Lead exposure and measure of IQ level among children in Alaverdi, Akhtala and Yerevan

Master of Public Health Integrating Experience Project

Research Grant Proposal Framework

by

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LIST OF ABBREVIATIONS

AUA SPH - American University of Armenia School of Public Health

BLL - Blood Lead Level

CNS - Central Nervous System

EPA - Environmental Protection Agency

IQ - Intelligence Quotient

IRB - Institutional Review Board

MAC - Maximum Allowable Concentration

NHANES - National Health and Nutrition Examination Survey

OSHA - Occupational Safety and Health Administration

SD - Standard Deviation

WAIS - Wechsler Adult Intelligence Scale

WHO - World Health Organization

WISC - Wechsler Intelligence Scale for Children

WPPSI - Wechsler Preschool and Primary Scale of Intelligence

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EXECUTIVE SUMMARY

Background Information: Lead (Pb) pollution is considered to be one of the top ten global environmental pollution problems. Exposure to lead among children, particularly six years old and younger causes lower Intelligence Quotient (IQ), behavioral changes, concentration disorder, mental deterioration after 18 months and leads to loss of motor skills and retarded speech development. Infants and young children are more sensitive to lead exposure because the developing nervous system is much more vulnerable to the effects of lead than the adult's brain. The risk for children's exposure is also higher because of children's hand to mouth behavior.

Alaverdi is a large industrial city in Armenia with a polymetallic smelter which emits heavy metals to the environment. The concentration of those heavy metals in residential soil exceeds the standard established by the United States (US) Environmental Protection Agency (400 mg/kg). In 2001, in Alaverdi, 34% of soil samples and 77% of loose dust samples exceeded the US Environmental Protection Agency (EPA) standard of 400 mg/kg for bare soil in children's play areas. In 2001, 36% of floor dust samples from apartments exceeded the US EPA standard of 40 μg /ft^2.

Specific Aims: The research questions of the study are:

- What is the children's IQ level in Alaverdi, Akhtala and Yerevan?
- Are there differences in IQ's of children living in Alaverdi, Akhtala and Yerevan?

Objectives of the study are:

- To determine IQ scores of children 4-6 years old in Alaverdi, Akhtala and Yerevan and check for differences between the places of residence
- To determine the association between children's IQ,BLL and place of residence after adjusting for other risk factors for children's low IQ

Methods/Study Design: To assess and compare IQ scores in children in cities Alaverdi, Akhtala and Yerevan, cross-sectional study will be conducted. Approximately 163 children will participate in the study. The study population will include those children whose blood lead levels were assessed during the fall 2013 as part of the study the American University of Armenia School of Public Health conducted. That study included 39 children randomly selected from Akhtala, 69 from Alaverdi and 55 from Yerevan (Erebouni region) by using information taken from polyclinic registers. Children's IQ will be determined by using the Wechsler Intelligence Scale for Children, which is designed for children 6-16 years old.

Data Entry/Data Analysis: Statistical analysis will be conducted by STATA statistical software; SPSS 17.0 software will be used for double data entry. Descriptive statistics will be used to describe the basic features of the data in the study. Simple and Multiple Linear Regression Models can identify the relationship between variables and control for possible confounding factors. Analysis of Variance (ANOVA) will be used to determine whether a difference exists between the means of three independent groups.

Budget: The research team will conduct the study in 2015 and it will last 3 months. The estimated budget for implementation of the proposed study is 2,573,226AMD or 6,230 USD.

INTRODUCTION

1. Literature review

1.1. Worldwide Environmental Issues

Environmental contamination and health problems are major concerns in the world. Though many of these problems have been solved in high income countries, problems still exist in low and middle income countries. One of the biggest issues is exposure to toxic chemicals. People can be exposed and intoxicated with chemical substances through water, food, soil and air[1]. Lead, mercury, cadmium, arsenic, chromium, nickel and copper are among heavy metals that have serious consequences on health[2]. These elements can be released into the environment from metal smelting, plastic and rubber industries, battery plants, chemical plants burning of waste that contains these heavy metals[2,3]. After being released to the air, these heavy metals move and accumulate in the soil, greenery and water, where the metals do not dissolve and are preserved in the environment for a long time, which can be dangerous for people who are exposed[2]. Tailing ponds, waste rock, heap leach, and dump leach facilities also have severe impacts on water quality, including contamination of groundwater and surface water. Toxic substances can seep from these facilities and contaminate groundwater, particularly if these facilities do not have impermeable liners[4].

People can be effected by heavy metals through inhalation, ingestion and through skincontact[2]. Heavy metals can cause serious health problems, such as reducing growth and development, cancer, nervous system damage, and death. Mercury and lead can also cause autoimmunity (when the immune system attacks and destroys its own cells), that can lead to rheumatoid arthritis, diseases of the kidneys, circulatory system and nervous system. They can also damage

the fetal brain, lead to learning difficulties, memory imparment, aggressiveness, and hyperactivity[5].

According to Blacksmith Institute's The World's Worst Toxic Pollution Problems Report 2011, lead pollution is one of the top ten global pollution problems[1]. Therefore, this proposal focuses on health problems related to exposure to lead. Soil, dust and air pollution are the most common sources of lead exposure[6,7]. Lead in air, dust, and soil can come from industrial sources such as smelters, lead-acid battery manufacturers, and waste incinerators. Lead-containing dust can enter into houses through the wind[7]. Lead can enter groundwater from natural weathering of rocks and soil, indirectly from atmospheric fallout and directly from industrial sources, as well as entering freshwater bodies from municipal sewage, from harbor activities and from lead storage sites and production plants, especially mining and smelting[3]. Lead-lined reservoirs, cisterns and water tanks are considered to be a source of lead contamination of drinking-water[3].

