Determinants of Blood Lead Concentration and Cognitive Function Among Children in the Visayas Region of the Philippines

By

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A Thesis

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CERTIFICATE OF APPROVAL

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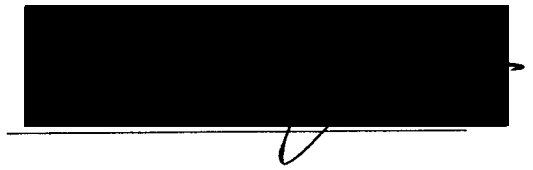

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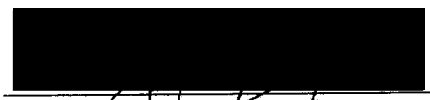

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This thesis is dedicated to the children of the Visayas and to

Wallace C. Riddell, my grandfather,
who participated in the liberation of the Visayas during World War II.

LIST OF ACRONYMS

AAS	Atomic absorption spectroscopy
BLL	Blood lead level (blood lead concentration)
BSID	Bayley Scales of Infant Development
GSRH	General self-rated health
Hb	Hemoglobin
HOME	Home Observation for the Measurement of the Environment
IQ	Intelligence quotient
LEST	Lead Exposure Study Team
LGU	Local governmental unit
ln	Natural logarithm
QIDS	Philippine Child Health and Policy Experiment, Quality Improvement Demonstration Study
TAPQOL	TNO-AZL Preschool Children Quality of Life
µg/dl	Micrograms per deciliter
WPPSI	Wechsler Preschool and Primary Scales of Intelligence

ABSTRACT

Background: Lead poisoning has been described as the most significant environmental health threat facing American children. Its insidious effects on child development, behavior, and cognitive function have been demonstrated at increasingly low levels of exposure. Although the sources of lead poisoning, clinical correlates and health effects have been relatively thoroughly described in U.S. pediatric populations, the characteristics and outcomes of lead poisoning among populations in less developed areas, particularly rural regions, have not been well characterized.

Methods: A large pediatric health study conducted among children 6 to 59 months of age in rural areas of the Visayas Islands, the *Philippines Child Health and Policy Experiment, Quality Improvement Demonstration Study* (QIDS) recently revealed high prevalence of elevated blood lead levels. In response, we conducted an analysis of cross-sectional data collected in 2003-2004 from 3182 children in the QIDS study to determine factors associated with blood lead concentration and cognitive function among children in this region.

Results: Twenty-nine percent of all children had blood lead concentration exceeding the 10 μg/dl action guideline of the U.S. Centers for Disease Control. In fact, the mean blood lead concentration in the sample was 10.02 μg/dl. Multiple individual and household characteristics were associated with blood lead concentration. After controlling for multiple confounders, older age, higher blood hemoglobin concentration, history of breastfeeding, province of residence, water source, and type of roof construction material were associated with higher blood lead concentration. Increasing blood lead concentration was associated with lower mental and behavioral function scores on the

Bayley Scales of Infant Development , but the associations did not persist after adjustment for multiple potential confounders.

Conclusions: Our study found multiple factors associated with blood lead concentration among children in the Visayas region of the Philippines. These findings will help direct lead exposure assessment investigations and suggest opportunities for interventions. An association was found between blood lead concentration and cognitive function among the youngest children, unadjusted for other covariates, is consistent with findings in developed populations. The lack of persistence of the association after adjustment for other potential determinants of cognitive function may reflect actual confounding or over-control of factors in the causal pathway, masking the true association. Regardless, the widespread elevation in blood lead levels among Philippine children indicates the immediate need for exposure control measures and population screening.

CHAPTER 1: INTRODUCTION

Lead poisoning in children: a global problem

Lead is a human toxin with no known physiologic value. Although it is a naturally occurring element in Earth's crust, it is normally present at only minimal levels in the environment and almost entirely in inorganic forms not readily absorbed by the human body. Humans, however, have exposed ourselves to increased concentrations of lead for millennia—it is one of the more malleable of the common metals. The Latin word for lead, *plumbum*, is a root for the modern English term plumbing; it has been widely conjectured that the use of lead pipes contributed to the demise of the Roman Empire (a historical term for lead poisoning is "plumbism") (Kitman 2000). Humans have also been aware of lead's toxic qualities for thousands of years; Greek physicians made the first diagnosis of lead poisoning in the second century B.C.

Despite this knowledge, however, human activities have continued to result in widespread contamination of the natural and built environment and unavoidable exposure. The development of organic lead-containing compounds in the U.S. for industrial purposes greatly increased the global distribution of lead and the bioavailability of lead as a human toxin (Rice 1988). In the twentieth century, as the uses for lead expanded, lead pollution became so ubiquitous that today even the most remote and least developed peoples in the world have measurable levels of lead in their body. Indeed, researchers were forced to use evidence from the bones of prehistoric man to prove that

lead is an anthropogenic pollutant and not naturally present in everyone (Flegal and Smith 1992).

Lead is a potent neurotoxin—the U.S. federal government has described lead exposure as the "most serious environmental disease of American children" (Needleman 1995). While regulations have significantly reduced childhood exposure to lead in the most developed countries over recent years, it remains largely unaddressed in many less developed nations (Romieu et al. 1997).

Children are particularly vulnerable to lead poisoning for several reasons. Children may be at higher risk for ingestion of lead-containing dust because of crawling, more contact with the ground, and hand-to-mouth behavior. Once ingested, a greater portion of lead is absorbed from the gastrointestinal tract of children than of adults (Leggett 1993). Additionally, a greater proportion of systematically circulating lead crosses the blood-brain barrier in children (particularly those less than five years old), and the developing nervous system is far more sensitive to lead's toxic effects than the mature brain (Lidsky and Schneider 2003).

Markedly elevated blood concentrations of lead can lead to serious acute neurologic damage in children. Fortunately, this is relatively rare. Perhaps more concerning is the fact that the majority of children with toxic lead levels are asymptomatic at the time of screening. Insidious and irreversible cognitive and behavioral consequences are thought to result at low blood concentrations from chronic low-level lead exposure (Bellinger 1991). Accumulating evidence suggests that there can be significant cognitive impairment resulting from blood lead levels lower than 10 μg/dl (Canfield et al. 2003, Mendelsohn 1998, Baghurst et al. 1992, McMichael et al. 1988).

Although current U.S. Centers for Disease Control define lead toxicity as blood lead concentration greater than 10 μg/dl, evidence suggests that here is no "safe" dose of lead exposure.

Although over the last 30 years regulatory reforms have finally had an impact on lead pollution in the developed world, the problem of lead toxicity remains particularly severe in less developed countries. A 1994 meta-analysis of international prevalence of lead toxicity found a far higher prevalence of toxicity in children from studies involving developing countries compared to developed countries. Outside of the developed world, research has not been sufficient to accurately characterize the population prevalence (Alliance to End Childhood Lead Poisoning and Environmental Defense Fund 1994).

Documented sources of lead poisoning in developing nations

Multiple sources of lead exposure for children have been identified in developing countries. Compared to more developed countries, regulations limiting lead pollution are less likely to be present or to be fully enforced (Alliance to End Childhood Lead Poisoning and Environmental Defense Fund 1994). While variation is observed between regions of the developing world, common sources of lead pollution include gasoline, paint, batteries, food contamination, traditional and cultural practices, and occupational and industrial point sources.

Gasoline

Globally, gasoline is the most pervasive and widespread source of lead contamination. Lead is not a naturally occurring component of gasoline—since in the

1920s, alkyl lead has been added as an "anti-knock" agent, increasing octane and allowing internal combustion engines to function at a higher compression. Although it was outlawed as a gasoline additive in the U.S. in 1986 (to protect exhaust system catalytic converters), American companies allegedly continue to provide lead additive to numerous other countries (Kitman 2000).

Although only tiny amounts of lead are added to gasoline, its combustion and expulsion as automobile exhaust is an efficient means of distribution into the environment. Lead from gasoline has been found in air, soil and water. After emission, lead may remain suspended in air as a particulate for up to two weeks (OECD 1993). As a fine particle, it is easily inhaled and systemically absorbed through alveolar tissue (Leggett 1993). As a result, children living on busy streets (Lyngbye et al. 1988) or near intersections (Rahbar et al. 2002) are at increased risk for lead exposure. After lead from gasoline settles out of the air, it is incorporated into dust and soil where it remains indefinitely as a chemically stable compound. Soil around urban centers and major roadways contains increased concentrations of lead—this may be a particular problem in less developed countries where there frequently is less pavement, more dust and dirt, and less road-cleaning. A study in Jakarta, Indonesia found higher lead levels among children in central urban areas than in surrounding areas (Heinze et al. 1998).

Although the majority of lead from vehicle emissions is deposited in the vicinity of their origin, up to 35 percent of lead emitted may be distributed globally via long-range atmospheric transport systems, as evidenced by lead found in the Greenland ice cap (Boutron et al. 1991). Thus, leaded gasoline is a truly global health threat—even children

in countries where lead has been removed from gasoline are being exposed to lead from emissions in other parts of the world (Bellinger 2004).

Paint

Lead in paint is another major source of lead exposure for children. Added to paint to increase its durability and mold resistance, lead becomes an environmental pollutant when paint wears or cracks and exposure occurs through ingestion of paint chips and inhalation of dust. Although at least 55 nations have set regulatory limits on the amount of lead in paint (Alliance to End Childhood Lead Poisoning and Environmental Defense Fund 1994), older and increasingly decaying buildings continue to contain large amounts of the element. However, it is likely that many of the developing countries that have passed legislation banning lead paint lack the resources to truly enforce such a ban. Like gasoline, the majority of research regarding lead paint has been performed in developed nations. Very little is known about the amount of lead paint in less developed countries (Alliance to End Childhood Lead Poisoning and Environmental Defense Fund 1994). Little is known about the lead content of paint in countries that do not have specific regulations, and even less is known about the amount in lead paint in homes built prior to regulation. Paradoxically, the problem of lead paint in developing nations may selectively affect children of relatively affluent families compared to poorer families. In most developing countries, the poorest individuals are those who live in rural areas, often in traditional dwellings that have no paint whatsoever. Even in urban areas, it may be likely that families living in painted homes tend to have a higher income. This is an important consideration because socioeconomic status has

been widely demonstrated to be an important confounder and/or modifier of the relationship between lead exposure and cognitive function in more developed countries (Bellinger et al. 1989). In certain conditions in less developed countries, it may be a negative confounder rather than a positive confounder.

Batteries

With the decline of lead in products such as gasoline in paint in recent years, lead-acid batteries have increasingly become the dominant manufacturing application of lead. Lead-acid is most often used in car batteries—a typical auto battery contains eight kilograms of lead (OECD 1993). Demand for lead by battery manufacturers increased by 79 percent between 1973 and 1993. As cars continue to pervade the developing world, so will lead-acid batteries. Although batteries are carefully designed to prevent exposure to lead acid among end-users during their useful life, battery waste is a major potential source of pollution. In the developed world, processes have been developed to handle battery waste (i.e. through recycling programs via auto mechanics), but no such processes exist in much of the developing world; expired batteries often end up in trash heaps or incinerators. Furthermore, in vast regions of the developing world where electrical utilities are nonexistent or highly unreliable, lead-acid car batteries are commonly used in households to power radios, televisions, and other appliances. Hypothetically, dead lead-acid batteries in homes, disposed of in trash heaps around homes, or incinerated into the atmosphere are likely to cause environmental contamination and thus human toxicity. Little research has been done on this potentially widespread contaminant in the developing world.

Food Contamination

Food may be contaminated by lead in several possible ways. Lead solder is sometimes used in food canning, resulting in leeching of lead into the canned food. The U.S. and Mexican canning industries banned the use of lead solder in the early 1990s, but many poor Eastern European countries continued to use decades-old canning equipment which likely includes lead solder (Alliance to End Childhood Lead Poisoning and Environmental Defense Fund 1994). Less developed countries elsewhere also are likely to continue to use lead solder in canning, including use of old and now-outdated equipment unloaded by companies in developed countries.

Other food packaging articles have been found to contain lead as well. Wrappers for a eucalyptus menthol candy produced in the Philippines were found by the U.S. FDA to contain 33,000 parts per million (ppm) lead, and the candy itself 0.88 ppm lead (Visto 2002). Lead may also be present in ceramic glazes used for pottery in much of Latin America. Avila et al. (1991) found the use of lead-based ceramics to be the primary determinant of lead levels in a cohort of Mexico City women. As a result, a number of public health organizations in the U.S. have recommended against the use of imported ceramics for food serving. However, the use of lead in glaze is a longstanding tradition in Latin America and continues despite the known risk.

Food may also be contaminated with lead during processing—an investigation in the West Bank of Palestine explained a cluster of lead poisoning by contamination from flour-grinding process in a particular mill (Hershko et al. 1984). Lead has also been found on green leafy vegetables and other agricultural products in Egypt, presumably

from emissions-related contamination (Dogheim et al. 2004). It is likely that lead is introduced into the food supply in other ways which have yet to be discovered, particularly in the developing world where food quality regulations are scant.

Home Remedies and Traditional Cosmetics

Another source of lead in the developing world is the use of traditional home remedies and cosmetics, many of which are used specifically in children. Empacho, a traditional Mexican home remedy for childhood colic, has been widely found to contain lead. A similar home remedy, called Bint Al Zahab (BAZ), is used in the Middle East. A study in the United Arab Emirates found that BAZ contains 80% lead, and that short-term use among infants resulted in severe lead poisoning (Rahman et al. 1986).

Lead is also present in surma, a cosmetic applied around children's eyes in areas of South Asia. Rahbar et al. (2002) found an increased incidence of lead toxicity in children who wear surma. These are a few examples of the home-made substances which have been discovered to contain lead. Like the problem of food contamination, it is likely that there are other lead-containing substances commonly used in the developing world which, due to lack of regulation and quality control, are insidiously poisoning children.

Industrial and Occupational exposure

A final potential way in which children in developing countries may be exposed to lead is though industry. Industrial and occupational safety regulations in developing countries are often either nonexistent or incompletely enforced. As a result, individuals

working in industries with lead exposure can easily transport lead home on their bodies or clothing, potentially exposing their children. Furthermore, enterprises such as battery recycling are often cottage industries in developing nations, with work occurring directly in or within close proximity to the home and thus directly exposing children. A study of battery recycling and repair workers in Manila, Philippines found significantly increased lead levels among the children of workers (Suplido and Ong 2000). The authors found little demarcation between living areas and working areas in the small-scale cottage operations they studied, resulting in significant, constant exposure for both workers and their families. Of course, children may also themselves be workers, resulting in direct occupational exposure.

Lead and cognitive function in children

Lead is the single most studied developmental neurotoxicant (Rice 1988). The neurochemical mechanism of lead toxicity may involve multiple pathways; it has been shown to interfere with capillary integrity, synaptogenesis, myelination, and catecholamine metabolism in the central nervous system (Deitrich 2000).

The relationship between lead exposure and cognitive function has been studied in multiple prospective and cross-sectional observational studies. In nearly all cases, studies have relied on standardized psychometric measures of intelligence or behavior (Deitrich 2000). Several well-powered studies utilizing multivariate adjustment for confounding have found significant associations between lead exposure and declining IQ and/or behavioral indices (Canfield et al. 2003, Mendelsohn 1998, Bellinger and Deitrich

1994, Pockock Smith and Baghurst 1994, Baghurst et al. 1992, Needleman and Gatsonis 1990, McMicheal et al. 1988).

However, not all well designed studies have found a significant association (Rice 1988). A 1995 meta-analysis performed by the International Programme on Chemical Safety (IPCS 1995) used full-scale IQ as the outcome measure and performed separate analyses for comprehensive sets of prospective and cross-sectional studies. After weighting each study by the inverse of its variance to account for differences in power, neither the combined prospective nor the combined cross-sectional studies produced statistically significant results.

Studies conducted in the 10 years since the IPCS meta-analysis have generally supported the conclusion that lead exposure causes cognitive impairment in children and the causal association is now generally accepted by the scientific community. Increasing evidence suggests that there is no threshold of lead exposure below which there is no cognitive effect (Canfield 2003). However, groups such as the American Council on Science and Health continue to purport that lead exposures currently found around the world are "categorically safe" for children (Juberg 2000).

One possible explanation for the differences between study outcomes is confounding by socioeconomic status. The relationship between lead exposure, socioeconomic status and cognitive function is complex, and may not be adequately adjusted for in all multivariate analyses of observational studies. One potential solution to this problem is to examine the relationship between lead exposure and cognitive function in a novel population in which the relationship between exposure, outcome, and confounding factors is fundamentally different.

Gaps in the current research

Virtually all research on the adverse neurobehavioral effects of lead exposure has occurred in the U.S., Western Europe, or Australia (Pockock et al. 1994). Little is known about the effect of chronic low-level lead exposure on the cognitive development of children in less developed countries, and wide variation exists in the strength of the association among the few published studies. At one extreme, Wang and colleagues (1989) report a strong relationship between blood lead and impaired cognitive performance, with a 0.91 point decrease in full scale IQ (95% CI 0.68, 1.1) per one μg/dl increase in blood lead concentration (as measured by the Wechsler Intelligence Scale for Children [revised]) among 6 to 14 year old children living around a battery manufacturing plant in Shanghai.

At the other extreme, Wolf and colleagues (1994) could not demonstrate a statistically significant association between blood lead concentration and Wechsler IQ among Costa Rican children. The substantial variation among reports from studies in less developed countries is not surprising given the variation observed in studies conducted in developed countries (Pockock et al. 1994). Regardless of the setting, epidemiological studies must address challenging methodological issues of exposure misclassification and confounding.

Several factors prevalent in less developed countries may modify the effect of lead on cognitive function. For this reason, studies of the relationship between lead and cognitive function in industrialized nations may not fully pertain to populations of

children potentially exposed to lead in less developed conditions. Malnutrition, for example, may affect the relationship between lead and cognitive function in several ways. Bradman et al. (2001) showed that children living in lead-contaminated environments tend to have higher lead levels when iron deficient. Several mechanisms have been postulated for this association, including concomitant uptake and binding of iron and lead, resulting in increased uptake and decreased excretion of lead in the presence of iron deficiency (Ruff et al. 1996). Lacasana et al. (2000) reported an inverse relationship between lead level and calcium intake among Mexico City children.

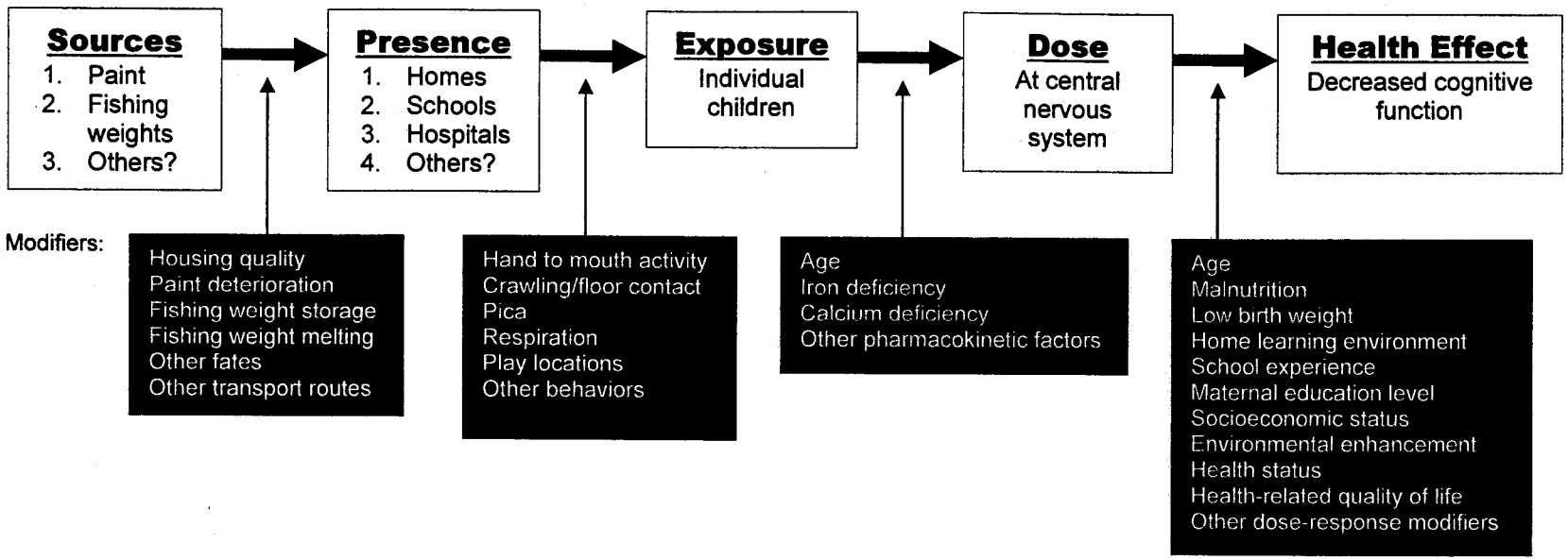
Besides nutrition, several other factors such as poverty and low education may also affect the relationship between lead exposure and cognitive function, as has been recognized in more developed countries (Canfield et al. 2003, Baghurst et al. 1992, Bellinger 1991, Bellinger and Dietrich 1994, Wasserman et al. 1997, McMichael et al. 1992). These effect-modifying factors complicate efforts to assess and understand the relationship between lead exposure and cognitive function. In less developed countries exposure to poverty, low education, malnutrition, and other factors is particularly extreme; appropriately addressing effect modification of the relationship between lead and cognitive function due to these factors is a critical in understanding the relationship.

