries searched	6
	Search software used, name and version, including special features used (e.g. explosion)	6
	Use of hand searching (e.g., reference lists of obtained articles)	6
	List of citations located and those excluded, including justification	12, Appendix D
	Method of addressing articles published in languages other than English	6
	Method of handling abstracts and unpublished studies	6
	Description of any contact with authors	None
Study Selection	Types of study designs considered	5
	Relevance or appropriateness of studies gathered for assessing the hypothesis to be tested	5
	Rationale for the selection and coding of data (e.g., sound clinical principles or convenience)	7
	Documentation of how data were classified and coded (e.g., multiple raters, blinding, and inter-rater reliability)	7
	Assessment of confounding (e.g. comparability of cases and controls in studies where appropriate)	7

	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	7
	Assessment of heterogeneity	7
	Statistical methods (e.g., complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	7
Results	Present:	
	A graph summarizing individual study estimates and the overall estimate	19
	A table giving descriptive information for each included study	12, 13
	Results of sensitivity testing (e.g., subgroup analysis)	20
	Indication of statistical uncertainty of findings	19
Discussion	Discuss:	
	Strengths and weaknesses	24, 25
	Potential biases in the review process (e.g., publication bias)	25
	Assessment of quality of included studies	24
	Consideration of alternative explanations for observed results	23
	Generalization of the conclusions (i.e., appropriate for the data presented and within the domain of the literature review)	26
	Guidelines for future research	26
	Disclosure of funding source	Part B:16

From: Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008–12.
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Appendix F. Author Instructions: Aggression and Violent Behaviour

GUIDE FOR AUTHORS

Your Paper Your Way

We now differentiate between the requirements for new and revised submissions. You may choose to submit your manuscript as a single Word or PDF file to be used in the refereeing process. Only when your paper is at the revision stage, will you be requested to put your paper in to a 'correct format' for acceptance and provide the items required for the publication of your article.

To find out more, please visit the Preparation section below.

Submission checklist

You can use this list to carry out a final check of your submission before you send it to the journal for review. Please check the relevant section in this Guide for Authors for more details.

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Graphical Abstracts / Highlights files (where applicable)

Supplemental files (where applicable)

Further considerations

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• All references mentioned in the Reference List are cited in the text, and vice versa

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• A competing interests statement is provided, even if the authors have no competing interests to declare

• Journal policies detailed in this guide have been reviewed

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Before You Begin

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Results

Results should be clear and concise.

Discussion

This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

Conclusions

The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

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March 2003.

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Engle, E.K., Cash, T.F., & Jarry, J.L. (2009, November). The Body Image Behaviours Inventory-3: Development and validation of the Body Image Compulsive Actions and Body Image Avoidance Scales. Poster session presentation at the meeting of the Association for Behavioural and Cognitive Therapies, New York, NY.

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