1.2. What is Lead?

Chemical symbol: Pb

Atomic number: 82

Atomic weight: 207.2

Melting point: 327.43° C

Boiling point: 1,740 °C

Forms of lead: Organic and Inorganic

Lead is an odorless blue-silver, white soft metal, which does not dissolve in water[3].It can travel in the environment through water, air and soil. Both organic and inorganic lead are considered to be toxic. Inorganic lead is found in paint, soil, and dust.Lead is used in different products such as batteries, ammunition, and other products[3]. Organic lead is more dangerous than inorganic

lead, asit is more easily transported to the brain and central nervous system (CNS)[8]. Tetraethyl lead and tetramethyllead are organic lead compounds[3]. These compounds are absorbed to a greater extent than inorganic lead compounds. In contrast to inorganic lead compounds, organic lead particles are also absorbed through the skin. Lead can have both acute and chronic impacts on human health[3].

According to the US Food and Drug Administration the lead limit for bottled water is 5 micrograms per liter (mcg/L)[9]. If lead level is above 15 mcg/L in more than 10% of homes, the water supplier must take actions for reducing the amount of lead so that it will not exceed the norms[9]. The US Occupational Safety and Health Administration(OSHA) has set a permissible exposure limit (PEL) for lead in workplace air at 50 $\mu g/m^3$ averaged over an 8-hour period[10]. The Maximum Allowable Concentration (MAC) for lead in soil in play areas is 400 ppm and 1200 ppm for non-play areas[11].Table 1 presents the US standards for air, soil, water, dust, and blood.

1.3. Exposure pathways of lead

Although natural sources exist, lead is primarily released into the environment from anthropogenic sources, such as metal mining and smelting, burning coal, oil, or waste, paint, recycled batteries, as well as from vehicles. It can settle on the soil/dust or may contaminate ground water[6,12].The exposure pathways of lead into the human body are inhalation, ingestion and dermal contact, however inhalation and ingestion are considered to be the main pathways of lead exposure[11]. Lead exposure can occur through inhalation of emissions from burning processes and through ingestion of lead-contaminated soil and dust. Lead particles can also reach residential areasfrom the wind-blown dust and contaminate livestock and crops[13].

It can also be found inside houses in paint, ceramics, pipes, plumbing materials, also in solders, gasoline, batteries, ammunition, and cosmetics. Additionally, people can be exposed to lead by burning fossil fuels, mining and manufacturing[6]. People, who live near hazardous areas, can be exposed to lead by breathing air, drinking water, eating food, or swallowing dust or dirt contaminated with lead[14]. Drinking lead contaminated water or ingesting lead-containing dust or soil can be the reasons for children's exposure to lead[5]. Infants and young children are particularly sensitive to ingestions of soil/dust because of hand-to-mouth activities and physiological factors (e.g., poorly developed blood brain barrier). Pregnant women are also considered vulnerable due to exposure of the developing fetus. This is further discussed below.

Main sources and pathways of lead exposure in children include[8,15]:

- Lead from an active mining industry (particularly air, soil and dust)
- Lead-based paints and pigments
- Artisanal recycling of automobile batteries
- Lead solder in food cans
- Drinking water system with lead solder and lead pipes
- Lead in products, such as herbal and traditional medicines, folk remedies, cosmetics and toys
- Lead released by burning of lead-containing waste
- Lead in the food chain, via contaminated soil
- Lead contamination from former industrial sites
- Parental occupations and hobbies.

1.4. Lead toxicity: Health effects of lead

Almost every organ and system in human body can be affected by lead. Children, particularly six years old and younger, are more vulnerable to lead exposure[6]. One of the reasons is that the risk is higher of ingesting environmental lead, as children often put objects in their mouths, which can contain lead paint chips and contaminated soil and dust[16]. Absorption from the gastrointestinal tract is higher in children than adults and thedeveloping nervous system is much more vulnerable to the effects of lead than adult's brain[17]. Additionally, children's skin is thinner and organic lead (e.g., tetraethyl) can be absorbed through the skin[16,18]. Table 2 presents health effects related to certain blood lead concentrations.

Children: Lead has a toxic effect on the central nervous system (CNS) especially among children. Symptoms include irritability, developing delirium, vomiting and convulsion[19]. Exposure to lead among infants and young children causes lower Intelligence Quotient (IQs), behavioral changes, concentration disorder, mental deterioration after 18 months and leads to loss of motor skills and retarded speech development.Low levels of lead in the blood can also lead to learning and hearing problems, slowed growth and anemia. Ingestion of lead may also cause convulsions, coma and even death[6].

In order to measure neuropsychological effects, 58 children with high and 100 with low dentine lead levels participated in the study conducted by Needleman et al[20]. Those children who had high lead levels had less IQ scores on the Wechsler Intelligence Scale for Children (Revised) compared to those who had low lead levels[20]. Studies conducted in Port Pirie, Australia show that the increase of blood lead concentration from 10μg/dL(0.48 μmol per liter) to 30 μg/dL (1.45 μmol per liter) can reduce children's IQ in the range of 4.4 points to 5.3 points[21].Another study conducted in New York examined the association between blood lead concentrations

assessed during early childhood and 6 year old children's IQ[22]. The result of the study shows that children who had lifetime average blood lead concentrations between 5 and 9.9 µg/dL scored 4.9 points lower on Full-Scale IQ than those whose blood lead concentrations were less than 5µg/dL[22]. A cross-sectional study conducted in Egypt concluded that the mean IQ was significantly lower in students with BLL≥ 10 µg/dL (mean IQ=88.8 and SD= 13.49) than those with BLL< 10 µg/dL (mean IQ=94.7 and SD=5.99)[23].