A proposed biologic impact pathway illustrating the relationship between lead exposure, cognitive function, and other confounding and effect-modifying factors is presented in Figure 1. The relationship between environmental lead and changes in cognitive function is complex; it depends on the source of the pollutant, the location of the source relative to individuals in the population, the dose experienced by individuals, and the pharmacokinetics and pharmacodynamics of a given dose. At each of these steps,

multiple factors play a role in determining the specific character of the exposure-response relationship. Clearly, additional research is needed in developing countries to characterize this relationship and its effect modifiers.

A children's health study in the Philippines, the *Philippines Child Health and Policy Experiment, Quality Improvement Demonstration Study* (the QIDS project), has collected blood lead levels and performed cognitive performance tests on a cohort of 3,000 children living in rural areas of the Visayan islands (see map, Figure 2). Unexpectedly, a high prevalence of lead poisoning has been found; the source of the lead is currently under investigation. 29% of all children had elevated blood lead concentration as defined by current U.S. Centers for Disease Control guidelines. The mean BLL in the cohort was 10.02 ug/ml and the median concentration was 8.2 ug/ml (see Appendix 1). The addition of alkyl lead to gasoline was regulated in the Philippines approximately 15 years ago, there are no known industrial point sources of lead emissions in this area, and there are no household products currently distributed in the area that are known to contain lead. The baseline data collected in the QIDS study provide demographic, socioeconomic, household characteristic, and health information that may allow the identification of sources. Also, the QIDS data provide a unique opportunity to evaluate the relationship between blood lead level and cognitive function in this cohort of rural Filipino children.

Figure 1. Biologic impact pathway of lead and cognitive function in the Philippines



Objectives and implications for public health

This study is a secondary analysis of data from the *Philippines Child Health and Policy Experiment, Quality Improvement Demonstration Study*, the "QIDS Project". The objectives of the analysis were twofold:

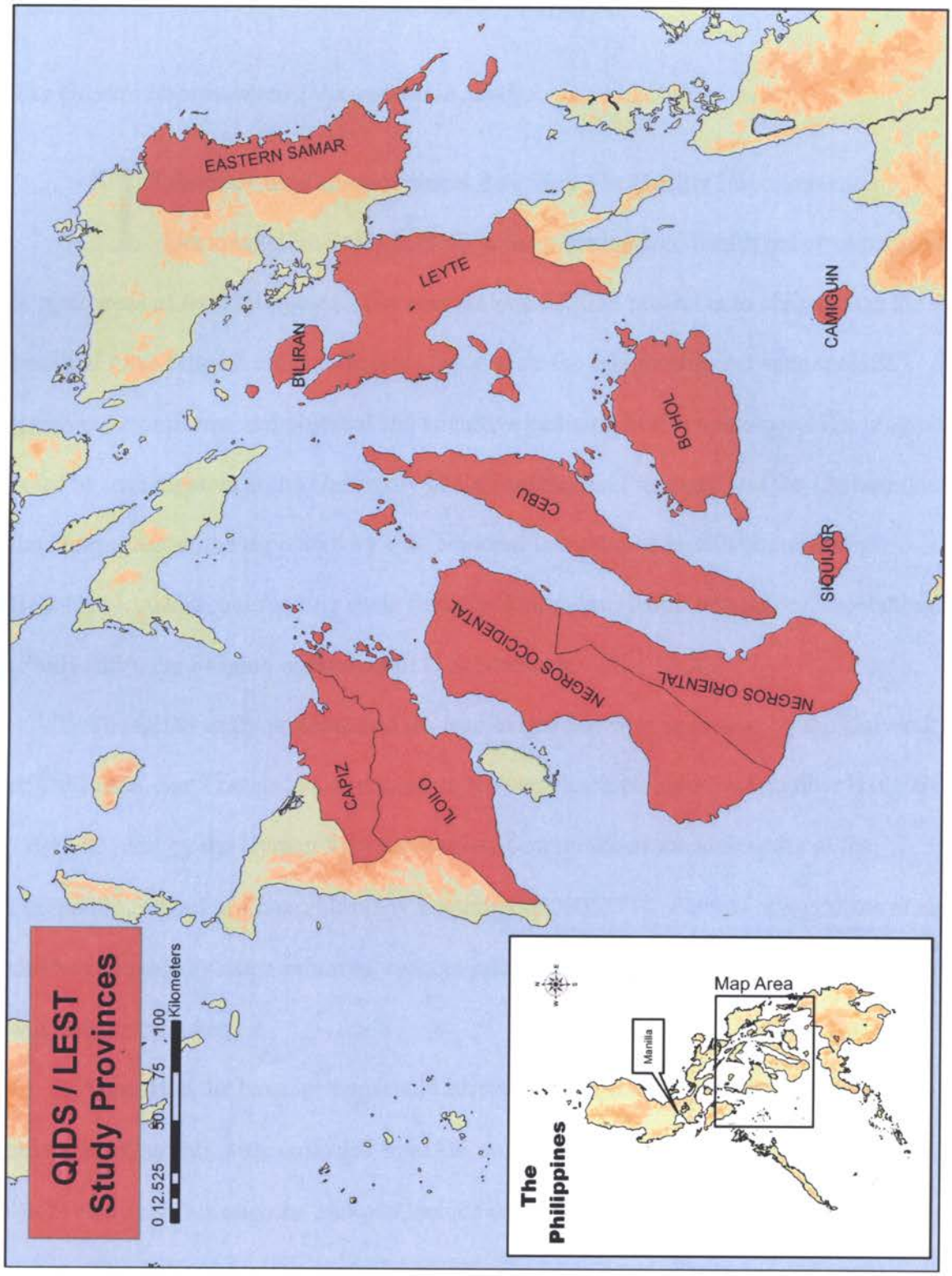
The first objective was to identify factors associated with elevated blood lead levels in children in the Visayan islands of the Philippines including household, demographic, and socioeconomic characteristics. This information was utilized to develop an environmental exposure assessment study to more precisely determine the sources to child lead exposure in this region.

The second objective was to determine associations between measured blood lead concentration and cognitive performance as measured by the Bayley Scales of Infant Development and the Wechsler Preschool and Primary Scales of Intelligence in this unique population while controlling for confounding factors such as age, socioeconomic status, general health status, hemoglobin, educational experience, and general home environment.

This information is critically important for two reasons. First, the sources of lead poisoning among this cohort of children must be identified. Analysis of these data has directed exposure assessment studies to definitively identify environmental lead sources, leading to development of mitigation strategies. Second, Children in rural areas of less developed countries experience a myriad of circumstances that may confound and/or modify the relationship between lead exposure and cognitive function, including extremely low socioeconomic conditions, malnutrition, and increased prevalence of numerous diseases. Identification of these factors may allow design of interventions to

mitigate the consequences of lead exposure. This large cohort provides the opportunity to characterize the relationship between blood lead level and cognitive function in an understudied population—the very type of population that is suffering from the highest levels of exposure to this toxin.

Figure 2.


EASTERN SAMAR
LEYTE
BILIRAN
BOHOL
CAMIGUIN
CEBU
SIQUIJOR
NEGROS OCCIDENTAL
NEGROS ORIENTAL
CAPIZ
ILOILO
QIDS / LEST
Study Provinces
0 12.525 50 75 100 Kilometers
The Philippines
Manilla
Map Area

CHAPTER 2: METHODS

The Quality Improvement Demonstration Study

This study uses cross-sectional data from The Quality Improvement Demonstration Study (QIDS), a large randomized health policy experiment in rural areas of the Philippines. The purpose of the QIDS project is to characterize the health of rural Filipino children and to demonstrate the relationship between specific health policy reforms and physical and cognitive pediatric health outcomes. The program is led by investigators at the University of California, San Francisco and the University of the Philippines and is supported by U.S. National Institutes of Health Grant R01 HD042117. Additional funding came from the Philippine Health Insurance Corporation (PhilHealth), the Filipino equivalent of U.S. Medicare.

The QIDS study protocol and the lead evaluation were approved by the University of California, San Francisco Committee on Human Research (approval number H10609-19947-03) and by the Human Subjects Review Committee of the University of the Philippines School of Economics (FWA number 000005371). Parents or guardians of all children provided written informed consent prior to enrollment. All study participation was strictly voluntary.

Data from the baseline household survey of the QIDS project are used in this study; baseline data were collected from December 2003 through September 2004. The QIDS study itself is ongoing and will include collection of further longitudinal data in the future. The data used in this analysis were checked for completeness and accuracy,

coded and keyed by project staff at the University of the Philippines in Manila using double keyboard entry on a Microsoft Access® platform. After entry, the dual entries were checked for discrepancies due to coding error and all discrepancies were corrected by reference to the original survey forms. Data were then subjected to internal consistency checks, logic checks, and range checks; inconsistent data were corrected whenever possible using the original paper surveys. Discrepant and inconsistent data that could not be resolved were excluded from the analysis data set.

Study subjects:

As part of the overall QIDS project children of ages 6 months to fifth birthday were eligible for enrollment. Subjects were recruited into the study through stratified random sampling. Thirty local governmental units (LGUs) on 11 islands were identified for participation in the study and approximately 100 children were enrolled from each LGU. Two groups of children were enrolled: a population-based group and a hospital-based group. Approximately one-half of the subjects are from the population-based group; they were identified from randomly selected households enumerated in existing census frames from the National Statistics Office.

The remaining half of children were enrolled after they were admitted to the local hospital in the catchment area of the 30 pre-identified LGUs. These subjects can be further divided into two groups: randomly selected hospitalized children and hospitalized children with one of two index conditions. Children with the conditions of lower respiratory tract infection or diarrhea were intentionally over-sampled to ensure adequate representation of these two regionally most prevalent childhood illnesses. Consecutive

children admitted to study hospitals with one of the two index conditions were ascertained from each hospital's daily activity reports and recruited for participation if they met age eligibility criteria (between six and 59 months of age at the time of admission). Additionally, patients without one of the index conditions (randomly selected hospitalized children) were listed then randomly sampled over the same data collection interval to control for case mix and clinical severity. The sample frame for this study was designed to meet the goals of the QIDS study, which did not initially include assessment of the relationship between lead exposure and cognitive function. However, the sampling scheme does not preclude use of the data for such an analysis since neither index condition has been associated with chronic low-level lead poisoning.

The survey data used in this analysis are from an in-home survey. The two groups (population-based and hospital-based) were administered identical surveys, and were subjected to the same battery of testing including blood lead analysis. The hospital based group was administered the survey in a follow-home interview 30 to 45 days after discharge. Lead testing occurred on the day of discharge for hospital-based subjects and during the home visit for population-based subjects. No more than one child per household was enrolled in either group or in the study as a whole. In the population-based group, the youngest child at least 6 months old from each selected household was selected for enrollment. In the hospital-based group, only the first child from any given household admitted to the hospital during the study period was eligible for enrollment.

Study variables:

Household survey instruments were administered to collect information on health status, anthropometrics, and cognitive development of the children. Detailed information about socioeconomic and health status was obtained, including household characteristics and expenditures, sources of water, sanitation, labor force participation, wages, and education. Health measures collected included a general child health questionnaire, birth history, anthropometrics, and blood tests for hemoglobin, folate, and lead. The household survey and physical health measures were collected by trained medical technicians. Data collection methods were monitored by project leaders to ensure quality and uniformity.

Blood lead levels were obtained from venous samples which were analyzed at a central laboratory using the LeadCare® Analyzer (ESA Inc., Chelmsford, Mass.). The device uses anodic stripping voltammetry to determine blood lead concentration. In clinical performance trials, the LeadCare system was equivalent to the current "gold standard" for measurement of blood lead concentration, atomic absorption spectroscopy (see Appendix 5). The FDA approved the LeadCare device for use in clinical measurement of blood lead concentration in 1997 (FDA 1997) and it has been used previously in field studies in remote areas of developing nations (Counter et al. 1998).

Hemoglobin and folate levels were determined from venous blood samples by an automated blood analyzer at a central laboratory. Weight and height were measured in each child twice during the survey visit and the mean values for each measure were used to calculate body mass index (kg/m^2).

To evaluate cognitive development, each child in the study was tested with validated psychometric instruments that were administered by bachelors- or masters-level psychologists fluent in English as well as Tagolog, and/or local dialects. All psychologists received study-specific training by a nationally-recognized expert in child development and active field monitoring was performed with re-training as needed. Incoming data from each psychologist were monitored for internal and external consistency, completeness, and compliance with study procedures. All psychometric instruments were translated into Tagolog, Hiligaynon/Ilongo, Bisayan/Cebuano and Waray by qualified, nationally recognized child psychologists. The psychometric instruments were administered in compliance with instructions published by their original authors (see below). The following measures of cognitive function were used:

Bayley Scales of Infant Development (BSID), Second Edition: The BSID was administered to infants and children from 1-42 months of age. It consists of three scales: mental, motor, and behavioral (Bayley 1993). Mental and motor scores were indexed by age group and behavior was treated as a percentage score.

Wechsler Preschool and Primary Scales of Intelligence (WPPSI), Third Edition: The WPPSI has two versions - "young" for ages 2.5 through 3 years and "old" for ages 4 through 7.25 years. Both versions produce the following three index scores: verbal IQ, performance IQ, and full IQ (Wechsler 1989).

To account for environmental effects of cognitive development, the psychologists administered the *Home Observation for Measurement of the Environment (HOME), Third Edition*, which was used as a covariate in cognitive function modeling. The HOME Infant/Toddler (IT) version was administered to children six through 35 months

of age and the Early Childhood (EC) version was administered to children 36 through 59 months of age. HOME is a well established tool administered by psychologists to detect high-risk environment—it is not a measure of cognitive function per se. The IT version includes measures of responsivity, acceptance, organization, learning materials, involvement, and variety in the child's home environment. The EC version includes measures of learning materials, language stimulation, physical environment, responsivity, academic stimulation, modeling, variety and acceptance. Children scoring less than 25% have been considered to be living in a deprived environment that has been shown to hinder cognitive development (Caldwell and Bradley 2003).

Statistical Analysis:

Statistical analysis involved three parts: dataset preparation and descriptive analysis; analysis of socioeconomic, demographic, household, and child health characteristics to characterize the factors associated with elevated blood lead levels; and assessment of the association between blood lead level and cognitive function. All statistical tests were performed using Stata® Version 7.0 Intercooled (College Station, TX).

1) Dataset preparation and descriptive analysis

All study variables were examined to verify data cleanliness and completeness. Distributions of each variable were checked and obviously out-of range values were discarded. Next, univariate comparisons were made between data from the population-based group and the hospital-based group for all study variables. An additional

univariate comparison was made between observations with complete versus incomplete data for all study variables. In all descriptive analyses, student's t-tests were used to assess between-group differences for continuous variables and chi-squared tests were used to assess between-group differences for categorical variables.

2) Analysis of factors associated with blood lead concentration (model 1)

All children enrolled in the QIDS project with complete household survey data and a blood lead level were included in this exploratory analysis. The outcome of interest, blood lead concentration, was considered as a continuous variable. Linear regression was used for all analyses. Statistical analysis consisted of individual single linear regression for each predictor of interest in addition to multiple linear regression accounting for multiple independent variables. The goal of multivariate analysis was the creation of an exploratory best-fit model to describe the variation in blood lead concentration in the study population.

A preliminary main effects model was created after consideration of the independent variables of interest listed in Table 1.

Independent variables were introduced into the model according to the custom forward stepwise model building process described by Kutner et al. (2005). Independent variables with p-values less than 0.25 in simple linear regression were included in the preliminary main-effects model. The remaining independent variables were then entered into the model individually. Age, however, was retained *a-priori* in all models due to the high likelihood of interaction between age, lead exposure, and blood lead level.

Table 1. Study variables considered in exploratory analysis of factors associated with blood lead concentration (model 1)
Roof construction material (a marker of home construction)
Water source/plumbing type
Motor vehicle ownership (including type of vehicle)
Household location (urban vs. rural barangay status)
Household income
Household expenditures
Maternal education level
Paternal education level
Parental employment status
Blood folate concentration (a marker of nutritional status)
Hemoglobin concentration (a marker of anemia)
Home Observation and Measurement of the Environment (HOME) score
Age
Source group (population or hospital-based)
Province
Local Governmental Unit

After a preliminary main-effects model was generated, in separate confirmatory process an automated backwards stepwise selection process was employed utilizing the same initial set of variables in order to assess the impact of variables excluded in the forward selection process on a full model. These forward and backward modeling processes yielded main effects models with identical independent variables. Scaling of continuous independent variables was assessed visually and by fitting fractional polynomials, which were tested for significance. Interactions between independent variables were assessed. Since it is considered likely that subjects in the same LGU are exposed to the same type of environmental lead source, observations were clustered by LGU; a procedure which produced a mixed model allowing for the assumption that individual subjects are independent between LGUs but not necessarily independent within LGUs.

Finally, the model was assessed using residual vs. fitted-value plots to determine the distribution of error variance and normal-probability plots to assess model normality.

3) Analysis of association between blood lead level and cognitive function (models 2a-2i)

Children enrolled in the QIDS project with complete household survey data, a blood lead level, and cognitive function testing were eligible for inclusion in the cognitive function analysis. Children were excluded from the analysis if mothers reported that their child was born prematurely (less than 37 weeks gestational age), was underweight (less than 2500 grams) at birth, or had a known disability due to a congenital neurologic lesion.

Cognitive outcomes varied according to the measure designed for each particular age group and thus modeling was stratified by cognitive function outcome. For children aged six months through 35 months, BSID scores were used as the assessment of cognitive function. Outcome variables will include mental, motor, and behavioral BSID scores. For children ages 36 to 59 months, WPPSI scores were used as the assessment of cognitive function. The WPPSI has two sections depending on age: the WPPSI "young" for children 36 to 47 months of age, and the WPPSI "old" for children 48 to 59 months of age. In both WPPSI sections, cognitive function scales include verbal IQ score, performance IQ score, and full IQ score. Thus, analysis was stratified into three age groups depending on the test available: BSID outcomes for children 6-35 months old, WPPSI young outcomes for children 35-47 months old, and WPPSI old outcomes for children 48-59 months old.

The predictor of interest was venous blood lead concentration as measured by the LeadCare device.

Previous studies of the relationship between pediatric lead exposure and cognitive function have established an *a priori* set of covariates based on established predictors of children's intellectual outcomes (Canfield et al. 2003, Baghurst et al. 1992, Bellinger 1991, Bellinger and Dietrich 1994, Wasserman et al. 1997, McMichael et al. 1992). These variables include child's sex, age, birth weight, iron status, mother's IQ, years of education, race, maternal tobacco use during pregnancy, yearly household income, and HOME score.

Several differences between this study and previous studies make use of a strict set of *a priori* confounders inadvisable, however. First, the population in this study is quite different from that of previous studies, and different confounding factors may come into play. Also, since this analysis used data from a project not initially conceived to assess the relationship between lead exposure and cognitive function not all of the conventional confounders were measured. Wherever possible, measures that approximated these factors were utilized.

Of the confounders listed above, all but iron status, maternal tobacco use during pregnancy, and mother's IQ were available in the QIDS dataset. However, strong proxy measures were available for our analysis. Iron status was approximated by hemoglobin concentration, maternal tobacco use during pregnancy was approximated by current maternal smoking status, and maternal IQ was replaced by maternal educational attainment. Race and ethnicity was not considered as a potential covariate because all subjects were Filipino.

As previously discussed, factors associated with life in a rural area of a developing nation may confound the relationship between lead level and cognitive

function. To address this concern, we considered blood folate concentration and body mass index (as markers of nutrition status), general self-rated health (GSRH) score as a measure of overall health status (DeSalvo et al. 2005), TNO-AZL Preschool Children Quality of Life (TAPQOL) score as a measure of health-related quality of life (Fekkes et al. 2000), history of breastfeeding, and total yearly household expenses. Total yearly household expenses are considered a potentially more accurate assessment of economic status in this population than yearly household income due to the prevalence of subsistence farming and other informal economic activities (Deaton & Dreze 2002). Of the two measures of household economic status, the one more strongly associated with cognitive function was retained in the model. History of breastfeeding, source group (hospital-based or community-based), and province of residence were also considered as potential covariates. The variables listed in Table 2 were considered in multivariate analysis.

Separate preliminary main-effects models were created for each dependent variable within the three age strata, for a total of nine models for the nine outcomes of interest. Independent variables were introduced into the models according to the custom forward stepwise model building process described by Kutner et al. (2005). Independent variables with p-values less than 0.25 in simple linear regression were included in the preliminary main-effects model. Those independent variables with p-values greater than 0.25 were removed from the model and not considered further. Scaling of continuous independent variables was assessed visually and by fitting higher order polynomial models and testing for significance of higher order terms. Interactions between independent variables were assessed.

In the same manner as the blood lead concentration model, observations were clustered by LGU producing a mixed model allowing for the relaxed assumption that individual subjects are independent between LGUs but not necessarily independent within LGUs.

Table 2. Study variables considered in analysis of association between blood lead level and cognitive function (models 2a through 2i)

Dependent variables	Independent variables
Outcomes of interest:	**Predictor of interest:**
Children 6-35 months old:	Blood lead level
BSID† mental function score (2a)	***A-priori* covariates:**
BSID† motor function score (2b)	Age
BSID† behavioral function score (2c)	Sex
Children 36-47 months old:	Birth weight
WPPSI‡ young verbal IQ (2d)	Mother's educational attainment
WPPSI‡ young performance IQ (2e)	Years of education
WPPSI‡ young full IQ (2f)	Hemoglobin
Children 48-59 months old:	Maternal smoking status
WPPSI‡ old verbal IQ (2g)	Yearly household income or yearly household expenses
WPPSI‡ old performance IQ (2h)	HOME* score
WPPSI‡ old full IQ (2i)	**Additional covariates:**
	Folate concentration
	Body mass index
	GSRH** score
	TAPQOL*** score
	History of breastfeeding
	Source group (hospital or community)
	Province of residence

† Bayley Scales of Infant Development
‡ Wechsler Preschool and Primary Scales of Intelligence
* Home Observation for Measurement of the Environment
** General Self-Rated Health
*** TNO-AZL Preschool Children Quality of Life

Age was a variable of particular interest due to the potential for interaction with environmental factors, lead exposure, and cognitive function. Multiple methods were employed to assess this relationship. An age-lead interaction term was introduced into all models. Additionally, models were stratified into 1-year age groups and the relationship was assessed within each age group. To assess for colinearity between lead concentration and other varaiables, lead concentration was removed from the final models and the

changes to the remaining variables was assessed. The same process was repeated by removing other variables and assessing the impact on the lead concentration variable.

Finally, the models were assessed using residual vs. fitted-value plots to determine the distribution of error variance, residual vs. predictor plots to assess linearity of relationship and consistency of variance, normal-probability plots to assess normality of model error, leverage-value plots for identify potential outliers, and Cook's Distance-value plots to identify potential influential points. Further transformations were applied as indicated.

CHAPTER 3: RESULTS

A total of 2779 subjects enrolled in the QIDS study had a measured blood lead level (BLL). Complete data were available for 1733 subjects (62.4%). Data were incomplete for some subjects for several reasons, mostly related to incomplete respondent knowledge. Mothers or other caregivers were sometimes unable to report some health-related data and frequently did not know the child's birth weight. In rare instances, medical technicians were unable to obtain sufficient venous blood samples or psychologists were unable to complete their assessments due to technical difficulties.

Data from the two source groups were generally comparable; with the exception of several expected factors, differences were small and statistically insignificant. BLL was equal between the population-based and hospital-based groups (10.10 μg/dl in both groups). Comparison of other study variables between population-based and hospital-based groups revealed several expected differences (see Table 3). Children in the hospital-based group were significantly younger, with a mean age of 20.11 months compared to a mean of 29.12 months in the population-based group ($p<0.001$); they were also less likely to have attended at least one year of school. Mean maternal education level was lower in the hospital-based group (mean 8.74 years versus 9.13 years in the population-based group, $p=0.002$). Children in the hospital-based group tended to have a lower TAPQOL score and a higher GSRH score, indicating decreased health-related quality of life and lower general health status respectively ($p<0.001$ in both cases).

Additionally, children in the hospital-based group tended to have slightly higher BSID motor and behavior scores, were more likely to be male, and had a slightly higher HOME score. The causes of these differences are unclear but may be related to differences in exposure to pathogens, access to hospitals, or, in the case of HOME score, parental concern for sick children. Among children in the hospital-based group, children with a diagnosis of diarrhea tended to have higher BSID motor scores than those diagnosed with pneumonia. Otherwise, no significant differences were seen between diagnostic groups among hospitalized children.

Characteristics associated with blood lead level

Several household and demographic features were associated with measured BLL. In univariate analyses, roof construction material, water source, blood hemoglobin concentration, blood folate concentration, age, HOME score, birth weight, history of breastfeeding, and province of residence were associated with BLL (see Table 4). Roof construction material, water source, yearly household income, yearly household expenses, blood hemoglobin concentration, blood folate concentration, HOME score, age, sex, birth weight, TAPQOL score, history of breastfeeding, history of prematurity, source group, and province of residence were introduced into a multiple regression model. After adjustment for multiple covariates in multiple linear regression, roof construction material, water source, blood hemoglobin concentration, HOME score, age, and province of residence were significantly associated with BLL (see Table 5). Blood lead level was natural log (ln) transformed in all multiple regression analyses. A marginally significant quadratic relationship was found between ln(BLL) and months of

Table 3. Inter-group characteristics of children and comparison of complete and incomplete observations†

Characteristic†	Population group (n = 1356)			Hospital group (n = 1423)			Population vs. Hospital group p-value
	Complete (n = 904)	Incomplete (n = 445)	p-value	Complete (n = 826)	Incomplete (n = 601)	p-value	
Blood lead concentration (µg/dl)	10.27	9.72	0.252*	9.83	10.92	0.100*	0.987*
BSID							
Motor scale	96.9	96.2	0.642*	99.2	98.1	0.373*	**0.036***
Mental scale	87.7	87.3	0.783*	89.5	87.8	0.064*	0.131*
Behavior scale	76.7	74.2	**0.021***	79.6	78.3	0.110*	**<0.001***
WPPSI Young							
Full IQ	97.0	95.1	0.292*	98.18	92.5	**0.040***	0.815*
Verbal IQ	94.6	92.3	0.119*	95.4	90.1	**0.012***	0.722*
Performance IQ	100.3	99.3	0.624*	101.5	96.9	0.135*	0.938*
WPPSI Old							
Full IQ	90.8	86.1	0.123*	87.2	85.3	0.640*	0.354*
Verbal IQ	84.3	82.8	0.447*	81.5	82.5	0.766*	0.387*
Performance IQ	101.2	94.6	0.038*	96.5	91.2	0.271*	0.147*
Age at testing (mo)	29.1	29.2	0.830*	19.8	20.5	0.227*	**<0.001***
Female Sex (%)	49.6	49.4	0.965**	44.4	42.5	0.457**	**0.002****
Maternal education level (yr)	9.18	9.01	0.396*	8.77	8.71	0.735*	**0.002***
At least 1 year of education (%)	1.77	1.26	0.504**	0.24	0.70	0.197**	**0.002****
Hemoglobin concentration (g/dl)	12.0	11.7	**<0.001***	11.8	11.7	0.366*	**0.003***
Presence of smokers in the house (%)	61.1	57.1	0.161**	59.81	53.91	**0.026****	0.195**
Household income (1,000 Pesos)	64.1	62.2	0.601*	59.9	58.9	0.734*	0.086*
Household expenses (1,000 Pesos)	106.8	119.0	0.263*	107.9	92.5	0.116	0.183*
HOME total score (%)	62.9	60.1	**0.002***	64.5	62.7	**0.023***	**0.003***
Folate (ng/ml)	2.19	2.17	0.808*	1.95	1.82	**0.043***	0.556*
GSRH score (1-5)	2.67	2.80	**0.007*****	2.96	3.06	**0.010*****	**<0.001*****
TAPQOL score (0-100)	90.4	88.8	**0.004***	87.1	87.0	0.960*	**<0.001***
Body Mass Index (kg/m^2)	16.4	16.3	0.775*	16.3	16.0	0.082*	0.211*
History of Breastfeeding (%)	91.9	90.2	0.309**	92.3	91.5	0.620**	0.596**
Preterm birth (%)	3.10	3.00	0.925**	3.63	4.08	0.664**	0.280**

† Continuous values are presented as means and categorical values are presented as percentages, * Two-tailed T-test, ** Chi-squared test, *** Wilcoxon rank-sum test

age (p=0.061); the quadratic term was retained in the model. No other significant nonlinear relationships were found.

Roof construction types included strong materials (usually corrugated metal or cement), light materials (usually wood products), salvaged/makeshift materials, or mixed construction predominantly consisting of one of the three main types. Of these, salvaged/makeshift roofs were associated with the lowest BLL (mean 7.97μg/dl), and therefore this type was used as the referent category in multiple regression. Roofs made of mixed but predominantly salvaged materials were associated with the greatest increase in BLL, 1.72 times higher than strictly salvaged/makeshift roofs (95% CI 1.32, 2.25; p<0.001). All other roof types were also associated with significant or nearly significant increases in BLL compared to salvaged/makeshift roofs.

Water sources included communal/municipal systems, tubed or piped wells, dug wells, surface sources (springs, rivers, streams, etc.), rain, bottled water from peddlers, and other sources. BLL was lowest among those who purchased their water from a peddler, and therefore this group was used as the referent category in multiple regression. In the preliminary main effects model, rain and surface water were associated with the greatest increases in BLL compared to bottled water (2.32 and 1.79 times increases respectively, 95% CI 1.67, 3.22 and 1.34, 2.39 respectively, p<0.001 in both cases). Communal water sources and wells were also associated with significantly increased BLL (see Table 5).

Study provinces included Biliran, Bohol, Camiguin, Capiz, Cebu, Eastern Samar, Iloilo, Leyte, Negros Occidental, Negros Oriental, and Siquijor. The highest mean lead

Table 4. Univariate analyses of factors associated with blood lead concentration

Covariate	No. of Children	Mean blood lead (µg/dl)	p-value*
Roof Construction			**<0.001**
Strong materials	732	9.66	
Light materials	775	10.99	
Salvaged/makeshift materials	59	7.97	
Mixed but predominantly strong materials	627	10.13	
Mixed but predominantly light materials	542	9.50	
Mixed but predominantly salvaged materials	32	10.81	
Water Source			**<0.001**
Communal water system	1198	10.15	
Tubed/piped well	796	9.99	
Dug well	571	9.96	
Spring, river, stream, etc.	136	10.56	
Rain	16	11.91	
Peddler	9	4.84	
Other	42	12.19	
Motor vehicle ownership			0.464
Car	23	10.14	
Motorcycle/tricycle	386	9.71	
None	2352	10.16	
Census designation of barangay (neighborhood)			0.955
Urban	876	10.28	
Rural	1739	9.80	
Household income			0.203
<25,000 pesos	602	10.25	
25,000 – 75,000 pesos	1566	10.10	
>75,000 pesos	611	9.96	
Household expenses			0.132
<25,000 pesos	651	10.67	
25,000 – 75,000 pesos	843	10.02	
>75,000 pesos	1285	9.87	
Maternal education level			0.379
<10 yr	1101	10.18	
10 yr	603	9.94	
>10 yr	706	10.13	
Paternal education level			0.424
<10 yr	1408	10.20	
10 yr	564	9.94	
>10 yr	807	10.04	
Employment Status of primary wage earner			0.505
Self-employed	1387	10.32	
Employed by government	303	9.57	
Employed by private company	966	9.82	
Unpaid worker	72	11.05	
Blood Hemoglobin Concentration			**0.007**
<11 g/dl	664	10.80	
11-13 g/dl	1569	10.06	
>13 g/dl	546	9.41	
Blood Folate Concentration			0.074
<1.20 ng/ml	566	10.38	
1.20-2.40 ng/ml	1259	10.46	
>2.40 ng/ml	954	9.49	
HOME percentage score			**<0.001**
Low (<50%)	427	10.73	
Middle (50-75%)	1518	10.10	
High (>75%)	834	9.78	

Table 4. (continued)

Covariate	No. of Children	Mean blood lead (μg/dl)	p-value*
Age†			**0.003**
6 mo. - 1 yr	481	9.06	
1 yr	1071	9.77	
2 yr	599	10.71	
3 yr	412	10.97	
4 yr	216	10.41	
Sex			0.061
Male	1481	10.39	
Female	1287	9.80	
Birth weight			**0.026**
<2500 g	413	9.41	
2500-3500 g	1240	9.94	
>3500 g	1126	10.54	
Years of education			0.564
none	2319	10.14	
at least 1	23	10.11	
Smokers in the household			0.301
No smokers present	1155	10.07	
At least one smoker	1624	10.13	
GSRH score			0.757
1-2	838	10.66	
3	1495	9.77	
4-5	446	10.09	
TAPQOL score			0.143
<85	581	10.68	
85-95	1342	9.79	
>95	856	10.20	
Breastfeeding			**0.001**
Hx of Breastfeeding	2172	10.27	
No Breastfeeding	204	8.54	
Prematurity			0.240
Preterm birth	95	11.78	
Term birth	2659	10.03	
Source group			0.176
Population-based	1349	10.10	
Hospital-based	1427	10.10	
Province			**<0.001**
Biliran	92	12.74	
Bohol	269	10.71	
Camiguin	85	7.18	
Capiz	275	9.78	
Cebu	273	9.34	
Eastern Samar	249	10.97	
Iloilo	272	8.30	
Leyte	529	12.28	
Negros Occidental	301	7.78	
Negros Oriental	325	10.88	
Siquijor	109	7.48	
Local governmental unit			**<0.001**

*p-value from global F-test of single linear regression using natural log transformation blood lead concentration.

† Quadratic transformation of age used in single linear regression

Abbreviations: HOME Home Observation for the Measurement of the Environment, GSRH general self-rated health, TAPQOL TNO-AZL Preschool Children Quality of Life

level was found in Leyte (mean BLL=12.28 μg/dl), which was used as the referent category in modeling. Compared to Leyte, BLL was significantly lower in Camiguin, Capiz, Negros Occidental, and Siquijor (See Table 5 for coefficients, confidence intervals, and p-values).

Additionally, blood hemoglobin concentration was found to be inversely associated with BLL; a 1 g/dl increase in Hb was associated with a 3 % μg/dl decrease in

Table 5. Changes in blood lead concentration (μg/dl) associated with environmental and personal factors

Characteristic	Coefficient (95% CI)*	p-value
Roof construction		
Strong materials	1.51 (1.27, 2.03)	**0.008**
Light materials	1.60 (1.20, 2.14)	**0.003**
Salvaged/makeshift materials	(referent category)	
Mixed but predominantly strong materials	1.34 (1.05, 1.72)	**0.022**
Mixed but predominantly light materials	1.28 (-1.00, 1.63)	0.052
Mixed but predominantly salvaged materials	1.72 (1.32, 2.25)	**<0.001**
Water Source		
Communal water system	1.62 (1.25, 2.08)	**0.001**
Tubed/piped well	1.54 (1.14, 2.07)	**0.007**
Dug well	1.60 (1.19, 2.14)	**0.003**
Spring, river, stream, etc.	1.79 (1.34, 2.39)	**<0.001**
Rain	2.32 (1.67, 3.22)	**<0.001**
Peddler	(referent category)	
Other	1.80 (1.05, 3.10)	**0.033**
Hemoglobin (g/dl)	0.97 (0.94, 0.99)	**0.043**
Folate (ng/ml)	0.97 (0.93, 1.01)	0.112
HOME (percentage score)	0.99 (0.99, 0.99)	**0.019**
Months of age		
Months	1.00 (1.00, 1.04)	**0.017**
Months^2	0.99 (0.99, 0.99)	0.073
Female sex	0.93 (0.87, 1.00)	0.061
Birthweight (kg)	1.05 (1.01, 1.11)	0.108
History of breastfeeding	1.21 (1.05, 1.38)	**0.009**
Province		
Biliran	1.81 (1.56, 2.10)	**<0.001**
Bohol	1.53 (1.34, 1.76)	**<0.001**
Camiguin	(referent category)	
Capiz	1.39 (1.16, 1.66)	**0.001**
Cebu	1.57 (1.32, 1.87)	**<0.001**
Eastern Samar	1.27 (-1.23, 1.98)	0.282
Iloilo	1.23 (1.04, 1.46)	**0.016**
Leyte	1.81 (1.51, 2.18)	**<0.001**
Negros Occidental	1.02 (-1.15, 1.19)	0.819
Negros Oriental	1.48 (1.21, 1.81)	**<0.001**
Siquijor	1.01 (-1.09, 1.11)	0.819

* These coefficients and confidence intervals are obtained using the inverse-logarithmic transformation on the original regression coefficients. A transformed coefficient of 1.5 indicates that increasing a continuous explanatory variable by 1 unit, results in an estimated 50% increase in BLL and similarly a transformed coefficient of 1.5 for a categorical variable indicates that BLL for the associated category is estimated to be 50% higher than that for the reference category.

Abbreviations: HOME Home Observation for the Measurement of the Environment

BLL (95% CI 1%, 6%; p=0.043). HOME score was also inversely associated with BLL; a ten percent increase in HOME score was associated with a 10% decrease in BLL (95% CI 10.0%, 10.7%, p=0.019). History of breastfeeding was associated with a 1.21 times increase in BLL (95% CI 1.05, 1.38, p=0.009), and female sex was associated with a marginally significant decrease in BLL of 1.07 times (95% CI 1.00, 1.15; p=0.061). The coefficient of determination (r^2 value) for the model was 0.12.

Regression diagnostic procedures were performed on the final multiple regression model. Diagnostic plots are presented in Appendix 3. A residual versus fitted-value plot showed no clear trends in error variance. Normal probability plots showed moderate departure from normality despite natural-log transformation of the dependent variable. Trials of other nonlinear transformations did not improve the model fit or its conformation to assumptions.

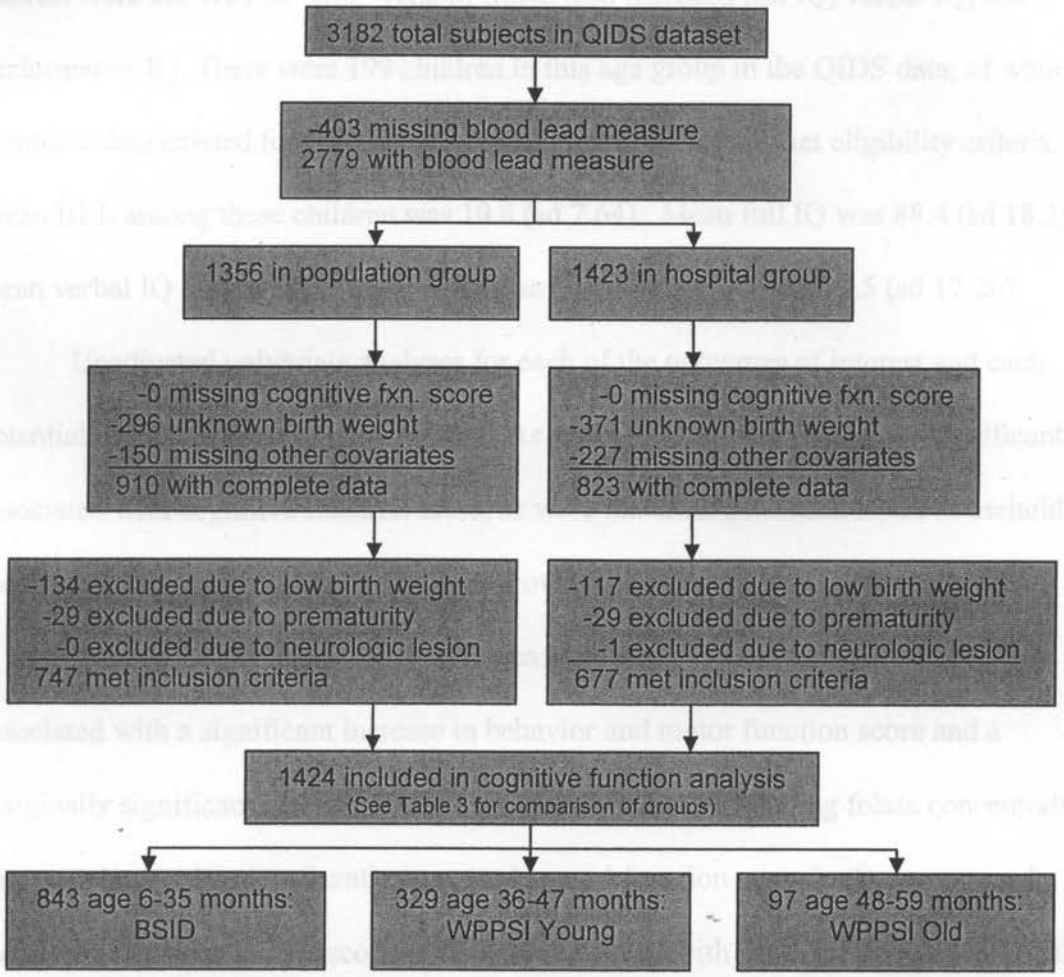
Characteristics associated with cognitive function

A total of nine cognitive function measures were employed to assess associations between cognitive function and other characteristics including blood lead concentration. Children were divided into three age groups in accordance with the cognitive function tests used for each age group. There were three cognitive function outcomes for each of the three age groups studied.

In the youngest age group, children 6-35 months old, the Bayley Scales of Infant Development (BSID) were used. These included mental function score, motor function score, and behavioral function score. A total of 1708 children in this age group from the

QIDS data were available for inclusion in this analysis. Of these, 1044 (61%) had complete data. (Reasons for incompleteness of data are described above and in Figure 3.) Among the subjects with complete data, 843 children (80%) met eligibility criteria were included in the analyses. Mean BLL in this group was 9.69 μg/dl (sd 8.47). Mean mental function score was 88.4 (sd 15.9), mean motor function score was 98.4 (sd 19.4), and mean behavioral function score was 78.0 (sd 12.9).

Figure 3. Assembly of cognitive function analysis dataset



In children 36-47 months of age, the middle age group, the outcomes of interest were the Wechsler Preschool and Primary Scales of Intelligence (WPPSI), "Young"

version; these included full IQ, verbal IQ, and performance IQ. 615 children in this age group from the QIDS data were available for inclusion. Of these, 408 (66%) had complete data and 329 (81% of those with complete data) met eligibility criteria and were included in analyses. Among these children, mean BLL was 11.4 (sd 9.94). Mean full IQ was 97.3 (sd 17.8), mean verbal IQ was 94.7 (sd14.5), and mean performance IQ was 100.5 (sd 19.8).