For three decades health response activities have been carried out in Bunker Hill Superfund Site (Idaho) that has a population of 7,000 people and a territory of 21 square miles with contaminated hillsides and floodplain because of an abandoned lead/zinc smelter[24]. In 1991, CDC established 10 µg/dL as the federal level of concern. In the 1970s, 75% of children in this area were exceeding 40 µg/dl blood lead. Due to a 11-year health intervention program, the number of children with excessive blood lead levels went down from 56% (1989) to 3% (2001). Biokinetic pathways models were used during the cleanup[24]. Structural equations models indicate that from 40% to 50% of the blood lead absorbed from soils and dusts came through house dust. Application of the site-specific model accurately predicted mean blood lead levels and percent of children to exceed 10 µg/dl throughout the 11-year cleanup period. The indicators showed significant reduction, which meant that it was possible to achieve the blood lead goal[24].

Pregnant Women: Pregnant women are particularly vulnerable to lead exposure[19]. Absorbed lead can easily enter the blood, soft tissues (brain, heart, lungs, liver, spleen, kidneys and muscles) and mineralizing tissues (bones and teeth)[25]. After accumulating in the human body, lead is stored in bones and teeth, replacing calcium[6,26]. This can cause direct exposure to the developing fetus, even for mothers exposed years before pregnancy[6]. All metals have the ability to go throughthe placental barrier and maternal exposure can lead to fetal toxicity[19]. During

pregnancy lead accumulated in woman's bones can easily pass from mother to child. Lead can enter the developing brain of the fetus through the immature blood-brain barrier[8]. Those women who do not have enough dietary calcium, lead is released from bones as maternal calcium for bone formation of the fetus. Lead exposure in pregnant women can cause miscarriage, stillbirth, reduced growth of the fetus, premature birth, as well as minor malformations[27,28]. Drinking alcohol during pregnancy and breastfeeding can cause damage to the developing brain, particularly more than 1-2 units once or twice a week can cause problems (1 unit equals 10ml or 8g of pure alcohol)[29,30].

Adults: High level of lead exposure causes neurological disorders; low levels of lead exposure can lead to hyperactivity, deficits in motor function, hand-eye coordination, and lowered performance on intelligence tests. Chronic lead exposure can cause high blood pressure, decrease of fertility, cataracts, nerve disorders, muscle and joint pain, memory or concentration problems[31]. It can also damage the reproductive system (in both men and women), the nervous system and the kidneys[6,32]. Chronic exposure to lead can lead to interstitial nephritis and damage kidney tubular cells[19].

Genotoxicity and neurotoxicity: Lead has genotoxic and neurotoxic impacts. It has genotoxic effects particularly on brain, bone marrow, liver, and lung cells. Lead has genotoxic effect particularly on eukaryotic cells[33]. It can cause chromosomal derivations and DNA damage.It has a harmful impact on the central nervous system (CNS) and exposure to lead in early life can result in neurodegeneration. Neurotoxic effect can cause apoptosis (programmed cell death)[34].

Carcinogenicity:According to the International Agency for Research on Cancer (IARC), inorganic lead compounds are considered to be probable human carcinogens (Group 2A) based

on limited evidence in humans and sufficient evidence in lab animals. Organic lead compounds are classified into Group 3 (unclassifiable as to carcinogenicity in humans)[9,35].

The Environmental Protection Agency (EPA) classifies lead compounds as probable human carcinogens[9]. Some studies show the relationship between lead exposure and cancers of the lung, stomach, brain, kidney, bladder, colon and rectum[9]. However, these studies did not take into consideration other risk factors. Studies in lab animals show links between lead exposure cancer; in particular, large doses of lead can cause kidney tumors in rats and mice[9,36].

Cardiovascular toxicity: Studies report that there is an association between blood lead level and blood pressure. According to the National Health and Nutrition Examination Survey (NHANES), blood lead level was positively associated with blood pressure and the impact of lead exposure on blood pressure could cause hypertensive heart disease and stroke[34].

Gastrointestinal Effects: Lead poisoning can cause colic among children including abdominal pain, constipation, cramps, nausea, vomiting, anorexia and weight loss[37].

Renal Effects: Acute exposure to lead can damage proximal renal tubule. Chronic exposure to lead can cause nephropathy[38]. Lead exposure leads to mitochondrial changes and cytomegaly of the proximal tubular epithelial cells, aminoaciduria, glucosuria and phosphaturia, hypophosphatemia[37].

Reproductive toxicity: Lead exposure can lead to changes in endocrine function and effect reproductive health. Exposure to inorganic lead can decrease spermatologic parameters, especially among men who work in battery plants[34].

1.5. Environmental issues in Armenia

Armenia was an industrialized republic with 36.7 million tons of industrial waste generated during 1985-1990[39]. Later the number decreased. There were 251,000 tons of industrial waste produced per year from 1991-1996; 16,000-18,000 tons of hazardous waste were produced per year in 1995-1996. Large amounts of tailings are generated as a result of mining activities and are not properly treated in Armenia[39]. The tailings are leaching into rivers[40].

One of the reasons of air pollution is emissions from automobile vehicles. According to data of the Ministry of Nature Protection of the Republic of Armenia, in 2005 the number of hazardous emissions, particularly nitrogen dioxide, benzene, tropospheric ozone and carbon oxide, were estimated at 197,900 tons, of which 146,900 tons were emitted into the atmosphere only because of vehicle emissions[41]. Other industrial sources that produce air emissions were power generation, ceramicmanufacturing, and manufacturing of building materials[42].

In Yerevan, the total number of emissions was 76,200 tons and 73,400 tons of emissions were resulting from vehicles. There were 49,900 tons of industrial hazardous substances emitted in 2005; 2,100 tons were emitted in Yerevan[41]. In Armenia, lead was emitted to the environment through metallurgy, chemical industry, lead-acid battery production, machine-building, light manufacturing, crystal manufacturing, mining, and ore reprocessing[39]. There are health and environmental problems in different parts of the country, but the biggest problems are around big mining areas in the northern (Lori marz) and southern parts (Syunik marz) of the country[43]. One of the biggest issues in the northern part of the country is the smelter in Alaverdi. Unfiltered surface water samples (n=110) were collected throughout Armenia in the period of 1996-1999; 16 out of 110 were collected from the Alaverdi mining region[44]. Debed river, which accepts water from acid mine drainage streams, contained lead exceeding 3,000 micrograms/liter[42,44].