The oldest group of children was 48-59 months of age, for whom the outcomes of interest were the WPPSI "Old" version which also included full IQ, verbal IQ, and performance IQ. There were 199 children in this age group in the QIDS data, of whom complete data existed for 119 (60%). Among these, 97 (82%) met eligibility criteria. Mean BLL among these children was 10.8 (sd 7.64). Mean full IQ was 88.4 (sd 18.2), mean verbal IQ was 83.3 (sd 11.6) and mean performance IQ was 97.5 (sd 17.26).

Unadjusted univariate analyses for each of the outcomes of interest and each potential covariate are shown in Table 6. As expected, age was frequently significantly associated with cognitive function score, as were maternal education level, household income, HOME score, GSRH score, and province of residence.

Among the youngest children, increasing hemoglobin concentration was associated with a significant increase in behavior and motor function score and a marginally significant increase in mental function score. Increasing folate concentration was associated with significantly increased mental function score in this group, and increasing BMI and GSRH score were both associated with significant increases in all three cognitive function scores.

Table 6. Univariate analyses of covariates for cognitive function models (in parentheses: p-values from unadjusted single linear regression)

Covariate	Number of children	Mean blood lead level	6-35 months: Mean BSID Score			36-47 months: Mean WPPSI Young IQ			48-59 months: Mean WPPSI Old IQ		
			Mental	Behavior	Motor	Full	Verbal	Perform -ance	Full	Verbal	Perform -ance
Age											
6 mo - 1 yr	233	9.06	91.00	78.20	92.61	-	-	-	-	-	-
1 yr	498	9.77	89.56	77.82	102.12	-	-	-	-	-	-
2 yr	275	10.71	80.45	77.36	92.26	98.84	96.82	101.16	-	-	-
3 yr	188	10.97	-	-	-	94.78	91.91	99.13	-	-	-
4 yr	59	10.41	-	-	-	-	-	-	88.38	83.31	97.54
			(<0.001)	**(0.180)**	**(<0.514)**	**(<0.001)**	**(<0.001)**	**(0.007)**	**(0.872)**	**(0.448)**	**(0.857)**
Sex											
Male	671	10.39	88.01	78.05	97.47	96.15	93.26	100.14	86.62	81.55	96.42
Female	582	9.80	88.74	77.55	98.37	96.48	94.26	99.68	90.27	85.20	98.95
			(0.370)	**(0.480)**	**(0.396)**	**(0.817)**	**(0.353)**	**(0.797)**	**(0.121)**	**(0.022)**	**(0.356)**
Maternal education level											
<10 yr	590	10.18	86.71	76.38	95.99	91.20	89.95	94.74	85.73	81.61	94.66
10 yr	303	9.94	87.99	78.28	97.65	97.52	94.47	101.36	87.00	82.61	95.83
>10 yr	360	10.13	91.45	80.02	101.71	102.57	98.58	106.01	93.51	86.74	103.57
			(<0.001)	**(<0.001)**	**(<0.001)**	**(<0.001)**	**(<0.001)**	**(<0.001)**	**(0.005)**	**(0.018)**	**(0.004)**
Years of education											
none	1241	10.14	88.46	77.96	98.06	95.94	93.64	99.34	87.01	82.43	96.19
at least 1 yr	12	10.11	88.00	78.46	90.00	104.71	95.43	113.86	102.24	92.06	111.12
			(0.682)	**(0.715)**	**(<0.001)**	**(0.274)**	**(0.812)**	**(0.030)**	**(0.010)**	**(0.046)**	**(0.003)**
Blood Hemoglobin Concentration											
<11 g/dl	307	10.80	95.71	76.44	68.78	99.26	96.07	102.64	93.95	89.42	97.74
11-13 g/dl	682	10.06	100.86	78.58	71.55	96.27	93.56	100.03	88.37	82.55	98.91
>13 g/dl	264	9.41	104.07	78.01	73.39	95.07	93.20	98.32	86.75	82.88	95.31
			(0.069)	**(0.013)**	**(0.032)**	**(0.217)**	**(0.402)**	**(0.191)**	**(0.428)**	**(0.188)**	**(0.902)**
Smokers in the household											
No smokers present	492	10.07	88.82	77.57	98.44	97.78	94.76	101.44	93.32	86.45	102.39
At least one smoker	761	10.13	87.98	78.02	97.62	95.21	93.10	98.74	84.77	81.02	94.17
			(0.298)	**(0.555)**	**(0.350)**	**(0.059)**	**(0.063)**	**(0.098)**	**(0.003)**	**(0.004)**	**(0.009)**
Household income											
<25,000 pesos	284	10.25	85.38	76.43	92.82	92.11	90.94	95.28	88.25	82.73	96.25
25,000 – 75,000 pesos	692	10.10	88.44	77.68	99.42	96.13	93.34	100.04	85.12	81.36	94.75
>75,000 pesos	277	9.96	91.06	79.73	99.19	100.51	97.19	103.77	95.77	88.21	105.35
			(0.007)	**(0.048)**	**(0.020)**	**(0.001)**	**(0.007)**	**(0.006)**	**(0.008)**	**(0.016)**	**(0.006)**
HOME percentage score											
Low (<50%)	208	10.73	81.50	69.38	91.63	86.03	86.17	89.50	84.28	79.88	91.72
Middle (50-75%)	769	10.10	87.82	77.33	97.28	94.71	92.76	98.08	88.28	82.45	98.62
High (>75%)	276	9.78	93.38	83.92	103.24	108.19	102.08	112.37	89.33	84.52	98.42
			(<0.001)	**(<0.001)**	**(<0.001)**	**(<0.001)**	**(<0.001)**	**(<0.001)**	**(0.001)**	**(0.001)**	**(0.001)**

Table 6. (continued)

Covariate	Number of children	Mean blood lead level	Mean BSID Score			Mean WPPSI Young IQ			Mean WPPSI Old IQ		
			Mental	Behavior	Motor	Full	Verbal	Perform -ance	Full	Verbal	Perform -ance
Blood Folate Concentration											
<1.20 ng/ml	273	10.38	85.85	77.21	74.06	98.57	94.60	98.72	90.68	82.26	100.08
1.20-2.40 ng/ml	619	10.46	87.21	78.51	72.02	98.26	93.75	100.85	87.19	84.09	95.75
>2.40 ng/ml	361	9.49	90.87	77.43	68.19	97.27	93.22	90.90	88.87	82.71	98.90
			(0.002)	**(0.867)**	**(0.100)**	**(0.907)**	**(0.870)**	**(0.943)**	**(0.424)**	**(0.792)**	**(0.479)**
Body mass index											
<15 kg/m^2	397	10.13	86.72	76.98	96.56	94.49	93.03	97.33	88.59	82.49	98.26
15-20 kg/m^2	750	10.04	88.34	77.97	98.28	97.28	94.02	101.38	89.63	84.61	99.51
>20 kg/m^2	106	10.28	90.66	78.67	98.95	98.68	95.35	102.47	84.30	83.00	90.41
			(<0.001)	**(0.003)**	**(0.015)**	**(0.054)**	**(0.096)**	**(0.072)**	**(0.596)**	**(0.787)**	**(0.808)**
GSRH score											
1-2	415	10.66	87.79	76.36	98.49	97.64	94.84	101.22	87.63	82.51	96.71
3	659	9.77	89.75	78.89	99.05	95.44	93.38	98.70	89.65	84.74	98.60
4-5	179	10.09	84.84	76.78	93.98	95.73	91.91	100.70	85.62	80.05	96.95
			(0.002)	**(0.001)**	**(<0.001)**	**(0.141)**	**(0.609)**	**(0.164)**	**(0.550)**	**(0.111)**	**(0.880)**
TAPQOL score											
<85	289	10.68	83.85	74.44	95.08	90.16	89.44	93.47	82.47	82.47	96.50
85-95	697	9.79	89.78	79.25	99.31	97.28	94.46	100.94	90.15	90.15	99.12
>95	267	10.20	89.59	78.26	98.00	97.57	94.61	101.17	88.57	88.57	96.31
			(<0.001)	**(0.039)**	**(0.067)**	**(0.001)**	**(<0.001)**	**(0.002)**	**(0.050)**	**(0.007)**	**(0.621)**
Breastfeeding											
Hx of Breastfeeding	1161	10.27	88.42	77.94	97.85	101.39	97.65	104.96	91.00	84.71	101.05
No Breastfeeding	92	8.54	87.54	76.96	98.60	95.89	93.41	99.51	88.13	83.18	97.36
			(0.559)	**(0.650)**	**(0.657)**	**(0.024)**	**(0.067)**	**(0.024)**	**(0.551)**	**(0.562)**	**(0.441)**
Province											
Biliran	36	12.74									
Bohol	130	10.71									
Camiguin	39	7.18									
Capiz	119	9.78									
Cebu	118	9.34									
Eastern Samar	81	10.97									
Iloilo	132	8.30									
Leyte	290	12.28									
Negros Occidental	150	7.78									
Negros Oriental	112	10.88									
Siquijor	46	7.48									
			(<0.001)	**(<0.001)**	**(<0.001)**	**(<0.001)**	**(<0.001)**	**(<0.001)**	**(<0.001)**	**(<0.001)**	**(0.002)**

History of breastfeeding was associated with significant increases in all three IQ measures in the middle age group, but was not associated with significant changes in cognitive function in either the youngest or the oldest age group.

In the oldest age group, at least one year of education was associated with increased cognitive function across all three measures; female sex was associated with increased verbal IQ. Presence of smokers in the household was associated in decreased cognitive function across all three measures in the oldest age group.

Blood lead level and cognitive function

Unadjusted and adjusted associations between BLL and cognitive function outcomes are summarized in Table 8. Model building revealed a significant improvement in the relationship between BLL and all cognitive function measures after natural log transformation of BLL; natural log-transformed BLL was used in all subsequent modeling. For all cognitive function measures, increasing BLL was associated with decreasing cognitive function score. This relationship was statistically significant for BSID mental function score and BSID behavioral function score. A doubling of BLL was associated with a 1.25 point decrease in BSID mental function score (95% CI -2.21 to -0.30, p=0.010), and a 1.00 point decrease in BSID behavioral function score (95% CI -1.77 to -0.23, p=0.011). Regression plots of these two significant associations are presented in Figure 4. Additionally, there were marginally significant relationships between BLL and WPPSI Old verbal and performance IQ scores. A doubling of BLL was marginally associated with a -1.93 point decrease in verbal IQ (95% CI -4.23 to 0.28, p=0.086) and a

Table 7. Mean cognitive test scores by province (in parentheses: p-value from test comparing mean score from province to mean score of all other provinces)

	Age 6-35 months: BSID				Age 36-47 months: WPPSI Young IQ				Age 48-59 months: WPPSI Old IQ			
Province	No. of Children	Mental	Behavior	Motor	No. of Children	Full	Verbal	Per-formance	No. of Children	Full	Verbal	Per-formance
Biliran	54	85.18 (0.109)	**69.87 (<0.001)**	**91.57 (0.009)**	54	95.59 (0.920)	93.94 (0.671)	98.24 (0.821)	11	88.00 (0.594)	**75.36 (0.016)**	103.00 (0.454)
Bohol	125	90.49 (0.079)	**80.55 (0.007)**	98.49 (0.728)	113	97.72 (0.123)	93.81 (0.594)	**102.42 (0.038)**	38	89.23 (0.565)	81.87 (0.206)	98.82 (0.930)
Camiguin	50	85.26 (0.182)	**87.58 (<0.001)**	**89.68 (0.004)**	0	*	*	*	5	90.20 (0.894)**	84.60 (0.958)**	97.20 (0.897)**
Capiz	288	**100.09 (<0.001)**	**86.95 (<0.001)**	**107.71 (<0.001)**	2	106.5 (0.250)**	101.00 (0.267)**	101.00 (0.335)**	10	**117.50 (<0.001)**	**107.40 (<0.001)**	**107.40 (<0.001)**
Cebu	203	**90.69 (0.036)**	**81.17 (<0.001)**	97.80 (0.915)	99	94.18 (0.475)	92.84 (0.799)	96.99 (0.324)	14	83.28 (0.099)	80.21 (0.216)	99.93 (0.793)
E. Samar	154	**83.38 (<0.001)**	**69.64 (0.001)**	98.72 (0.606)	44	92.36 (0.244)	89.36 (0.061)	97.41 (0.626)	32	91.72 (0.734)	87.72 (0.096)	97.53 (0.760)
Iloilo	231	90.03 (0.159)	**81.52 (<0.001)**	**104.25 (<0.001)**	46	94.09 (0.613)	92.28 (0.656)	97.35 (0.602)	28	95.14 (0.156)	**90.36 (0.006)**	104.54 (0.096)
Leyte	363	**81.84 (<0.001)**	**73.34 (<0.001)**	96.47 (0.138)	137	94.41 (0.484)	92.82 (0.749)	97.54 (0.404)	49	**83.14 (<0.001)**	**77.37 (<0.001)**	**89.91 (0.001)**
Negros Oc.	151	86.58 (0.078)	76.56 (0.116)	**89.37 (<0.001)**	153	94.71 (0.610)	93.01 (0.871)	98.08 (0.601)	22	92.91 (0.541)	86.32 (0.422)	102.41 (0.348)
Negros Or.	219	89.31 (0.361)	77.65 (0.834)	97.92 (0.981)	69	97.70 (0.247)	94.20 (0.518)	101.61 (0.224)	17	89.88 (0.834)	81.12 (0.287)	97.12 (0.717)
Siquijor	50	90.77 (0.0.210)	**74.59 (0.043)**	100.35 (0.329)	33	97.15 (0.550)	96.42 (0.169)	98.52 (0.926)	7	92.57 (0.778)	84.86 (0.898)	93.29 (0.484)
All Provinces	1904	88.31	77.84	97.95	754	95.36	93.17	98.83	265	90.73	84.26	98.55

* no data available, ** Wilcoxon sign rank test used due to small sample in this group (Student's t-test used otherwise)

Table 8. Unadjusted and adjusted changes in IQ for each doubling of blood lead concentration (μg/dl)*

Type of Cognitive function measurement	No. of children	Unadjusted change		Adjusted change	
		β (95% CI)	p-value	β (95% CI)	p-value
BSID (6-35 mo.)					
Mental Function	843	-1.25 (-2.21, -0.30)	**0.010**	0.20 (-0.73, 1.14)	0.666
Motor Function	843	-0.46 (-1.62, 0.70)	0.440	0.13 (-0.98, 1.25)	0.811
Behavioral Function	843	-1.00 (-1.77, -0.23)	**0.011**	0.23 (-0.36, 0.83)	0.428
WPPSI Young (36-47 mo.)					
Full IQ	329	-0.87 (-2.70, 0.96)	0.350	0.41 (-1.00, 1.81)	0.557
Verbal IQ	329	-0.94 (-2.41, 0.55)	0.217	-0.21 (-1.85, 1.42)	0.795
Performance IQ	329	-0.57 (-2.61, 1.46)	0.582	0.28 (-1.32, 1.88)	0.724
WPPSI Old (48-59 mo.)					
Full IQ	97	-2.14 (-5.63, 1.34)	0.226	-0.65 (-4.53, 3.22)	0.729
Verbal IQ	97	-1.93 (-4.13, 0.28)	0.086	-2.25 (-5.66, 1.17)	0.187
Performance IQ	97	-3.06 (-6.32, 0.22)	0.067	-0.16 (-4.03, 3.75)	0.934

* Coefficients and confidence intervals reflect linear interpretation of natural log transformation of blood lead concentration and robust standard errors with clustering of subjects by local governmental unit (see text for detailed explanation).

3.06 point decrease in performance IQ (95% CI -6.32 to 0.22, p=0.067). Other associations between BLL and cognitive function scores were not statistically significant.

Additional covariates were added to the BLL/cognitive function models to adjust for potential confounding. All models contained age, sex, mother's educational attainment, years of education, presence of smokers in the household, yearly household income, and HOME score as covariates. Due to uncertainty in the accuracy of birth weight data, birth weight was not included as a covariate (however all subjects reported to be born underweight were excluded from analysis as per the exclusion criteria). Additional covariates were added as indicated based on the parameters discussed in the

methods section. All additional covariates were assessed for nonlinear relationships, but no other significant nonlinear relationships were identified between cognitive function variables and other continuous covariates. All models were also assessed for the presence of effect modification between BLL and other covariates; no significant interactions were found. To assess for colinearity between independent variables, selected variables were removed from the final multiple regression model and the impact on other covariates was assessed—no significant colinearity was identified. Final multiple regression models are presented in Appendix 4.

After adjustment for covariates, all associations between BLL and cognitive function outcomes became statistically insignificant. However, several characteristics remained significantly associated with cognitive function scores in multiple regression for BSID and WPPSI Young measures. For WPPSI Old measures, multiple regression models were unstable with wide confidence intervals.

Many of the characteristics associated with cognitive function were expected. Increasing HOME score was associated with increasing cognitive function score in all BSID and WPPSI Young measures. All BSID scores and WPPSI Full and performance IQ varied significantly by province. Age (in months) was associated decreasing BSID mental score, WPPSI Young full IQ, and WPPSI Young verbal IQ. Increasing TAPQOL score was associated with increasing WPPSI Young verbal IQ.

Unexpectedly, presence of smokers in the household was associated with increased BSID behavior score.

Coefficient of determination (r^2) values for multiple regression BSID models were 0.24 for mental function score, 0.34 for behavior function score, and 0.16 for motor

function score. For WPPSI Young models, r-squared values were 0.48 for full IQ, 0.23 for verbal IQ, and 0.43 for performance IQ. WWPSI Old models yielded r-squared values of 0.18 for full IQ, 0.46 for verbal IQ, and 0.18 for performance IQ. Full models are presented in Appendix 2.

Regression diagnostics were performed on all final multiple regression models and did not result in any changes to the models. Diagnostic plots are presented and individually interpreted in Appendix 4.

CHAPTER 4: DISCUSSION

Factors associated with blood lead concentration

Several household and individual characteristics were associated with blood lead concentration. Univariate analyses (Table 4) and multiple regression (Table 5) yielded similar results: roof construction, water source, HOME score, age, history of breastfeeding, and hemoglobin concentration were significantly associated with blood lead level (BLL) in both analyses. In the univariate analysis, increasing birth weight was associated with increasing BLL, but the association did not persist after adjusting for covariates in the multiple regression analysis.

The two household characteristics associated with increases in BLL after adjusting for other factors were roof construction material and water source. These may both be markers for other sources of lead exposure, or they may themselves represent pathways of lead exposure. Children living in households with roofs made of salvaged/makeshift materials, often natural materials and unpainted scrap wood, tended to have the lowest BLL. The child occupants of homes with roofs made of painted or treated wood materials, and metals, would be expected to have greater opportunity for lead exposure.

BLL was significantly lower among children in households whose main water source was bottled water from a peddler compared to all other sources. This suggests that there may be lead contamination of water either in the local collection and distribution system or within storage systems of individual households. The highest mean lead levels were seen in children whose water source was from rain or "other" sources. More research is needed to determine the nature of these water sources and their potential lead

contamination. Alternatively, water source may, like roof material, be a proxy for another lead exposure not measured in this study. For example, households using bottled water may also be less likely to contain older, lead-containing paint.

As expected, increasing HOME score was associated with decreasing BLL. The HOME infant-toddler version contains six sections: "responsivity," "acceptance," "organization," "learning materials," "involvement," and "variety." A child in an environment with increased organization and caregiver involvement is intuitively less likely to exposure him or herself to lead by ingestion of paint chips, dust, etc. Additionally, a child in a more nurturing home environment is likely to benefit from environmental enhancement resulting independently in improved cognitive function.

Additionally, there was significant regional variation in BLL among study children. The highest mean BLLs were found in Leyte and Biliran, followed by Eastern Samar, Bohol, and Negros Oriental. This may represent differences in regional distribution of household-level lead pollutants or it may indicate possible point sources of lead in some specific areas, possibly including, mines, factories, and/or lead smelters. The Visayas area of the Philippines—particularly Leyte—also saw active combat during the Second World War. It is possible that lead residue from military munitions in certain areas could be contaminating the soil and/or water.

Individual factors associated with BLL in children included hemoglobin concentration and history of breastfeeding. Both of these have been reported in previous research studies. An inverse dose-response gradient was seen between hemoglobin (Hb) concentration and BLL; subjects with Hb less than 11 g/dl had a mean BLL 10.80 μg/dl, those with Hb between 11 and 13 g/dl had a mean BLL of 10.06 μg/dl, and those with a

Hb greater than 13 g/dl had a mean BLL 9.41 μg/dl. The inverse association between hemoglobin concentration and BLL has been theorized to be related to parallel iron and lead uptake (Barton et al. 1978). It has been demonstrated that children with iron deficiency anemia are at increased risk to develop subsequent lead poisoning (Wright et al, 2003). The proposed mechanism for this association involves increased absorption of ingested lead in iron-deficient individuals compared to iron-replete individuals. It has been suggested that this effect may be mediated through a common absorptive receptor (Barton et al. 1978). Another possible mechanism for the association is confounding, since both lead poisoning and iron deficiency are commonly associated with a variety of circumstances related to lower socioeconomic status. However the fact that the relationship persisted despite adjustment for multiple confounders in this study suggest that confounding is not a primary mechanism for the association. Additional research is needed to determine whether an intervention including dietary iron supplementation can reduce risk of lead toxicity.

History of breastfeeding was associated with a significant increase in BLL; mean BLL in breastfed children was 10.27 μg/dl, compared to a BLL of 8.54 μg/dl in children with no history of breastfeeding. Previous research indicates that lead may be transferred via breast milk. A study of 255 mother-infant pairs in Mexico found a direct association between lead content in breast milk and subsequent infant BLL; lead in breast milk accounted for 10% of variance of infant blood lead levels at six months of age (Ettinger et al. 2004). Although the role of breast milk in overall lead exposure likely declines with increasing age, the results of this analysis suggest that it remains a significant predictor of BLL in a population ranging 6 months to 5 years of age. Breast milk is widely considered

to be the optimal mode of nutrient delivery to term infants, particularly in less developed areas where alternative nutrition sources may be less available (WHO 1995). The health benefits of breastfeeding in this population are likely to outweigh the neurotoxic effects associated with lead exposure received through breast milk. Rather, this finding should be taken as evidence that maternal lead exposure may be an important contributor to eventual child exposure.

Additionally, it can be postulated from this finding that mothers as well as children in the Visayas are exposed to lead. This may indicate that the exposure sources are more universally distributed and affect all persons, as opposed to a unique source (a toy) or behavior (hand-to-mouth activity) that places children at higher risk for exposure.

Several significant interactions were found in the BLL model, but they were complex and did not add to understanding of the correlates of BLL. Overall, the main effects model accounted for 11.5% of variation in BLL and the interaction model accounted for 18.6% of variation in BLL. This suggests that major sources of lead exposure were not accounted for in this analysis and that further field study is required to definitively identify lead sources.

Factors associated with cognitive function

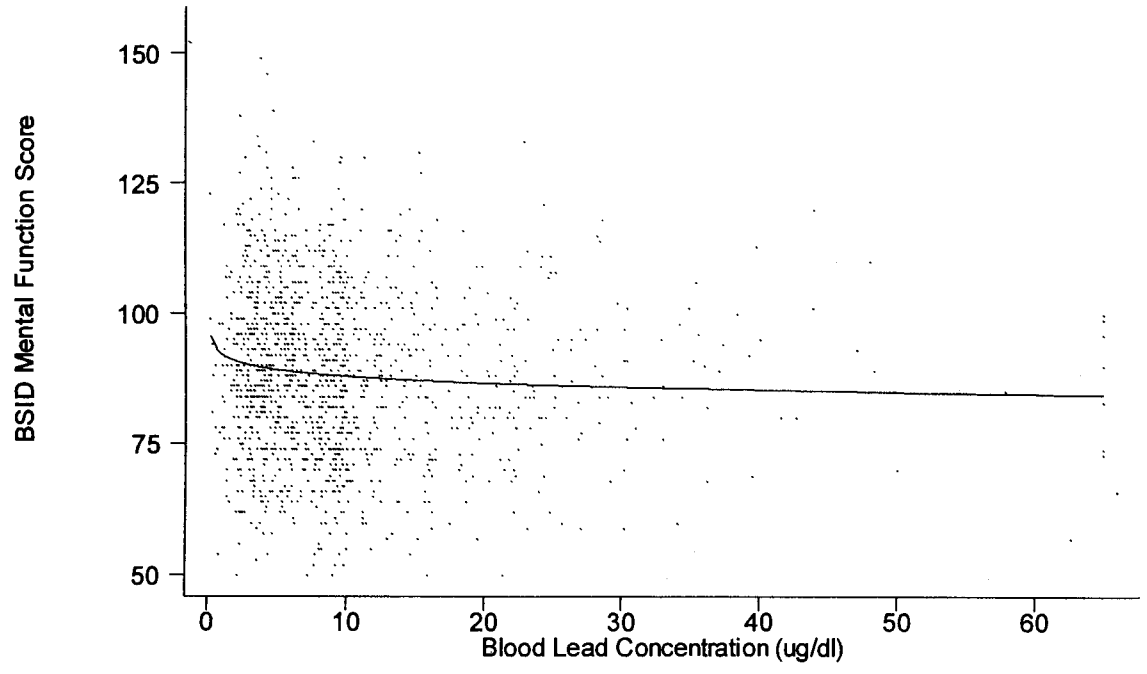
Expected associations between personal characteristics and cognitive function were found, including associations with age, maternal education level, years of education (in older children), hemoglobin concentration, folate concentration, body mass index, household income, HOME score, GSRH score, and TAPQOL score. The ability of this analysis to demonstrate associations with factors identified in previous reports, albeit in

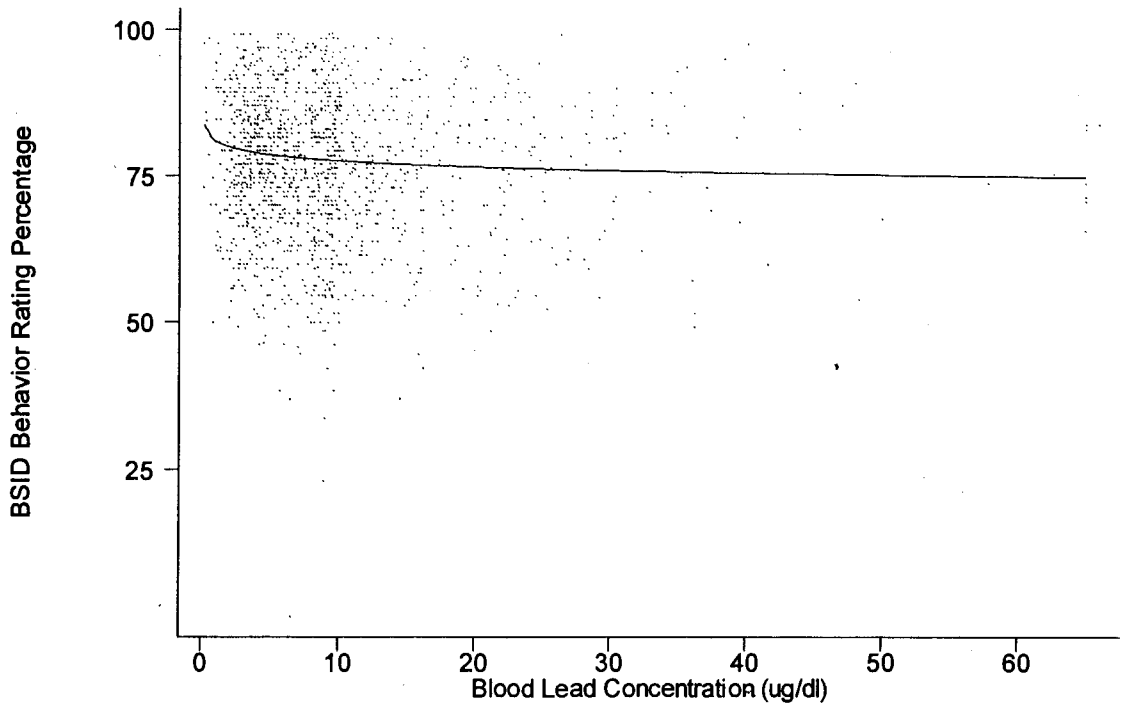
developed countries, suggests that the measurement methods used in the current study are reliable and valid.

There was an inverse relationship between all measured cognitive function scores and BLL before adjustment for covariates, consistent with the widely recognized association between lead and cognitive function demonstrated in other populations. However, in this analysis the association was statistically significant only for BISD mental and behavioral function scores. It was marginally significant for WPPSI Old verbal and performance IQ scores. As shown in Figure 4, the largest decreases in cognitive function were observed in the lower range of blood lead concentration, a finding also reported by Canfield and colleagues (2003) among children in the U.S. This is further evidence that even low levels of lead exposure may result in significant cognitive impairment and a "safe" threshold does not exist.

The BSID measures are used for younger children than the WPPSI measures—in the case of this study the BSID was applied to children 6-35 months old, while WPPSI measures were applied to children 36-59 months of age. Previous studies in other populations have found persistent, significant relationships between lead exposure and BSID score in younger populations (Mendelsohn 1998, Johnson et al. 1992, Sciarillo, Alexander and Farrell 1992) as well as Wechsler IQ scales in older children (Canfield et al. 2003, Bellinger and Deitrich 1994, Pockock Smith and Baghurst 1994, Baghurst et al. 1992, Needleman and Gastonis 1990, McMichael et al. 1988). Factors which make this study population unique, namely the decreased level of development in the study area

Figure 4. Regression plots of Blood Lead Concentration and Bayley Scales of Infant Development Mental Function Score and Behavior Rating Percentage





relative to that of other study populations, may have an effect on cognitive function over and above any effect of lead toxicity. This is supported by the findings in this study of the strong associations between cognitive function and maternal education, household income, and HOME score. With age, the effect of these socioeconomic and environmental factors can be reasonably expected to exacerbate or ameliorate the adverse effects of lead exposure. Additionally, the fact that an unadjusted association between cognitive function was seen among infants but not older children may be in part due to the cognitive function tests used to assess cognitive function in this study. The BSID assesses basic developmental progress in the areas of mental, behavioral and motor function which are essentially global phenomena in human development. Any sort of IQ test, including the WPPSI indicies, however, are more complex and subject to a degree of interpretation based on cultural identification. Although the WPPSI tests have been used in the past in the Philippines, there is likely some degree of cultural dissonance between the test and the individuals in this study who were subjected to the test. This likely resulted in some degree of error variance between testing score and true underlying cognitive function which likely resulted in an underestimate of associations with cognitive function as measured by WPPSI IQ scores.

The observed associations between BLL and BSID mental and behavioral function scores did not persist after adjustment for covariates. It is possible that adjustment for covariates may have eliminated actual confounding. It is also possible that adjustment may have resulted in over-control for factors which are part of the casual pathway.

The unadjusted associations between BLL and infant mental and behavioral function may be due to confounding. Factors such as blood hemoglobin concentration,

age, maternal education level and HOME score are associated with both BLL and cognitive function in this analysis. If the observed associations between BLL and cognitive function scores were in fact due to their shared association with other confounding factors, adjustment for those factors reveals the true lack of association between blood lead concentration and cognitive function in this population.

Alternatively, adjusting for covariates this analysis may, to some extent, have over-adjusted for factors that determine exposure to lead. For example, maternal education level, one measure of social class, is widely considered to confound the relationship between BLL and cognitive function (Belllinger Leviton and Waternaux 1989)—individuals who are of low socioeconomic status tend to have higher BLL and lower cognitive function scores. However, social class can convey information about a child's lead exposure opportunities—in fact, since blood lead concentration can fluctuate over the short-term, a child's socioeconomic status might convey more information about his cumulative lifetime lead exposure than a single BLL measure (Bellinger 2004). Adjusting for social class in a multiple regression model eliminates the variability in BLL that is determined by social class thereby resulting in an underestimation of the association between lead and cognitive function. In other words, a covariate such as social class may be part of the causal pathway of the relationship between lead exposure and cognitive function rather than a confounder that, by definition, is outside of the causal pathway. Similarly to social class, it may be argued that hemoglobin concentration, HOME score, and even measures of health-related quality of life may be parts of the causal pathway between lead and cognitive function rather than true confounders.

Implications

The findings of the factors associated with BLL analysis contributed to the design of an environmental exposure assessment field study to identify environmental lead contamination in this population. Although the assessment is ongoing, multiple lead sources have been identified thus far. Lead paint was found on the walls of homes, schools, and hospitals in the study area. Cribs in several pediatric wards of local hospitals also tested positive for lead paint.

Additionally, lead-containing fishing weights were commonly found in homes. They were found in children's play areas and dust samples from the areas surrounding the fishing weights were found to contain significant amounts of lead. Some families reported melting down and re-shaping lead weights inside their homes within the presence of children for the purpose of fitting the weights to fishing nets. Small quantities of lead were found in gasoline sold in the study area, as well as in the motor oil added to fuel tanks in locally ubiquitous motorcycles and tricycles using two-stroke engines; the potential health impact of these concentrations is under investigation.

The association between blood hemoglobin concentration and BLL suggests that in addition to environmental remediation, dietary iron supplementation may be an effective means of decreasing BLL in children in this population; further research is needed to assess the potential efficacy of such an intervention.

The effect of lead exposure on cognitive function in this study population remains unclear. However, there is no reason to suspect that the accumulating evidence supporting the case for neurotoxic effects of lead on children's brain from the rest of the world does not apply to children in the Visayas region of the Philippines. The fact that the association

between BLL and cognitive function does not persist after adjusting for confounding may suggest that other more important determinants of child cognitive development may deserve priority over the problem of lead exposure. In similarly less developed regions around the world where childhood is commonly wrought with the perils of poverty, malnutrition, and infectious disease, low level lead poisoning may have relatively little impact on overall health and cognitive function. Nonetheless, these children need every advantage they can get. Especially when the sources of lead poisoning are potentially identifiable and amenable to mitigation, lead hazard abatement may be a reasonable and useful intervention.

The first step in such a process is education. Lead poisoning is not a currently recognized clinical entity in the Visayas—local healthcare providers, public health professionals and government leaders must be apprised of these new findings and given guidance on the recognition and treatment of lead poisoning. Relatively low-cost interventions such as home-, school-, and hospital-based education programs about lead poisoning prevention may be an efficient means to lessen whatever lead-poisoning burden is present.

Additionally, the introduction of lead screening programs in this region may be warranted. With the availability of relatively low-cost and efficient testing devices such as the LeadCare® device used in this study, population-based or hospital-based screening may be efficient and cost-effective.

Finally, specific lead abatement projects may be warranted, particularly in public areas frequented by children, such as schools and hospitals. On a national level, regulation of lead-based paint should be considered in the Philippines.

The universally positive relationship between HOME score and all measures of cognitive function suggests a strong role of environmental enhancement in the determination of childhood cognitive function in this population. Interventions aimed at improving the home environment may be an effective means of mitigating other factors which are associated with decreased cognitive function.

Limitations

Several sources of potential bias were considered in the planning and execution of this analysis (see Methods), including selection bias, measurement (information) bias, and confounding factors.

Selection Bias - A significant portion of the subjects for this study were selected from a hospitalized population, raising a potential concern regarding the external validity of the study in regard to the overall population of this region. However, the hospital-based and population-based groups within this study were generally comparable. Differences, where significant, tended to be small. Of potential significance, the hospital group had a mean age nine months younger than the population-based group, and the hospital-based group scored higher on the BSID behavioral function scale. Age is not a particular concern since it is factored into the study analysis as both a means of categorizing subjects for cognitive function testing and as a covariate in multiple regression modeling—differences in age between the two groups is therefore not a major concern. No immediate explanation is available for the observed differences in BSID score, and therefore further investigation is needed to determine the potential significance of this difference.

Measurement Bias - Much of the demographic information and medical history used in this analysis were obtained by report from subjects' care providers. In many cases guardians were unable to provide full information regarding study subjects, particularly in relation to medical history information such as birth weight. A very conservative approach was used for addressing missing data and overall only 62.4% of respondents had complete data available for analysis. This relatively low completion rate may have resulted in an information bias if subjects with incomplete data tended to have different blood lead concentrations and different cognitive function scores. However, there was no significant difference between children with complete and incomplete data in terms of blood lead concentration, BSID scores, or WPPSI young scores. Children with incomplete data did tend to have different WPPSI Old scores, and therefore any interpretation of the results of the WPPSI Old cognitive function measures should be made with caution.

The cross-sectional nature of this study is a source of several potential difficulties. A single measure of blood lead concentration may not provide an accurate measure of cumulative lead exposure in the study population. In previous studies, however, there has generally been a strong correlation between concurrent BLL and measures of cumulative lead exposure (Canfield 2003, Bellinger 1991). Several subjects in this study had very high blood lead concentrations, and a single measure of cognitive function may not necessarily differentiate chronic cognitive impairment from transient impairment due to acute lead toxicity. However, the vast majority of subjects in the study had lead levels well below that which would be expected to result in acute toxicity.

The LeadCare device used to measure BLL in this study was developed for screening in the practice setting and has not been widely used in research. However, the

LeadCare device has undergone evaluation against the atomic absorption spectroscopy, regarded to be the "gold standard" (see Appendix 5) and has been approved by the FDA for use as a measure of blood lead concentration (FDA 1997). Field protocols provided a reasonable level of quality control and standardization of BLL measurements, and we assume that measurement error is small and nondifferential. This random error, to a limited extent, decreases our ability to detect an association between BLL and other factors.

The cognitive function measures used in this study were designed for and validated in the U.S. population. However, these measures are now widely used internationally, including in the Philippines, and issues of construct validity have not been identified. Additionally, their association with expected determinants of cognitive function is this study provides evidence of their suitability in the setting of the Philippines.

An additional potential limitation, inherent in use of these cognitive scales, is sensitivity. Scales such as the BSID and WPPSI were designed to maximize reliability. The demonstration of their stability across international settings may be evidence to their resilience against relatively small forces, limiting the utility in applications such as lead poisoning. Longitudinal research designs that prospectively characterize cognitive development and utilize new neurobehavioral tests on pre-school and school ages (Anger et al. 1998, Rohlman et al. 2005) would be expected to provide more sensitive measures of effect.

The data used in this analysis were not originally collected for the purpose of determining factors associated with BLL, or to assess the association between BLL and cognitive function. Therefore, information was not collected to control for all of the

covariates considered in previous studies testing the relationship between lead exposure and disturbance of cognitive development in children. While some of our covariates may differ from previous research studies, strong alternative measures were available and in our modeling they appeared to act as reasonable substitutes.

Future research

A longitudinal prospective study with repeated measures of BLL and cognitive function would be the optimal way to assess their potential causal relationship. Additionally, further analysis may be performed on this dataset utilizing statistical techniques beyond the scope of this master's thesis. These may include explorations of alternative methods to address the problems of missing data and confounding. In the ideal investigation, the association between BLL and cognitive performance would control for all socioeconomic, personal, physical, and environmental factors. In reality, many of these factors are difficult to measure conceptually, and data on some factors was not collected at all. Even so, the use of alternative regression techniques , such as path analysis (classification and regression tree analysis) and two-stage least squares linear regression, may allow additional exploration of the hypothesized causal relationship between BLL and cognitive impairment.

Given the extensive evidence of negative health effects documented in other studies, and the apparent prevalence of lead toxicity in this population, the development of lead exposure control programs for this population is appropriate at this time. Such programs should be developed in close collaboration with local leaders and officials, and

may offer an opportunity to evaluate the effectiveness of intervention approaches, such as educational efforts, lead screening, and environmental lead mitigation. Evaluation of the interventions is important because of the unique context and setting of the Vasayas.