1.6.Environmental issues in Yerevan

Yerevan is the capital and the largest city of Armenia. It consists of 12 Municipal communities: Adjapnyak, Avan, Arabkir, Davtashen, Erebuni, Kentron, Malatia-Sebastia, Nor-Nork, Nork-Marash, Nubarashen, Shengavit, and Kanaker-Zeytun[45]. In 2012, lead was found in dust and soil, particularly in the most polluted areas nearby "Pure Iron" and "Molybdenum Production" companies[46].

Chemical industry, which generates toxic air emissions, wasone of the concerns in Armenia[42]. The development of ferrous metallurgy in Armenia began in the early 1970s. The plant "Pure Iron" was established in Yerevan (Erebouni region) in 1968[47,48]. The plant produces ferromolybdenum, molybdenum and potassium perrhenate. The main activity of the plant is molybdenum concentrates processing and metal alloys production[48]. The Nairit chemical plantin Yerevan started production of rubber and other polymers in 1936. Asaresult15 million m^3 of liquid waste was discharged into the Hrazdan River until 1989[42]. Plants producing polyvinylacetate chemical reagents, vitamins, plant, lacquers and dyes/paints, mechanical rubber goods, and tires plant are also located in Yerevan[47].

"Armenian Molybdenum Production" is also located in Yerevan (Erebouni region) and was founded in 2003. It produces 3600 mt of ferromolybdenum per year[49].

1.7.Environmental issues in Akhtala

Akhtala is a city in Lori province located 10 km north-east from Alaverdi and 62 km from the province center[50]. The city is located on the left bank of Debed river, along the steepLalvarmountain[51,52]. There are copper, lead, and silver mines that have industrial importance and are exploited[52]. In 2012 the population of Akhtala was 2,400[53]. The Akhtala

Ore Processing Enterprise used to operate in Akhtala since 1957, receiving ore from Akhtala and Shamlugh, each of which had three mines[54]. The enterprise ceased functioning in 1988 and resumed operation in 2000 as a privately owned property renamed "Metal Prince". None of the mines in Akhtala are functioning today. The plant receives ore from Shamlugh only, which currently operates two copper pyrite mines[54].

The tailing pond of the former Akhtala Ore Processing Enterprise is located within the bed of the Nahatak river, 6.5 kilometers from the plant[54]. In 2012, the American University of Armenia School of Public Health (AUA SPH) conducted a rapid environmental health risk assessment in Akhtala and found significant lead and arsenic contamination in residential soils[55].

1.8. Environmental issues in Alaverdi

Alaverdi is considered to be one of the biggest industrial cities of Armenia. It is located about 170 km from Yerevan and 44 km from the province center (Lori marz), on the Debed River bank[56].In 2012 the population in Alaverdi city was 16,400 including Sanahin, Akner and Madan rural communities[55]. Copper smelting and mining activities in Alaverdi started in the 18th century, when Greek miners built the plant[57]. The mining industry was developed by the French in 19th century and in 1960's it was considered to be one of the major metallurgical and chemical industry centers among Soviet towns[57]. Although the copper plant was closed during 1988-1989, the area was used by different industrial facilities. The smelting plant of Alaverdi reopened in 1997[56]. About 27 tons of toxic substances are emitted annually from the stack; sulfur dioxidecomposes 95% of the air pollutants. In Soviet times, as a result of manufacturing of sulfuric acid, the smelter was receiving arsenic, which was buried in a specialdump[58]. The smoke stack of the Alaverdi copper-molybdenum plant had the height of 780 meters. In order to improve the ecological situation in Alaverdi, in 2011, the stack was increased to a height of

1,078 meters, but now the smoke spreads over the city, the gorge and the surrounding mountains covered by forests[59].

According to a pilot study conducted in 2001, residential soil lead concentration in Alaverdi was higher than in Shamlough and Akhtala[43]; 34% of soil samples and 77% of loose dust samples in Alaverdi exceeded the MAC (400 mg/kg). Lead concentrations were higher particularly in the areas closer to the smelter. AUA SPH study confirmed significant lead contamination of residential soil samples in Alaverdi in 2012[55].

According to the Alaverdi Health Center,an analysis of the health condition of the urban population in Alaverdi is needed[56]. There was an obvious increase in the number of cases of infectious diseases, tumors, respiratory disturbances, blood circulation, and nervous system disorders in 2008 compared to 2004[56].

2.Specific Aims

The main aim of this study is to measure children's IQ level and to see the differences of IQ's among children living in Akhtala, Alaverdi and Yerevan.

2.1.Objectives of the study

- To determine IQ scores of children 6-8 years old in Alaverdi, Akhtala and Yerevan and check for differences between the places of residence
- To determine the association between children's IQ, BLL and place of residence after adjusting for other risk factors for children's low IQ.

3.Methodology

3.1.Study design

The research team will conduct a cross-sectional study to measure the IQ level of 6-8 years old children whose blood lead levels were assessed in 2013 in Alaverdi, Akhtala and Yerevan[60]. The AUA SPH considered Alaverdi and Akhtala as communities polluted with lead and Yerevan as a control community, where the rapid risk assessment did not find significant lead pollution in residential soil.

3.2. Study population

Eligible participants are 163 children who will be 6-8 years old in 2015 living in Yerevan (55 children), Alaverdi (69 children) and Akhtala (39 children)[60]. AUA SPH measured the BLL of children 4-6 years old in 2013. This age group was chosen because children younger than six years old were more sensitive to lead exposure[6] and children 4-6 years old played outside with soil contaminated with high concentrations of lead. Information about these children was taken from the polyclinic registries. Mothers/legal guardians of those children will also participate in the study. A questionnaire will be used for mothers/legal guardians to collect information on potential risk factors for children's IQ levels.