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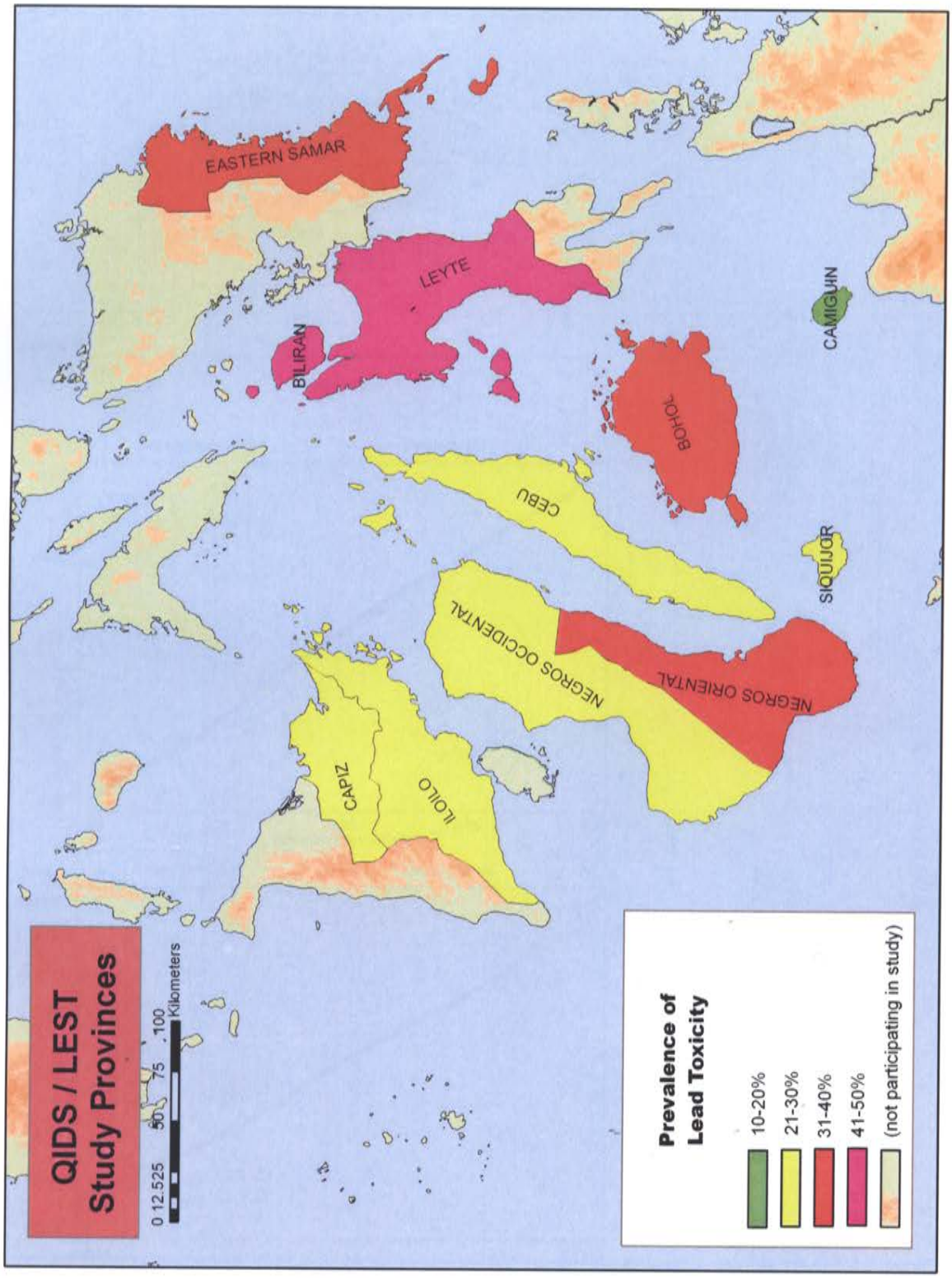
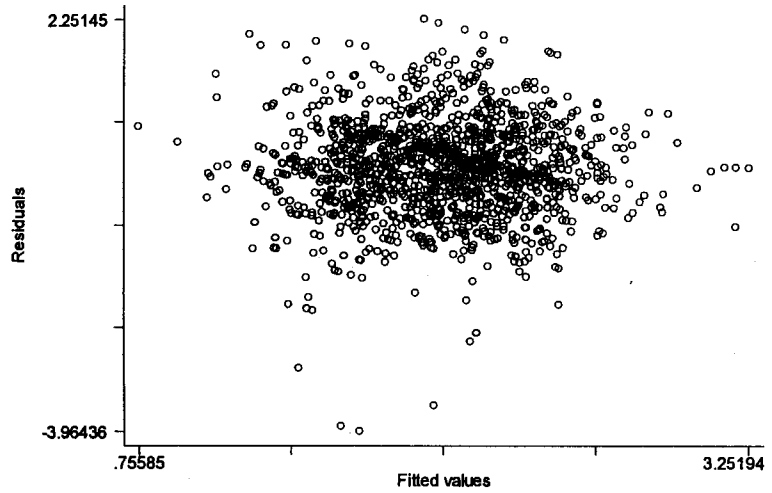
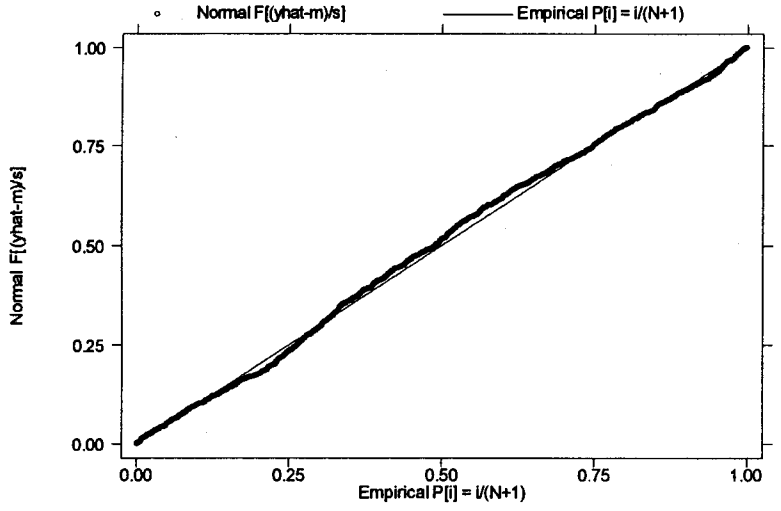
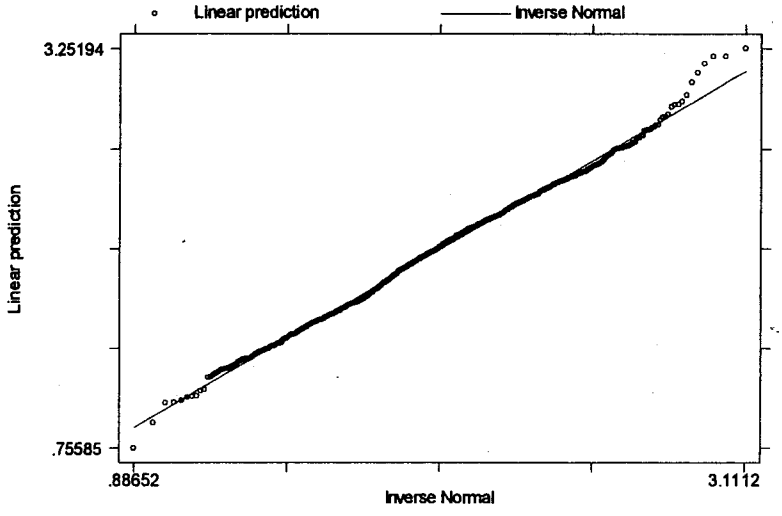
APPENDIX 1.


QIDS / LEST
Study Provinces
0 12.525 50 75 100 Kilometers
Prevalence of
Lead Toxicity
10-20%
21-30%
31-40%
41-50%
(not participating in study)
EASTERN SAMAR
LEYTE
BILIRAN
BOHOL
CAMIGUIN
CEBU
SIQUIJOR
NEGROS OCCIDENTAL
NEGROS ORIENTAL
CAPIZ
ILOILO

APPENDIX 2. Diagnostic plots for model of characteristics associated with blood lead concentration (Model 1)







APPENDIX 3. Single and multiple regression models of the associations between cognitive function score, blood lead concentration and other factors (Models 2a-2i)

2a: BSID MENTAL SCORE

```
. xi: regress  bsid_mentmdi ln_leadlevel if missing==0 & exclude==0

      Source |       SS       df       MS              Number of obs =     843
-------------+------------------------------           F(  1,   863) =    6.67
       Model |  1673.89842     1  1673.89842            Prob > F      =  0.0100
    Residual |  216550.483   863  250.927559            R-squared     =  0.0077
-------------+------------------------------           Adj R-squared =  0.0065
       Total |  218224.382   864  252.574516           Root MSE      =  15.841

------------------------------------------------------------------------------
bsid_mentmdi |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
ln_leadlevel |  -1.813646    .702202    -2.58   0.010    -3.191869   -.4354221
       _cons |   92.00531   1.494528    61.56   0.000     89.07198    94.93865
------------------------------------------------------------------------------


. xi: regress  bsid_mentmdi ln_leadlevel age_months female maternal_ed hb hhsmoke income
home100 bmi i.sfl i.a2a if missing==0 & exclude==0, cluster(lgu)
i.sfl             _Isfl_1-5           (naturally coded; _Isfl_1 omitted)
i.a2a             _Ia2a_1-11          (_Ia2a_8 for a2a==Leyte omitted)

Regression with robust standard errors                Number of obs =     834
                                                      F( 21,    29) =       .
                                                      Prob > F      =       .
                                                      R-squared     =  0.2393
Number of clusters (lgu) = 30                         Root MSE      =  13.917

------------------------------------------------------------------------------
             |               Robust
bsid_mentmdi |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
ln_leadlevel |   .2884226   .6616364     0.44   0.666    -1.064776    1.641621
  age_months |  -.5872173   .0917091    -6.40   0.000    -.7747835   -.3996511
      female |   1.858665   .8357242     2.22   0.034     .1494171    3.567913
 maternal_ed |   .2693719   .1705019     1.58   0.125    -.0793436    .6180874
          hb |   .3690362   .3120309     1.18   0.247    -.2691386    1.007211
     hhsmoke |  -.2518839   .9474219    -0.27   0.792    -2.189579    1.685811
      income |   .0000128   8.89e-06     1.44   0.160    -5.34e-06     .000031
    home100  |   .2002055    .046651     4.29   0.000     .1047935    .2956175
         bmi |   .2474545   .1592166     1.55   0.131      -.07818    .5730891
      _Isfl_2 |   .6899925   2.410768     0.29   0.777    -4.240581    5.620566
      _Isfl_3 |    3.28811   2.351122     1.40   0.173    -1.520475    8.096694
      _Isfl_4 |  -1.555319   2.739573    -0.57   0.575    -7.158374    4.047737
      _Isfl_5 |   3.029584   6.043639     0.50   0.620    -9.331045    15.39021
      _Ia2a_1 |   .2308981   1.115051     0.21   0.837    -2.049638    2.511434
      _Ia2a_2 |    4.77533   1.274131     3.75   0.001     2.16944     7.38122
      _Ia2a_3 |   1.414903   1.268844     1.12   0.274    -1.180176    4.009981
      _Ia2a_4 |   13.98274   2.504564     5.58   0.000     8.860326    19.10514
      _Ia2a_5 |   5.506377   2.893679     1.90   0.067    -.4118617    11.42462
      _Ia2a_6 |   .9708234   1.520622     0.64   0.528    -2.139197    4.080844
      _Ia2a_7 |   4.358199    1.75443     2.48   0.019      .769987    7.94641
      _Ia2a_9 |   1.684135   2.288061     0.74   0.468    -2.995475    6.363746
     _Ia2a_10 |   3.145457   1.953876     1.61   0.118    -.8506682    7.141583
     _Ia2a_11 |   4.537391   1.052949     4.31   0.000     2.383868    6.690914
        _cons |   66.64467   6.826218     9.76   0.000     52.68348    80.60585
------------------------------------------------------------------------------
```

2b: BSID BEHAVIOR SCORE

```
. xi: regress  bsid_brs100 ln_leadlevel if missing==0 & exclude==0

      Source |       SS       df       MS              Number of obs =     877
-------------+------------------------------           F(  1,   875) =    6.48
       Model |   1077.8515     1   1077.8515           Prob > F      =  0.0111
    Residual |  145585.921   875   166.38391           R-squared     =  0.0073
-------------+------------------------------           Adj R-squared =  0.0062
       Total |  146663.772   876  167.424398           Root MSE      =  12.899

------------------------------------------------------------------------------
 bsid_brs100 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
ln_leadlevel |  -1.441971   .5665428    -2.55   0.011    -2.553913   -.3300295
       _cons |   80.82814   1.207823    66.92   0.000     78.45757    83.19871
------------------------------------------------------------------------------


. xi: regress  bsid_brs100 ln_leadlevel age_months female maternal_ed hb hhsmoke income
home100 i.sf1 random i.a2a if missing==0 & exclude==0, cluster(lgu)
i.sf1             _Isf1_1-5           (naturally coded; _Isf1_1 omitted)
i.a2a             _Ia2a_1-11          (_Ia2a_8 for a2a==Leyte omitted)

Regression with robust standard errors                Number of obs =     844
                                                      F( 21,    29) =       .
                                                      Prob > F      =       .
                                                      R-squared     =  0.3449
Number of clusters (lgu) = 30                         Root MSE      =  10.683

------------------------------------------------------------------------------
             |               Robust
 bsid_brs100 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
ln_leadlevel |   .3406309    .423305     0.80   0.428     -.525125    1.206387
  age_months |   .0273717    .062405     0.44   0.664    -.1002608    .1550041
      female |   .2661196   .6845408     0.39   0.700    -1.133924    1.666163
 maternal_ed |     .44462   .0996091     4.46   0.000     .2408967    .6483434
          hb |   .3564504   .2408972     1.48   0.150    -.1362396    .8491404
      hhsmoke |   1.549336   .8222379     1.88   0.070    -.1323291    3.231001
      income |  -.0000126   5.71e-06    -2.21   0.035    -.0000243   -9.43e-07
     home100 |   .2654784   .0508021     5.23   0.000     .1615765    .3693802
     _Isf1_2 |   7.531382   4.581954     1.64   0.111    -1.839765    16.90253
     _Isf1_3 |   9.641799   4.055764     2.38   0.024      1.34683    17.93677
     _Isf1_4 |   8.871587   4.573925     1.94   0.062    -.4831401    18.22631
     _Isf1_5 |  -.9542413   4.655781    -0.20   0.839    -10.47638      8.5679
      random |  -2.792593    1.09929    -2.54   0.017    -5.040893   -.5442917
     _Ia2a_1 |  -3.639083   2.834407    -1.28   0.209    -9.436097    2.157931
     _Ia2a_2 |   4.909763    2.70768     1.81   0.080    -.6280633    10.44759
     _Ia2a_3 |   10.05918   2.712221     3.71   0.001     4.512062    15.60629
     _Ia2a_4 |   11.72928   3.406871     3.44   0.002      4.76145    18.69712
     _Ia2a_5 |   7.002336   3.024946     2.31   0.028     .8156256    13.18905
     _Ia2a_6 |  -5.725297   3.527639    -1.62   0.115    -12.94013    1.489536
     _Ia2a_7 |    6.48932   2.827152     2.30   0.029     .7071443    12.27149
     _Ia2a_9 |   2.666156   6.174746     0.43   0.669    -9.962617    15.29493
    _Ia2a_10 |   3.535078   2.902031     1.22   0.233    -2.400241    9.470398
    _Ia2a_11 |  -1.523368   2.766213    -0.55   0.586    -7.180908    4.134172
       _cons |   40.42087   5.801889     6.97   0.000     28.55467    52.28706
------------------------------------------------------------------------------
```

2e: BSID MOTOR SCORE

```
. xi: regress  bsid_motpdi ln_leadlevel if missing==0 & exclude==0

      Source |       SS       df       MS              Number of obs =     874
-------------+------------------------------           F(  1,   872) =    0.60
       Model |  225.273384     1  225.273384            Prob > F      =  0.4401
    Residual |  329320.243   872  377.660829            R-squared     =  0.0007
-------------+------------------------------           Adj R-squared = -0.0005
       Total |  329545.516   873  377.486273            Root MSE      =  19.433

------------------------------------------------------------------------------
 bsid_motpdi |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
ln_leadlevel |  -.6590877   .8533737    -0.77   0.440    -2.333994    1.015819
       _cons |   99.73191   1.815975    54.92   0.000     96.16772    103.2961
------------------------------------------------------------------------------


. xi: regress bsid_motpdi ln_leadlevel age_months  female maternal_ed hb hhsmoke income
home100 folate i.sf1 i.a2a if missing==0 & exclude==0, cluster(lgu)
i.sf1             _Isf1_1-5           (naturally coded; _Isf1_1 omitted)
i.a2a             _Ia2a_1-11          (_Ia2a_8 for a2a==Leyte omitted)

Regression with robust standard errors                Number of obs =     843
                                                      F( 21,    29) =       .
                                                      Prob > F      =       .
                                                      R-squared     =  0.1631
Number of clusters (lgu) = 30                         Root MSE      =  17.972

------------------------------------------------------------------------------
             |               Robust
 bsid_motpdi |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
ln_leadlevel |   .1905655   .7898342     0.24   0.811    -1.424827    1.805958
  age_months |    -.11034    .096899    -1.14   0.264    -.3085208    .0878408
      female |   1.288622   1.243878     1.04   0.309    -1.255394    3.832638
 maternal_ed |   .5785931   .2557486     2.26   0.031     .0555285    1.101658
          hb |   .8580738   .3796589     2.26   0.031     .0815842    1.634563
      hhsmoke |   1.023706   1.459912     0.70   0.489    -1.962149    4.009562
      income |  -8.06e-06   9.23e-06    -0.87   0.390    -.0000269    .0000108
     home100 |   .2820832   .0555998     5.07   0.000     .1683688    .3957975
      folate |  -1.528503   .6186691    -2.47   0.020    -2.793823   -.2631825
      _Isf1_2 |   5.850771   4.722153     1.24   0.225    -3.807117    15.50866
      _Isf1_3 |   9.063038    4.11172     2.20   0.036     .6536271    17.47245
      _Isf1_4 |   6.524134   5.098037     1.28   0.211    -3.902522    16.95079
      _Isf1_5 |  -.9791082   4.985827    -0.20   0.846    -11.17627    9.218053
      _Ia2a_1 |  -5.993019   2.346757    -2.55   0.016    -10.79268   -1.193361
      _Ia2a_2 |  -1.429511   2.632781    -0.54   0.591    -6.814152     3.95513
      _Ia2a_3 |  -7.914756   2.859253    -2.77   0.010    -13.76259   -2.066927
      _Ia2a_4 |   6.474472   2.642058     2.45   0.021     1.070856    11.87809
      _Ia2a_5 |  -.7532373   4.021859    -0.19   0.853    -8.978862    7.472387
      _Ia2a_6 |  -.1986389   2.616597    -0.08   0.940    -5.550181    5.152904
      _Ia2a_7 |   6.799537   2.744451     2.48   0.019     1.186505    12.41257
      _Ia2a_9 |  -9.849496    2.52463    -3.90   0.001    -15.01294   -4.686047
     _Ia2a_10 |  -2.059557   2.820724    -0.73   0.471    -7.828586    3.709472
     _Ia2a_11 |  -.7673336   2.609931    -0.29   0.771    -6.105241    4.570574
        _cons |   62.47407   5.577311    11.20   0.000     51.06719    73.88095
------------------------------------------------------------------------------
```

2d WPPSI YOUNG FULL IQ

```
. xi: regress  wppsi_young_fullcs ln_leadlevel if missing==0 & exclude==0

      Source |       SS       df       MS              Number of obs =     399
-------------+------------------------------           F(  1,   327) =    0.88
       Model |  278.998671     1  278.998671            Prob > F      =  0.3501
    Residual |  104173.555   327  318.573561            R-squared     =  0.0027
-------------+------------------------------           Adj R-squared = -0.0004
       Total |  104452.553   328  318.452906            Root MSE      =  17.849

------------------------------------------------------------------------------
wppsi_yo~lcs |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
ln_leadlevel |  -1.258257   1.344538    -0.94   0.350    -3.903293    1.386779
       _cons |   99.98429   3.077658    32.49   0.000     93.92979    106.0388
------------------------------------------------------------------------------


. xi: regress wppsi_young_fullcs ln_leadlevel age_months female maternal_ed schoolyears hb
hhsmoke income home100 i.a2a if missing==0 & exclude==0, cluster(lgu)
i.a2a              _Ia2a_1-11          (_Ia2a_8 for a2a==Leyte omitted)

Regression with robust standard errors                Number of obs =     296
                                                      F( 16,    28) =       .
                                                      Prob > F      =       .
                                                      R-squared     =  0.4786
Number of clusters (lgu) = 29                         Root MSE      =   12.95

------------------------------------------------------------------------------
             |               Robust
wppsi_yo~lcs |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
ln_leadlevel |   .5876604    .987489     0.60   0.557    -1.435119     2.61044
  age_months |  -.6065119    .115048    -5.27   0.000    -.8421771    -.3708467
      female |   .0732718    1.92616     0.04   0.970    -3.872288     4.018831
 maternal_ed |   .3745693    .299708     1.25   0.222    -.2393546     .9884933
 schoolyears |   16.86145   9.574464     1.76   0.089    -2.750952     36.47385
          hb |  -.0542195   .4685422    -0.12   0.909    -1.013985     .9055457
     hhsmoke |  -2.354815   1.578638    -1.49   0.147    -5.588509     .8788792
      income |   2.61e-06    .000011     0.24   0.814    -.0000199     .0000251
     home100 |   .3074424   .0691344     4.45   0.000     .1658271     .4490578
     _Ia2a_1 |   4.416169   1.305723     3.38   0.002     1.741517     7.090821
     _Ia2a_2 |   1.989471     1.7065     1.17   0.254    -1.506136     5.485078
     _Ia2a_3 |  -2.457351   1.646633    -1.49   0.147    -5.830325     .9156231
     _Ia2a_4 |   26.91467   2.742204     9.81   0.000     21.29752     32.53182
     _Ia2a_5 |   7.861135   1.973613     3.98   0.000     3.818372      11.9039
     _Ia2a_6 |   7.393975   1.742382     4.24   0.000     3.824867     10.96308
     _Ia2a_7 |   22.81384   3.171246     7.19   0.000     16.31784     29.30984
     _Ia2a_9 |     11.006   7.489036     1.47   0.153    -4.334593      26.3466
    _Ia2a_10 |   13.80105    1.88267     7.33   0.000     9.944573     17.65752
    _Ia2a_11 |   5.731653   1.435414     3.99   0.000     2.791341     8.671966
       _cons |   88.63343   6.777039    13.08   0.000      74.7513     102.5156
------------------------------------------------------------------------------
```

2e: WPPSI YOUNG VERBAL IQ

```
. xi: regress  wppsi_young_vercs ln_leadlevel if missing==0 & exclude==0

      Source |       SS       df       MS              Number of obs =     399
-------------+------------------------------           F(  1,   327) =    1.53
       Model |  319.110666     1  319.110666            Prob > F      =  0.2173
    Residual |  68294.4091   327  208.851404            R-squared     =  0.0047
-------------+------------------------------           Adj R-squared =  0.0016
       Total |  68613.5198   328   209.18756            Root MSE      =  14.452

------------------------------------------------------------------------------
wpps~g_vercs |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
ln_leadlevel |  -1.345671   1.088647    -1.24   0.217    -3.487306    .7959637
       _cons |   97.65716   2.49192     39.19   0.000     92.75495    102.5594
------------------------------------------------------------------------------


. xi: regress wppsi_young_vercs ln_leadlevel age_months female maternal_ed schoolyears hb
hhsmoke income home100 tapqs if exclude==0 & missing==0, cluster(lgu)

Regression with robust standard errors                Number of obs =     296
                                                      F( 10,    28) =   11.10
                                                      Prob > F      =  0.0000
                                                      R-squared     =  0.2332
Number of clusters (lgu) = 29                         Root MSE      =  12.646

------------------------------------------------------------------------------
             |               Robust
wpps~g_vercs |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
ln_leadlevel |  -.3032613   1.153503    -0.26   0.795    -2.666105    2.059583
  age_months |  -.6261343   .1457842    -4.29   0.000    -.9247596   -.3275089
      female |   .9059856    1.50363     0.60   0.552    -2.174061    3.986032
 maternal_ed |   .3844028   .2661593     1.44   0.160    -.1607998    .9296053
 schoolyears |    11.7589   10.04893     1.17   0.252    -8.825392     32.3432
          hb |   .0842711   .434535     0.19   0.848    -.8058336    .9743757
      hhsmoke |  -.6777003   .9489594    -0.71   0.481    -2.621556    1.266155
      income |  -5.24e-07   .000013    -0.04   0.968    -.0000271    .0000261
     home100 |   .3064695   .0683413     4.48   0.000     .1664786    .4464603
       tapqs |   .2071364   .0888259     2.33   0.027     .0251848    .3890881
       _cons |   75.88871   9.906762     7.66   0.000     55.59563     96.1818
------------------------------------------------------------------------------
```

2f: WPPSI YOUNG PERFORMANCE IQ

```
. xi: regress  wppsi_young_percs ln_leadlevel if missing==0 & exclude==0

      Source |       SS       df       MS              Number of obs =     399
-------------+------------------------------           F(  1,   327) =    0.30
       Model |  119.661205     1  119.661205            Prob > F      =  0.5818
    Residual |  128758.187   327  393.755923            R-squared     =  0.0009
-------------+------------------------------           Adj R-squared = -0.0021
       Total |  128877.848   328  392.920268            Root MSE      =  19.843

------------------------------------------------------------------------------
wpps~g_percs |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
ln_leadlevel |  -.8240336   1.494796    -0.55   0.582    -3.764663    2.116596
       _cons |   102.3222   3.421598    29.90   0.000     95.59104    109.0533
------------------------------------------------------------------------------


. xi: regress wppsi_young_percs ln_leadlevel age_months female bweight maternal_ed
schoolyears hb hhsmoke income home100 i.a2a if missing==0 & exclude==0, cluster(lgu)
i.a2a              _Ia2a_1-11          (_Ia2a_8 for a2a==Leyte omitted)

Regression with robust standard errors                Number of obs =     223
                                                      F( 17,    28) =       .
                                                      Prob > F      =       .
                                                      R-squared     =  0.4317
Number of clusters (lgu) = 29                         Root MSE      =  15.747

------------------------------------------------------------------------------
             |               Robust
wpps~g_percs |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
ln_leadlevel |   .4030751   1.129962     0.36   0.724    -1.911548    2.717698
  age_months |   -.344233   .1813773    -1.90   0.068    -.7157676    .0273016
      female |  -1.164417   2.437255    -0.48   0.637    -6.156906    3.828073
     bweight |   .0010854   .0014875     0.73   0.472    -.0019616    .0041325
 maternal_ed |   .0808972   .4095406     0.20   0.845    -.7580087    .9198032
 schoolyears |   16.13645     7.7765     2.08   0.047      .207014    32.06589
          hb |  -.8205393   .6398721    -1.28   0.210    -2.131258    .4901793
      hhsmoke |  -2.313738   2.122702    -1.09   0.285    -6.661895    2.034419
      income |   7.13e-06   .0000125     0.57   0.575    -.0000186    .0000328
     home100 |   .3277707    .098498     3.33   0.002     .1260067    .5295348
     _Ia2a_1 |   15.87252   2.854008     5.56   0.000     10.02635    21.71869
     _Ia2a_2 |   5.559492   2.518689     2.21   0.036      .400192    10.71879
     _Ia2a_3 |  -3.596429   3.117476    -1.15   0.258    -9.982289    2.789431
     _Ia2a_4 |   30.96454   4.544768     6.81   0.000     21.65501    40.27408
     _Ia2a_5 |   3.417859   3.425289     1.00   0.327    -3.598526    10.43424
     _Ia2a_6 |   8.795652   2.807854     3.13   0.004     3.044024    14.54728
     _Ia2a_7 |   22.91371   5.707332     4.01   0.000     11.22277    34.60465
     _Ia2a_9 |   17.79989   9.445298     1.88   0.070    -1.547927     37.1477
    _Ia2a_10 |   15.68198   2.765116     5.67   0.000     10.01789    21.34606
    _Ia2a_11 |   6.467613   2.853342     2.27   0.031     .6228079    12.31242
       _cons |   89.36137   13.75938     6.49   0.000     61.17657    117.5462
------------------------------------------------------------------------------
```

2g: WPPSI OLD FULL IQ

```
. xi: regress  wppsi_old_fullcs ln_leadlevel if missing==0 & exclude==0

      Source |       SS       df       MS              Number of obs =      97
-------------+------------------------------           F(  1,    95) =    1.49
       Model |  490.688045     1  490.688045            Prob > F      =  0.2257
    Residual |  31349.5594    95  329.995362            R-squared     =  0.0154
-------------+------------------------------           Adj R-squared =  0.0050
       Total |  31840.2474    96  331.669244            Root MSE      =  18.166

------------------------------------------------------------------------------
wppsi_ol~lcs |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
ln_leadlevel |  -3.089208   2.533368    -1.22   0.226    -8.118579    1.940164
       _cons |   96.09661   5.711481    16.83   0.000     84.75789    107.4353
------------------------------------------------------------------------------

. xi: regress wppsi_old_fullcs ln_leadlevel age_months age_months2 female maternal_ed
schoolyears hb hhsmoke income home100 if missing==0 & exclude==0, cluster(lgu)

Regression with robust standard errors                Number of obs =      55
                                                      F( 10,    21) =    1.84
                                                      Prob > F      =  0.1147
                                                      R-squared     =  0.1790
Number of clusters (lgu) = 22                         Root MSE      =  16.148

------------------------------------------------------------------------------
             |               Robust
wppsi_ol~lcs |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
ln_leadlevel |  -.9416814   2.686458    -0.35   0.729    -6.528476    4.645113
  age_months |   34.34288   26.24362     1.31   0.205    -20.23371    88.91947
 age_months2 |  -.3212004   .2444611    -1.31   0.203    -.8295851    .1871843
      female |   3.032787    3.49757     0.87   0.396    -4.240808    10.30638
 maternal_ed |   .9713067   .6077956     1.60   0.125    -.2926734    2.235287
 schoolyears |   8.295025   7.903438     1.05   0.306    -8.141075    24.73112
          hb |   .4952376   1.199158     0.41   0.684    -1.998547    2.989022
     hhsmoke |  -4.561504   4.686729    -0.97   0.341    -14.30809    5.185081
      income |  -.0000539   .0000569    -0.95   0.354    -.0001723    .0000645
     home100 |   .2198855   .2417802     0.91   0.373    -.2829239    .7226949
       _cons |  -845.2642   706.6571    -1.20   0.245    -2314.838    624.3096
------------------------------------------------------------------------------
```

2h: WPPSI OLD VERBAL IQ

```
. regress  wppsi_old_vercs ln_leadlevel if missing==0 & exclude==0

      Source |       SS       df       MS              Number of obs =      97
-------------+------------------------------           F(  1,    95) =    3.01
       Model |  396.367089     1  396.367089            Prob > F      =  0.0862
    Residual |  12524.9525    95  131.841605            R-squared     =  0.0307
-------------+------------------------------           Adj R-squared =  0.0205
       Total |  12921.3196    96  134.597079            Root MSE      =  11.482

------------------------------------------------------------------------------
wpps~d_vercs |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
ln_leadlevel |  -2.776471   1.601292    -1.73   0.086    -5.955438    .4024959
       _cons |   89.32623   3.610115    24.74   0.000     82.15925    96.49322
------------------------------------------------------------------------------

. xi: regress wppsi_old_vercs ln_leadlevel age_months female maternal_ed schoolyears hb
hhsmoke income home100 tapqs i.a2a if exclude==0 & missing==0, cluster(lgu)
i.a2a             _Ia2a_1-11          (_Ia2a_8 for a2a==Leyte omitted)

Regression with robust standard errors                Number of obs =      55
                                                      F( 15,    21) =       .
                                                      Prob > F      =       .
                                                      R-squared     =  0.4627
Number of clusters (lgu) = 22                         Root MSE      =  11.172

------------------------------------------------------------------------------
             |               Robust
wpps~d_vercs |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
ln_leadlevel |  -3.237737   2.371758    -1.37   0.187    -8.170078    1.694604
  age_months |  -.4444217   .4454865    -1.00   0.330    -1.370862    .4820182
      female |   2.043237   4.090858     0.50   0.623    -6.464168    10.55064
 maternal_ed |   .2047508   .4848243     0.42   0.677    -.8034964    1.212998
 schoolyears |  -.2385836   6.641074    -0.04   0.972    -14.04945    13.57228
          hb |  -.2483251    1.54554    -0.16   0.874    -3.462451    2.965801
     hhsmoke |   -1.50811   4.288011    -0.35   0.729    -10.42552    7.409296
      income |  -.0000193   .0000504    -0.38   0.705    -.0001242    .0000855
     home100 |   .0759978   .2200795     0.35   0.733    -.3816825    .5336781
       tapqs |   .2791111   .1264973     2.21   0.039     .0160455    .5421768
     _Ia2a_1 |  -4.098057   3.350147    -1.22   0.235    -11.06507    2.868955
     _Ia2a_2 |  -2.098288   4.160509    -0.50   0.619    -10.75054    6.553965
     _Ia2a_3 |  -5.243069   3.957322    -1.32   0.199    -13.47277    2.986633
     _Ia2a_4 |   45.25018   6.869262     6.59   0.000     30.96477    59.53559
     _Ia2a_5 |  -4.889307   5.666314    -0.86   0.398    -16.67305    6.894438
     _Ia2a_6 |  (dropped)
     _Ia2a_7 |   6.832201   5.035869     1.36   0.189    -3.640462    17.30486
     _Ia2a_9 |  -2.140804   4.128513    -0.52   0.610    -10.72652    6.444907
    _Ia2a_10 |   5.205488   6.210397     0.84   0.411     -7.70974    18.12072
    _Ia2a_11 |  -.8582904   7.429111    -0.12   0.909    -16.30797    14.59139
       _cons |   86.79644   31.50603     2.75   0.012     21.27607    152.3168
------------------------------------------------------------------------------
```

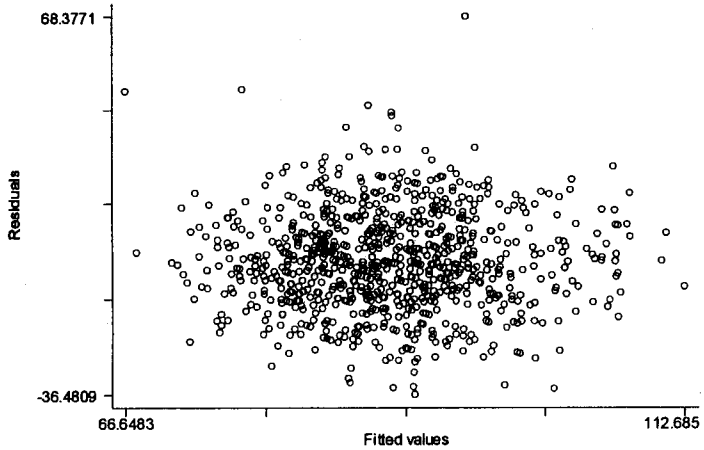
2i: WPPSI OLD PERFORMANCE IQ

```
. xi: regress  wppsi_old_percs ln_leadlevel if missing==0 & exclude==0

      Source |       SS       df       MS              Number of obs =      97
-------------+------------------------------           F(  1,    95) =    3.43
       Model |  998.140482     1  998.140482           Prob > F      =  0.0670
    Residual |  27627.6946    95  290.817838           R-squared     =  0.0349
-------------+------------------------------           Adj R-squared =  0.0247
       Total |  28625.8351    96  298.185782           Root MSE      =  17.053

------------------------------------------------------------------------------
wpps~d_percs |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
ln_leadlevel |  -4.405956   2.378236    -1.85   0.067    -9.127351    .3154382
       _cons |   109.3598   5.361735    20.40   0.000     98.71539    120.0042
------------------------------------------------------------------------------

. xi: regress wppsi_old_percs ln_leadlevel age_months age_months2 female maternal_ed
schoolyears hb hhsmoke income home100 if missing==0 & exclude==0, cluster(lgu)

Regression with robust standard errors                Number of obs =      55
                                                      F( 10,    21) =    2.10
                                                      Prob > F      =  0.0736
                                                      R-squared     =  0.1854
Number of clusters (lgu) = 22                         Root MSE      =  17.874

------------------------------------------------------------------------------
             |               Robust
wpps~d_percs |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
ln_leadlevel |  -.2261772   2.709816    -0.08   0.934    -5.861549    5.409194
  age_months |   37.80015   27.97826     1.35   0.191    -20.38383    95.98412
 age_months2 |  -.3530048   .2600074    -1.36   0.189    -.8937198    .1877101
      female |   1.226781   3.827925     0.32   0.752    -6.733825    9.187387
 maternal_ed |   .9890084    .706246     1.40   0.176    -.4797105    2.457727
 schoolyears |   11.25015   7.427327     1.51   0.145    -4.195826    26.69612
          hb |   1.852109   1.340393     1.38   0.182    -.9353918    4.639609
     hhsmoke |  -7.525717   5.027713    -1.50   0.149    -17.98142    2.929984
      income |  -.0000532   .0000528    -1.01   0.325    -.0001631    .0000567
     home100 |   .1151893   .2432576     0.47   0.641    -.3906927    .6210712
       _cons |  -939.3027   756.2762    -1.24   0.228    -2512.065    633.4597
------------------------------------------------------------------------------
```

APPENDIX 4. Diagnostic plots of Multiple regression models of the associations between cognitive function score, blood lead concentration and other factors.

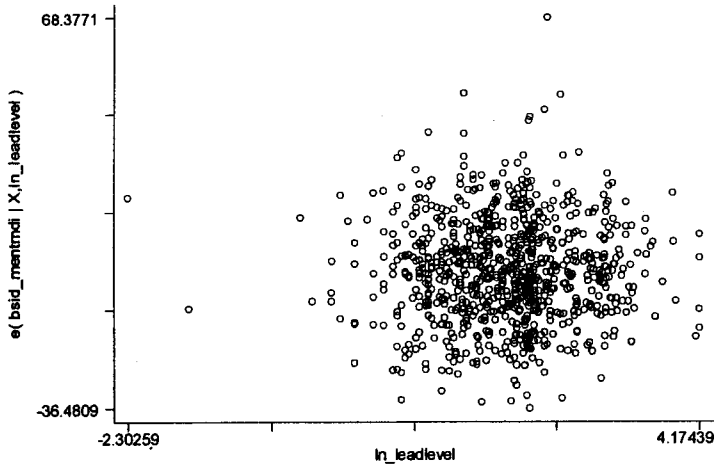
Regression Diagnostics for Model 2a: BSID Mental Score

1. Residual vs. Fitted Value plot assessing consistency of error variance



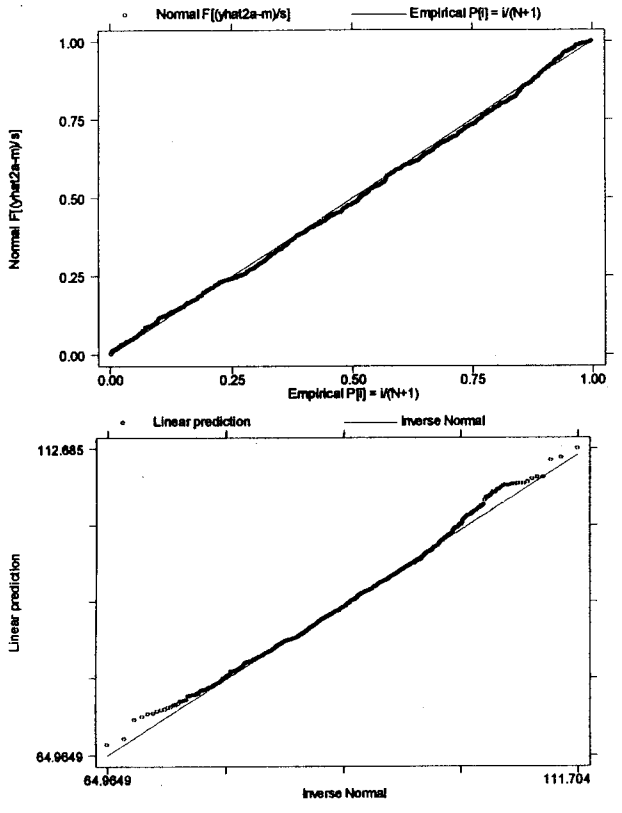
Interpretation: no clear trends in error variance. One observation with ? high residual. Removal of suspect observation did not significantly change model outcomes.

2. Residual vs. Predictor plot assessing linearity of relationship and consistency of variance



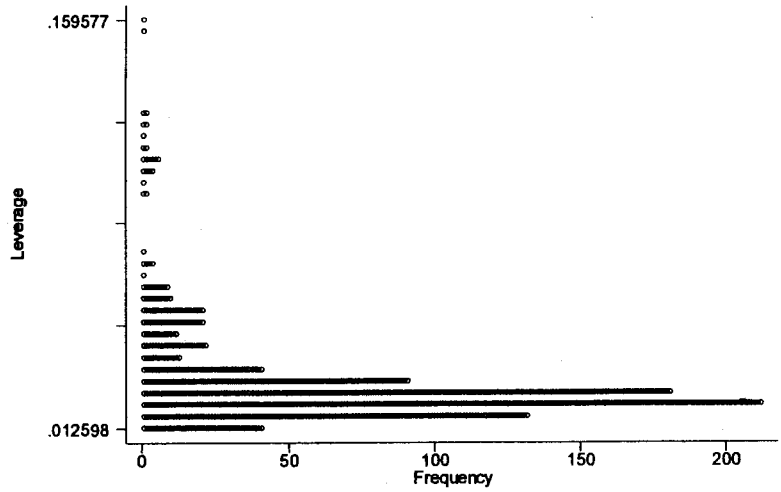
Interpretation: no trends indicating non-linear relationship. No clear trends in error variance. One observation with ? high residual. Removal of suspect observation did not significantly change model outcomes.

3. Normal probability plots



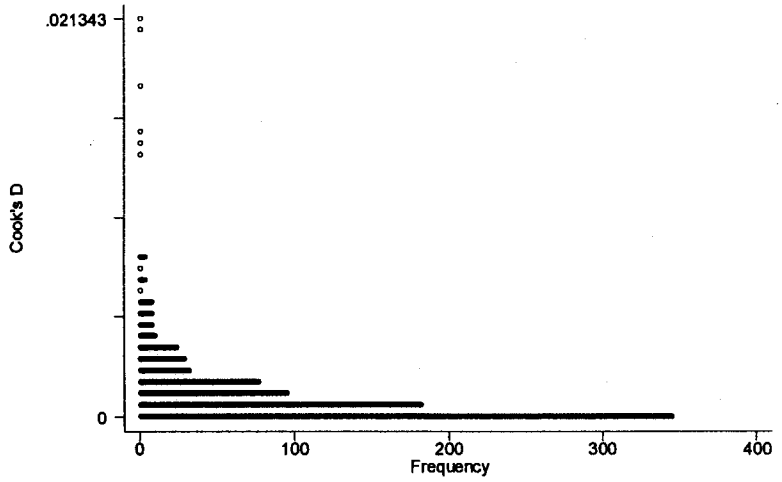
Interpretation: nearly linear, suggesting normality except at far tails.

4. Leverage values, assessing outliers



Interpretation: two moderate potential outliers identified. Removal of suspect observations did not significantly change model outcomes.

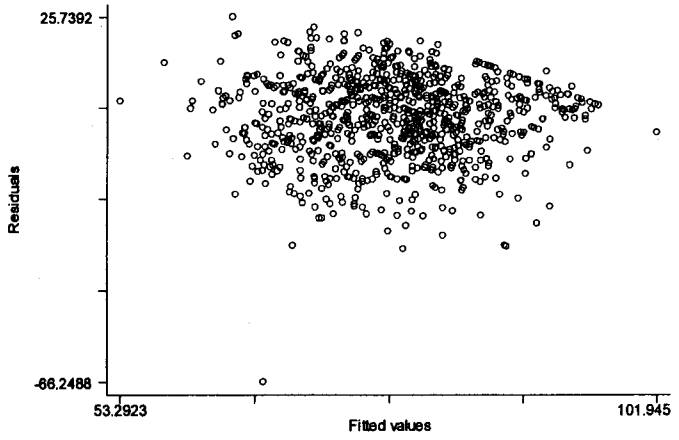
5. Cook's Distance values, assessing influential points



Interpretation: six potential influential points. Removal of suspect observations did not significantly change model outcomes.