***Inclusion criteria**:* Children who participated in the AUA SPH study will be included in the proposed study.

The goal is for 163 children from Yerevan, Alaverdi and Akhtala to participate in this study. AUA SPH selected those children in 2013 by using simple random sampling technique in Alaverdi and Yerevan. All children 4-6 years old from Akhtala were selected to participate in the study because of a small number of eligible children[60]. The selection and recruitment of

children for this study will be according to the study conducted by AUA SPH in 2013[60].AUA SPH has the names and addresses of children who participated in the study in 2013. They will contact the parents of these children to receive permission for sharing their contacts with the research team of the proposed study. Both groups of researchers will make sure that the confidentiality of the participants is protected and they will follow the protocols approved by the Institutional Review Board of the American University of Armenia.

3.3. Power calculation

Power calculation will be used for a fixed sample size n=163 after data analysis of the study. It will be used to estimate the magnitude of the difference between the means of the three groups. The Power will be calculated by using STATA statistical software using the following formula[61]:

$$Z_\beta = \sqrt{\frac{n_1\ r}{(r+1)}\frac{\Delta^2}{\sigma^2}} - Z_{\propto/2}$$

n_1- exposed population 1 (BLL≥ 10)

n_2- exposed population 2 (BLL < 10)

Δ- difference between IQ means in population 1 and 2

α (significance level) = 0.1

σ- standard deviation

$r = n_2/n_1$

1-β=Power

Based on the study conducted in Egypt the IQ mean in the group of students with BLL≥ 10 µg/dL was 88.8 and the IQ mean in the group with BLL< 10 µg/dL was 94.7[23]. Taking into consideration the data taken from the study conducted by AUA SPH, 19 children have BLL≥ 10

µg/dL and 144 children have BLL< 10 µg/dL. The study calculated actual statistical power by using STATA statistical software. The power based on the IQ means and number of children whose blood lead levels were assessed in 2013 in frames of a study conducted by the SPH of the AUA is 0.73 (Appendix 1).

3.4. Variables

Dependent variable (outcome)*:* The dependent variable is the IQ score of children measuring children's intelligence level. IQ is a continuous variable.

Independent variable*:* The main independent variables are the BLL (continuous variable) and place of residence (categorical variable). Other risk factors that can confound the relationship between the BLL and children IQ are mother's level of education (ordinal variable), marital status (categorical variable)[62] and socioeconomic status (ordinal variable)[21]; child's gender (categorical variable), birth weight (continuous variable), birth order of the child(continuous variable), maternal age (continuous variable), maternal tobacco consumption during the pregnancy (categorical variable)[63], maternal and paternal alcohol consumption during the pregnancy (categorical variable)[64,65].

3.5. Study instruments

Intelligence quotient (IQ) is a test measuring intelligence. It is equal to 100 times mental age divided by chronological age (IQ=MA/CA * 100)[66]. There are different IQ scales that measure the intelligence of children. The Wechsler Intelligence Scale is a test designed to measure intelligence in children and adults[67]. There are three types of Wechsler tests: WISC (Wechsler Intelligence Scale for Children), the WAIS (Wechsler Adult Intelligence Scale), and the WPPSI (The Wechsler Preschool and Primary Scale of Intelligence)[67]. The proposed study will use the

WISC Fourth Edition (individually administered intelligence test for 6-16 year old children) to measure IQ level of children 6-8 years old whose blood lead levels were previously assessed in 2013. The test consists of two subsections: verbal (information, comprehension, arithmetic, and similarities) and performance (picture arrangement andpicture completion)[67]. It will take 60-90 minutes. Appendix 2 presents the classification of IQ[68]. The study team will translate the WISC-IV instrument into Armenian and pre-test to improve the Armenian version. A trained psychologist will administer the test and will use the WISC to fully assess an individual's learning profile[67].

Besides, measuring children's IQ the study team will administer a survey of mothers of those children or their legal guardians to collect information on other risk factors related to IQ of children through interviewer-administered interviews. The mothers' questionnaire will have the following sections: socio-demographic characteristics (maternal education, place of residency, marital status, and socioeconomic status); parental lifestyle (prenatal smoking status, prenatal alcohol use, parental smoking habits); and information on children (birth weight, number of children, exposure to secondhand smoke and order of the child). Appendix 3 presents the questionnaire for collecting information from mothers. The research team will pre-test the questionnaire to make improvements. If the child does not have a mother, the legal guardian of the child will participate in the study. A trained interviewer will interview the mothers or legal guardians of eligible children. Appendix 4 presents the questionnaire for collecting information from legal guardians.

3.6. Data Management and Analysis

The research team will use SPSS 17.0 statistical software for double data entry and will clean the database identifying differences between the two datasets.Statistical analysis will be conducted

by STATA statistical software. Descriptive statistics will be used to describe the basic features (means, standard deviations and frequencies) of the data. Simple and Multiple Linear Regression Models can identify the relationship between the variables of interest and control for possible confounding factors. Analysis of Variance (ANOVA) will be used to determine whether a difference exists between the means of three independent groups.

4. Budget

The budget of the proposed project includes personnel, operational and other project related costs. The total estimated expenses for this proposed research are 2,573,226AMD or 6,230 USD. To conduct this study the research team will buy the WISC-IV instrument. The personnel salary was calculated based on the rates of international and non-governmental organizations operating in Armenia. As Alaverdi and Akhtala are about 185 km far from Yerevan, the research team will travel to Lori marz and stay there for the project duration. Appendix 5 presents the detailed description of the budget. The proposed study will be conducted in 2015 so that eligible children are 6-8 years old and the research team can use the WISC-IV instrument that is designed for 6-16 years old children. Appendix 6 presents the project implementation timeline.

5. Ethical considerations

The research team has received approval from the Institutional Review Board of the American University of Armenia (AUA IRB) to conduct the proposed study. The research team will present the written consent form to the mothers/legal guardians of children (Appendices 7 and 8) and ask them to sing it. After receiving their agreement informed voluntary assent will be obtained from children. An assent from children will be obtained in the presence of the mothers/legal guardians without pressure from them or the research team. Participants will be informed that their participation is voluntary and they can skip any question they do not want to

answer or they can stop their participation at any time without any consequence for them or their child. Only after this a trained psychologist will proceed to the test/interview for those who agree to participate. In addition, the student investigator will provide the copy of the written consent form to the mothers/legal guardians with the contact information of the Human Subject Protection Administrator of the American University of Armenia and the Principal Investigator. If parents have any questions about this study or feel that they/their child have not been treated fairly they should contact them. According to the decision of the AUA IRB, all norms of ethics will be followed and the confidentiality of the data will be protected. Study participants' names or other personal information will not be recorded on the survey questionnaire, instead a special ID system will be generated and recorded on the questionnaire. The completed questionnaires and database will be kept for further research purposes and only the study team will have access to them. The database will be password protected. Only summarized results will be presented in the final report.

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TABLES

Table 1. U.S. Standards for Lead Levels in Air, Soil, Water, Dust, and Blood

Agency	Media	Level
OSHA[11]	Air (workplace)	50 µg/m^3
EPA[11]	Air (ambient)	0.15 µg/m^3
EPA[11,69]	Soil (residential)	400 ppm (play areas) 1200 ppm (non-play areas)
EPA[11,70]	Water (drinking)	15 µg/L
EPA[69]	Dust	40 µg/ft^2 (floors) 250 µg/ft^2 (windows sills)
CDC[71]	Blood	5µg/dL

Table 2. Health Effects Associated with Certain Blood Lead Levels

Blood Lead Concentrations (µg/dL)		
Health Effects	**Children**	**Adults**
Cardiovascular effects[11] (Hypertension)	<10	< 30
Neurological effects[11]	≤ 10	
Encephalopathy	≥70-80	460
IQ deficit	≤10	40-120
Hematological effects[11]		
Decrease in hemoglobin	40	50
Renal effects[11,39]		<60
Nephropathy	40	40
Vit. D metabol.	< 30	---
Reproductive effects[11]	---	40

APPENDICES

Appendix 1. Power calculation

STATA Output Analysis

```
. sampsi 88.8 94.72, n(19) ratio(7.58)sd(13.49)sd(5.99) alpha(0.1)oneside

Estimated power for two-sample comparison of means

Test Ho: m1 = m2, where m1 is the mean in population 1
                    and m2 is the mean in population 2
Assumptions:

         alpha =   0.1000  (one-sided)
            m1 =     88.8
            m2 =    94.72
            sd1 =   13.49
            sd2 =    5.99
sample size n1 =       19
            n2 =      144
         n2/n1 =     7.58

Estimated power:

power =   0.7280
```

Appendix 2. IQ classification

Wechsler classification[68]

Very Superior	**130 and above**
Superior	**120-129**
High Average	**110-119**
Average	**90-109**
Low Average	**80-89**
Borderline	**70-79**
Extremely Low	**69 and Below**

Appendix 3. Mother's Questionnaire

Date (dd/mm/yy) ___/___/___/

Participant's ID

1.	Where did you live and for how long since birth? (name the place of residence in order)		Town	Marz	Duration in years
		1.			
		2.			
		3.			
		4.			
		5.			
2.	What is your current marital status? (select one)	1. Married 2. Divorced 3. Separated 4. Widowed			
3.	What is your age?	_____			
4.	Child's gender	1. Female 2. Male			
5.	Child's date of birth	(dd/mm/yy) ___/___/___/			
6.	What was your child's birth weight?	_____			
7.	What is your child's birth order?	1. First born 2. Middle born 3. Last born 4. Other (specify) _____			

8.	Do you currently smoke tobacco?	1. Yes 2. No---> Go to Q.11
9.	How often do you smoke?	1. Daily 2. Less than daily --> Go to Q.11
10.	On average, how many cigarettes do you smoke each day?	_____Cigarettes
11.	Have you smoked in the past?	1. Yes 2. No --> Go to Q.15
12.	In the past, how often have you smoked?	1. Daily 2. Less than daily --> Go to Q.15
13.	How old were you when you first started smoking daily?	_____Years old
14.	On average, how many cigarettes did you smoke each day?	_____Cigarettes
15.	How often does anyone smoke inside your home?	1. Daily 2. Weekly 3. Monthly 4. Less than monthly 5. Other _____
16.	How often did anyone smoke during your pregnancy?	1. Daily 2. Weekly 3. Monthly 4. Less than monthly 5. Other _____
17.	Did you smoke during pregnancy with this child?	1. Yes 2. No -------> Go to Q.20

18.	How often did you smoke during that pregnancy?	1. Daily 2. Less than daily----> Go to Q.20
19.	On average, how many cigarettes did you smoke each day during that pregnancy?	_____ Cigarettes
20.	Did you use alcohol during the pregnancy with this child?	1. Yes 2. No---> Go to Q.23
21.	When did you use alcohol during your pregnancy?	1. During the last 30 days before finding out your pregnancy 2. During the first 3 months of pregnancy 3. During the last 6 months of the pregnancy 4. Other _____
22.	How often did you use alcohol during the pregnancy?	1. More than once or twice a week 2. Once or twice a week 3. Once in two weeks 4. Once in three weeks 5. Other _____
23.	Did you use alcohol during breastfeeding?	1. Yes 2. No----> Go to Q. 25
24.	How often did you use alcohol during breastfeeding?	1. More than once or twice a week 2. Once or twice a week 3. Once in two weeks 4. Once in three weeks 5. Other _____
25.	What is the highest level of education that you have received?	1. School (less than 10 years) 2. School (10 years) 3. Professional technical education (10-13 years) 4. Institute/University(15 years and more)
26.	Are you currently employed? (Please, read and choose one answer)	1. Yes 2. Yes, but I am on the maternity leave 3. I am a seasonal worker/farmer

		4. No ------> Go to Q.28 5. Other(specify)_____		
27.	Where do you work? (please choose or write the town where you work in the first column, in the second column fill in the name of your workplace and in the third column – your position there)	Town	Place	Position
28.	Did you work during your pregnancy?	1. Yes 2. No----------->Go to Q.30		
29.	Where did you work during your pregnancy? (please choose or write the town where you worked in the first column, in the second column fill in the name of his workplace and in the third column – your position there)	Town	Place	Position
30.	Is your family registered in a family poverty benefit program (e.g., PAROS)?	1. Yes 2. No		
31.	In average, how much money does your family spend monthly?	1. Less than 50,000 AMD 2. From 51,000 to 100,000 AMD 3. From 101,000 to 200,000 AMD 4. From 201,000 to 300,000 AMD 5. Above 301,000 AMD		

Thank you!!!

Appendix 4. Questionnaire for the legal guardian of the child

Date (dd/mm/yy) ___/___/___/

Participant's ID

1.	Where did the child's mother live and for how long since birth in order? (name the place of residence)		Town	Marz	Duration in years
		1.			
		2.			
		3.			
		4.			
		5.			
		6. Don't Know			
Please answer to the questions 2 and 3 if child's mother is alive, if not skip to Q. 4.					
2.	What is her current marital status? (select one)	1. Married 2. Divorced 3. Separated 4. Widowed			
3.	What is her age?	_____			
4.	Child's gender	1. Female 2. Male			
5.	Child's date of birth	(dd/mm/yy) ___/___/___/			
6.	What was the child's birth weight?	1. _____ 2. Don't know			

7.	What is the child's birth order?	1. First born 2. Middle born 3. Last born 4. Other (specify) _____ 5. Don't know
8.	Did child's mother smoke tobacco products in the past?	1. Yes 2. No --> Go to Q.11 3. Don't know--> Go to Q.11
9.	In the past, how often did she smoke?	1. Daily 2. Less than daily --> Go to Q.11 3. Don't know--> Go to Q.11
10.	On average, how many cigarettes did she smoke each day?	1. _____Cigarettes 2. Don't know
11.	How often does anyone smoke inside your home?	1. Daily 2. Weekly 3. Monthly 4. Less than monthly 5. Other _____
12.	How often did anyone smoke during child's mother's pregnancy?	1. Daily 2. Weekly 3. Monthly 4. Less than monthly 5. Other _____ 6. Don't know
13.	Did child's mother smoke during the pregnancy with this child?	1. Yes 2. No -------> Go to Q.16 3. Don't know-------> Go to Q.16
14.	How often did she smoke during that pregnancy?	1. Daily 2. Less than daily----> Go to Q.16 3. Don't know----> Go to Q.16

15.	On average, how many cigarettes did she smoke each day during that pregnancy?	1. _____ Cigarettes 2. Don't know		
16.	Did she use alcohol during the pregnancy?	1. Yes 2. No---> Go to Q.19 3. Don't know---> Go to Q.19		
17.	When did she use alcohol during the pregnancy with this child?	1. During the last 30 days before finding out your pregnancy 2. During the first 3 months of pregnancy 3. During the last 6 months of the pregnancy 4. Other _____ 5. Don't know		
18.	How often did she use alcohol during the pregnancy?	1. More than once or twice a week 2. Once or twice a week 3. Once in two weeks 4. Once in three weeks 5. Other _____ 6. Don't know		
19.	Did she use alcohol during breastfeeding?	1. Yes 2. No----> Go to Q. 21 3. Don't know----> Go to Q. 21		
20.	How often did you use alcohol during breastfeeding?	1. More than once or twice a week 2. Once or twice a week 3. Once in two weeks 4. Once in three weeks 5. Other _____ 6. Don't know		
21.	What is her completed educational level?	1. School (less than 10 years) 2. School (10 years) 3. Professional technical education (10-13 years) 4. Institute/University (15 years and more)		
		Town	Place	Position

<table>
<tr><td rowspan="2">22.</td><td rowspan="2">Where does/did she work? (please choose or write the town where you work in the first column, in the second column fill in the name of your workplace and in the third column – your position there)</td><td></td><td></td><td></td></tr>
<tr><td colspan="3">Don’t know</td></tr>
<tr><td>23.</td><td>Did she work during the pregnancy?</td><td colspan="3">1. Yes
2. No----------->Go to Q.25
3. Don’t know----> Go to Q.25</td></tr>
<tr><td rowspan="2">24.</td><td rowspan="2">Where did she work during the pregnancy with this child? (please choose or write the town where she worked in the first column, in the second column fill in the name of the workplace and in the third column – her position there)</td><td>Town</td><td>Place</td><td>Position</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>25.</td><td>Is your family registered in a family poverty benefit program (e.g., PAROS)?</td><td colspan="3">1. Yes
2. No</td></tr>
<tr><td>26.</td><td>In average, how much money does your family spend monthly?</td><td colspan="3">1. Less than 50,000 AMD
2. From 51,000 to 100,000 AMD
3. From 101,000 to 200,000 AMD
4. From 201,000 to 300,000 AMD
5. Above 301,000 AMD</td></tr>
</table>

Thank you!!!

Appendix 5. Proposed Budget

Cost Type	Unit Cost in AMD	Number of Units	Total AMD
Transportation	100	3,530 km	353,000
Program Assistant/Psychologist	1,660	224 hours	371,840
Data enterer	1,480	80 hours	118,400
Hotel (2 persons)	8,000	18 nights	288,000
Per diem (2 persons)	5,000	19 days	190,000
Office supplies (pencils, pen etc.)	100	163	16,300
IQ test buying	1,135,686	1	1,135,686
Questionnaire translation	5,000	10	50,000
Printing questionnaire (for children and mothers), consent forms, assent forms and field work training manual	10	3000	30,000
Telephone	20,000	1	20,000
Total			2,573,226
Total in USD			**6,230 1USD=413AMD**

Appendix 6. Project Implementation Timeline

	Project Implementation											
	I month				II month				III month			
	Week 1	Week 2	Week 3	Week 4	Week 1	Week 2	Week 3	Week 4	Week 1	Week 2	Week 3	Week 4
Printing and translating questionnaire	●											
Permission from parents	●											
Training of interviewer	●											
Data collection		●	●	●	●							
Training of data enterer						●						
Data entry and cleaning						●	●	●				
Data Analysis								●	●	●	●	
Preparation of the final report											●	●

Appendix 7. Parental consent form in English

Dear mother,

Master of the Public Health Program of the School of Public Health in the American University of Armenia is conducting a study to investigate the IQ level among children living in Alaverdi, Akhtala and Yerevan. This study is part of a master project of Siran Grboyan, who is a graduate student of Master of the Public Health Program of the School of Public Health in the AUA. She conducts the study under supervision of her academic advisors. Many children will participate in this study from Alaverdi, Akhtala and Yerevan. Those children have participated in the blood lead level testing project in 2013. In order to do the study we need your permission and help. The study includes a test designed to measure intelligence in children and a brief interview with you. A trained psychologist will administer the interview to assess your child's learning profile, which will last from 60-90 minutes. After that we will ask you to participate in a brief interview, which will last 15-20 minutes. We will keep the data confidentially. Children's and your participation in this study is completely voluntary. You can skip any questions you do not want to answer or stop the interview at any time. You do not get a direct benefit from participating in the interviews, however your participation is important for understanding the connection between blood lead levels and children's IQ.

Your name will not appear on the questionnaire. Only summarized results will be presented in the final report.

If you have any questions about this study please feel free to contact the Principal Investigator Dr. Varduhi Petrosyan at (37410) 51 25 92. If you feel that you have not been treated fairly or think you have been hurt by joining the study you should contact Dr. Kristina Akopyan, the Human Subject Protection Administrator of the American University of Armenia (37410) 51 25 61.

"This project has been explained to my child in my presence, in language he/she can understand. He/She has been encouraged to ask questions both now, and in the future, about the research study."

Participant's signature_____

Appendix 8. Parental consent form in Armenian

Հարգելի մայրիկ,

Հայաստանի ամերիկյան համալսարանի Հանրային առողջապահության ֆակուլտետը իրականացնում է ուսումնասիրություն՝ հետազոտելու Ալավերդիում, Ախթալայում և Երևանում բնակվող երեխաների ինտելեկտի գործակցի (IQ) մակարդակը: Այս հետազոտությունը Սիրան Գրբոյանի մագիստրոսական թեզի մի մասն է, ով Հայաստանի Ամերիկյան Համալսարանի հանրային առողջապահության ֆակուլտետի ավարտական կուրսի ուսանող է: Նա իրականացնում է այս հետազոտությունը իր գիտական ղեկավարների հսկողության տակ: Շատ երեխաներ կմասնակցեն այս հետազոտությանը Ալավերդիից, Ախթալայից և Երևանից: Այդ երեխաները մասնակցել են արյան մեջ կապարի քանակության որոշման ծրագրին 2013 թվականին: Որպեսզի հետազոտությունը իրականացվի, մեզ պետք է Ձեր թույլտվությունը եւ օգնությունը: Ուսումնասիրությունը ներառում է թեստ, որը նախատեսված է չափելու համար երեխաների ինտելեկտի գործակիցը (IQ) և համառոտ հարցազրույց Ձեզ հետ: Փորձառու հոգեբանը հարցում կանցկացնի՝ գնահատելու համար Ձեր երեխայի մտավոր ունակությունները, որը կտևի 60-90 րոպե: Դրանից հետո մենք կխնդրենք Ձեզ մասնակցելու կարճ հարցազրույցի, որը կտևի 15-20 րոպե: Մենք կապահովենք տվյալների գաղտնիությունը: Երեխաների եւ Ձեր մասնակցությունը այս ուսումնասիրությանը լիովին կամավոր է: Դուք կարող եք բաց թողնել ցանկացած հարց կամ ընդհատել հարցազրույցը ցանկացած պահի: Դուք անմիջական շահ չունեք այս հետազոտությունից, այնուամենայնիվ, Ձեր մասնակցությունը կարևոր է հասկանալու համար արյան մեջ կապարի քանակության և երեխայի ինտելեկտի գործակցի միջև կապը:

Ձեր անունը չի հրապարակվելու հարցաթերթիկի վրա: Միայն ամփոփ տվյալներն են ներկայացվելու վերջնական զեկույցում:

Այս հետազոտության վերաբերյալ հարցեր ունենալու դեպքում կարող եք կապ հաստատել հետազոտության համակարգողի՝ Վարդուհի Պետրոսյանի հետ, հետևյալ հեռախոսահամարով՝ (37410) 51 25 92: Եթե Դուք կարծում եք, որ այս հետազոտությանը մասնակցելու ընթացքում Ձեզ լավ չեն վերաբերվել կամ մասնակցությունը Ձեզ վնաս է պատճառել, կարող եք զանգահարել Հայաստանի ամերիկյան համալսարանի Էթիկայի հանձնաժողովի համակարգող՝ Քրիստինա Հակոբյանին՝ (37410) 51 25 61 հեռախոսահամարով:

“Իմ երեխային այս նախագիծը բացատրել են իմ ներկայությամբ իրեն հասկանալի լեզվով: Նրան խրախուսել են հարցեր տալ հետազոտության վերաբերյալ ինչպես այժմ, այնպես էլ ապագայում:”

Մասնակցի ստորագրություն_____

Հետազոտողի ստորագրություն_____

Ամսաթիվ_____