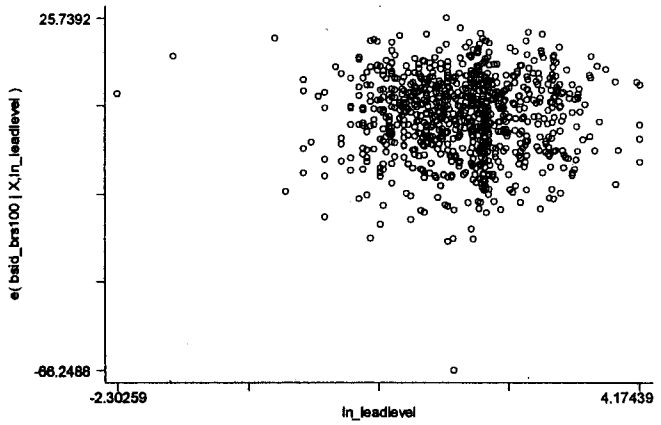
Regression Diagnostics for Model 2b: BSID Behavior Score

6. Residual vs. Fitted Value plot assessing consistency of error variance



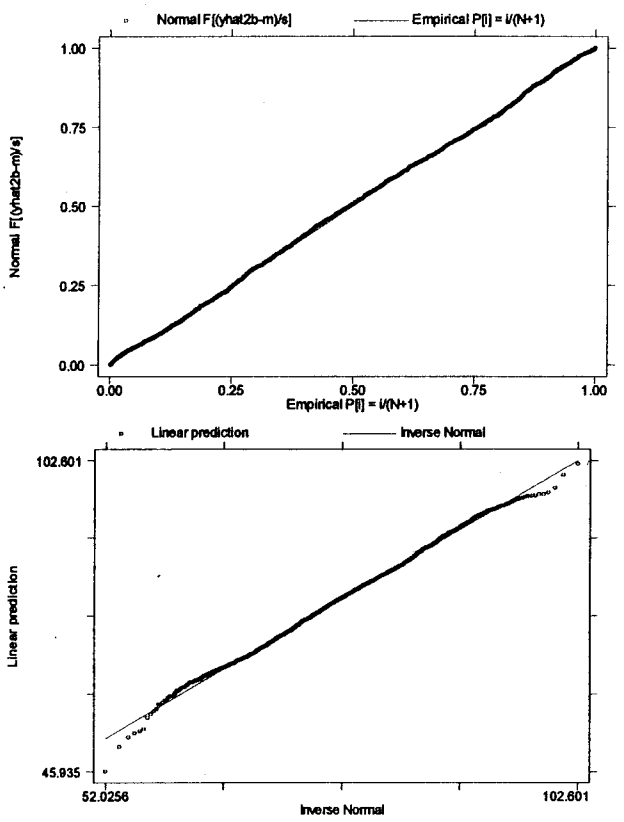
Interpretation: no clear trends in error variance. One observation with ? low residual. Removal of suspect observation did not significantly change model outcomes.

7. Residual vs. Predictor plot assessing linearity of relationship and consistency of variance



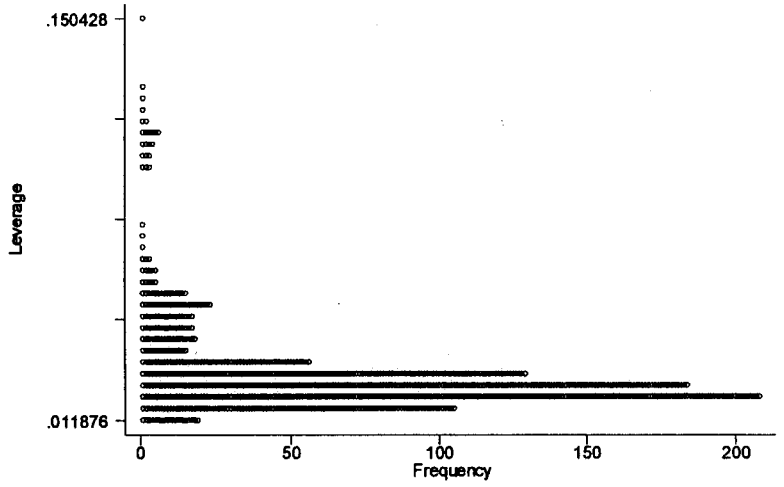
Interpretation: no trends indicating non-linear relationship. No clear trends in error variance. One observation with ? low residual. Removal of suspect observation did not significantly change model outcomes.

8. Normal probability plots



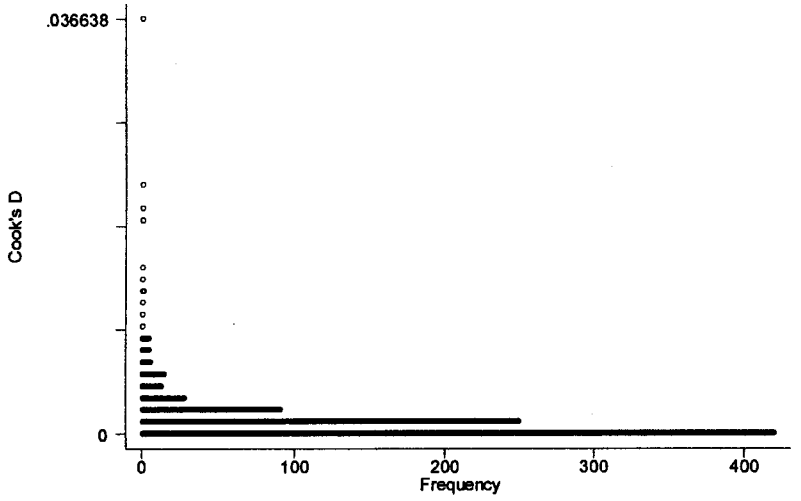
Interpretation: nearly linear, suggesting normality except at far tails.

9. Leverage values, assessing outliers



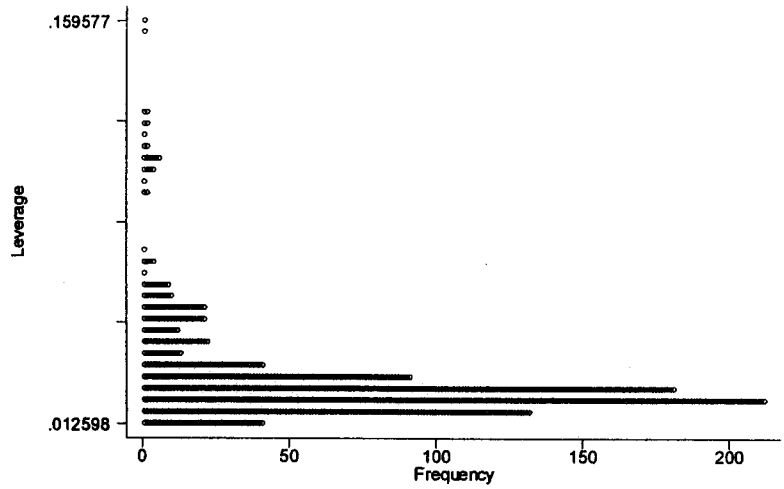
Interpretation: one moderate potential outlier identified. Removal of suspect observation did not significantly change model outcomes.

10. Cook's Distance values, assessing influential points



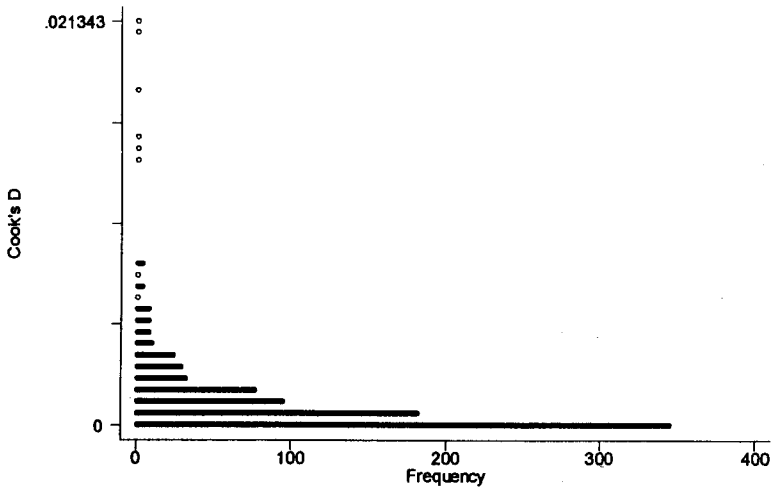
Interpretation: one potential influential point. Removal of suspect observation did not significantly change model outcomes.

11. Leverage values, assessing outliers



Interpretation: two moderate potential outliers identified. Removal of suspect observations did not significantly change model outcomes.

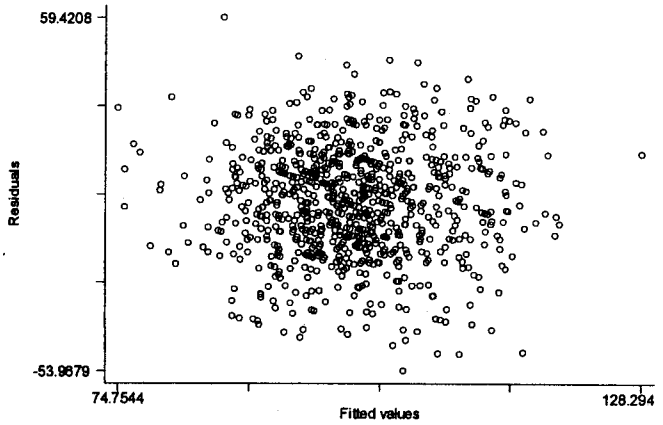
12. Cook's Distance values, assessing influential points



Interpretation: six potential influential points. Removal of suspect observations did not significantly change model outcomes.

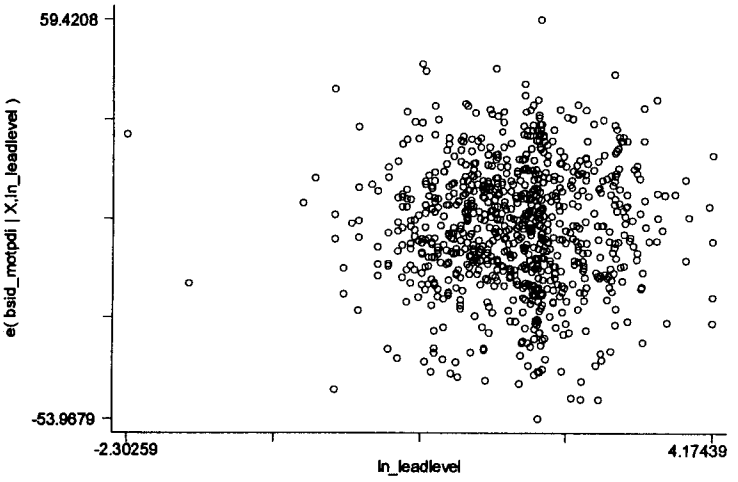
Regression Diagnostics for Model 2c: BSID Motor Score

13. Residual vs. Fitted Value plot assessing consistency of error variance



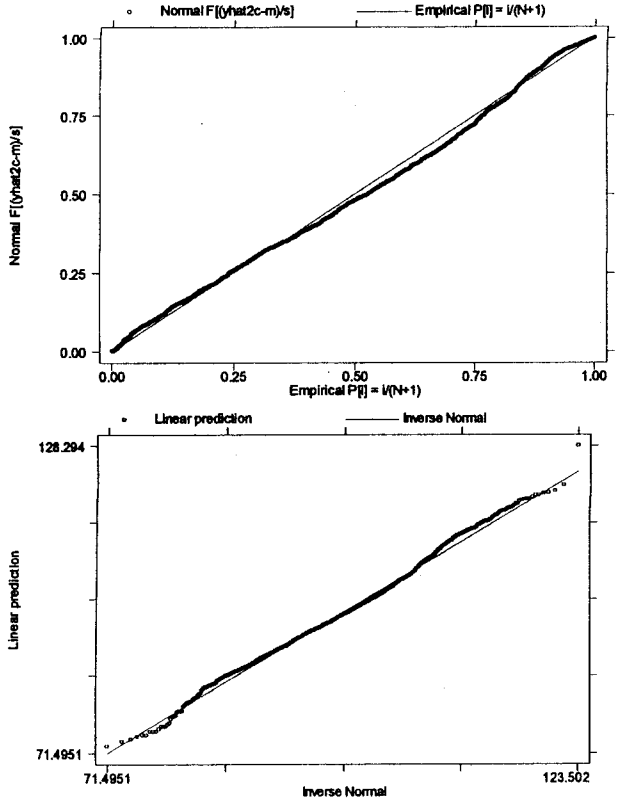
Interpretation: no clear trends in error variance. No observations with outlying residual values.

14. Residual vs. Predictor plot assessing linearity of relationship and consistency of variance



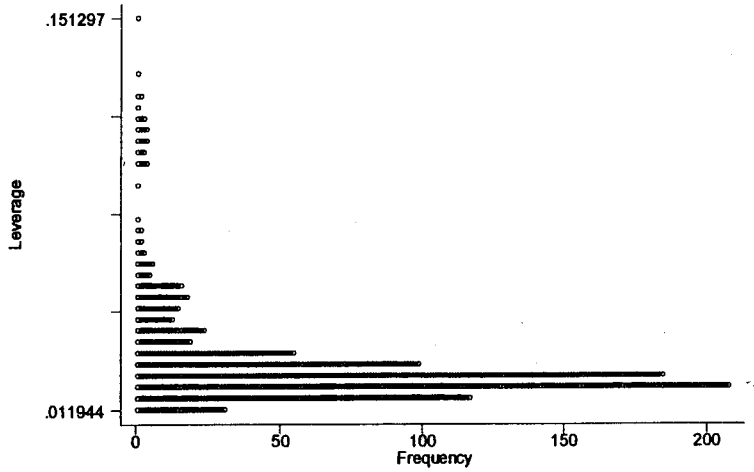
Interpretation: no trends indicating non-linear relationship. No clear trends in error variance. No observations with outlying residuals.

15. Normal probability plots



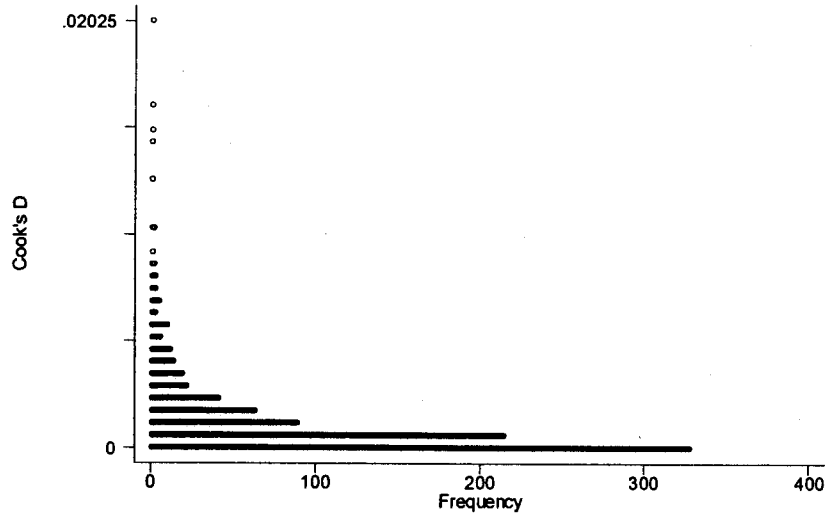
Interpretation: only minor departure form linearity, suggesting normality of prediction.

16. Leverage values, assessing outliers



Interpretation: one moderate potential outlier identified. Removal of suspect observation did not significantly change model outcomes.

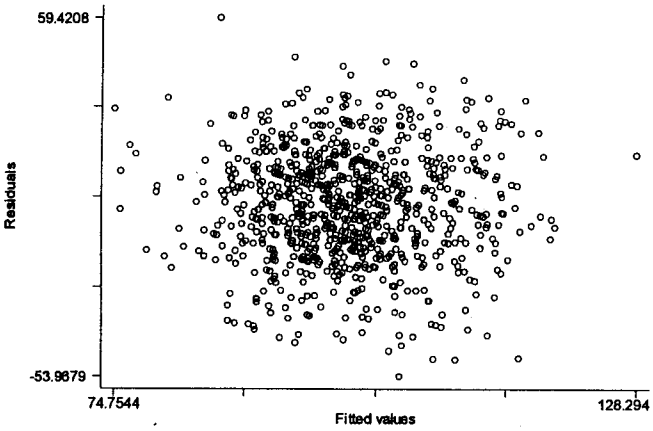
17. Cook's Distance values, assessing influential points



Interpretation: one potential influential point. Removal of suspect observation did not significantly change model outcomes.

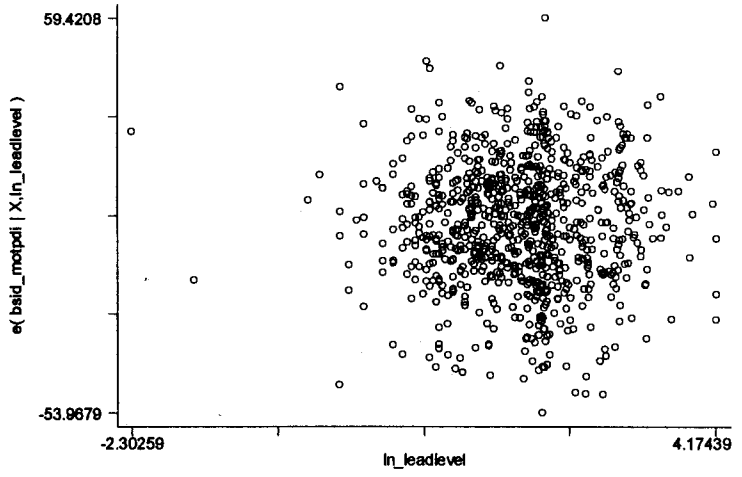
Regression Diagnostics for Model 2d: WPPSI Full IQ

18. Residual vs. Fitted Value plot assessing consistency of error variance



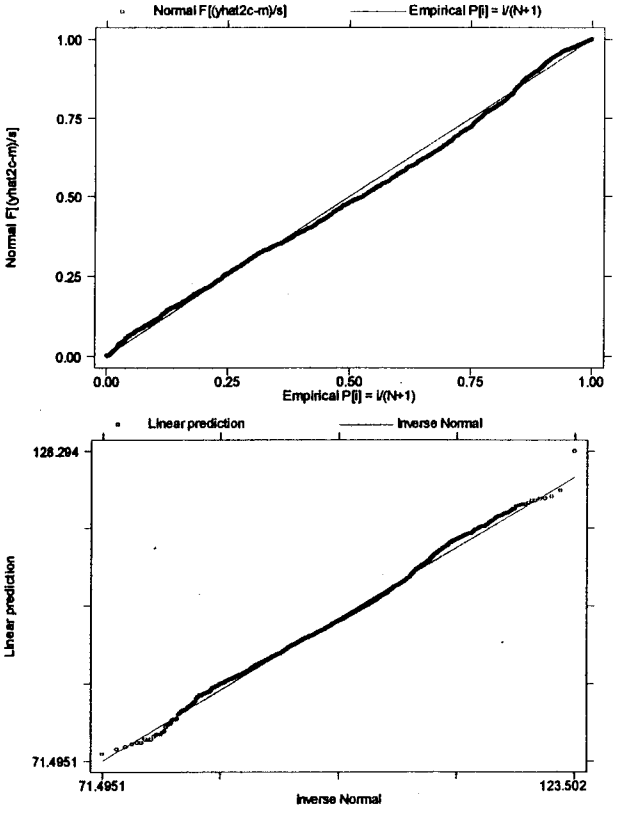
Interpretation: no clear trends in error variance. No observations with outlying residual values.

19. Residual vs. Predictor plot assessing linearity of relationship and consistency of variance



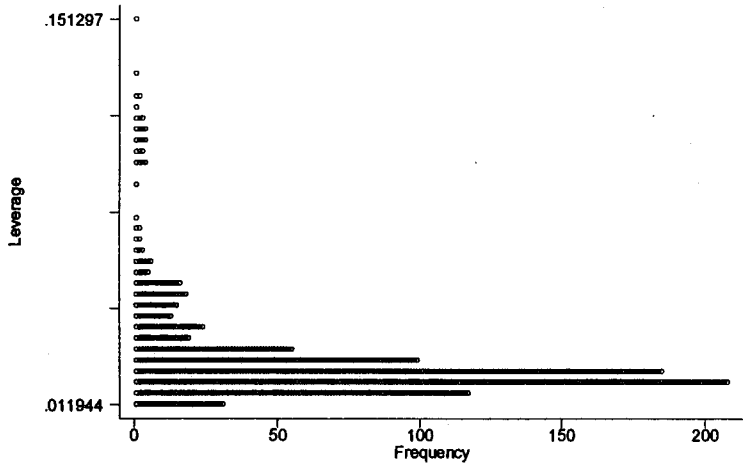
Interpretation: no trends indicating non-linear relationship. No clear trends in error variance. No observations with outlying residuals.

20. Normal probability plots



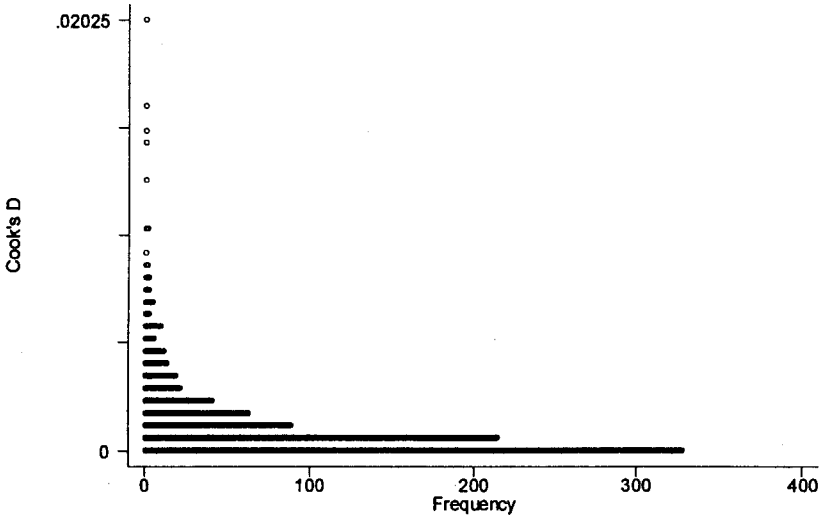
Interpretation: only minor departure form linearity, suggesting normality of prediction.

21. Leverage values, assessing outliers



Interpretation: one moderate potential outlier identified. Removal of suspect observation did not significantly change model outcomes.

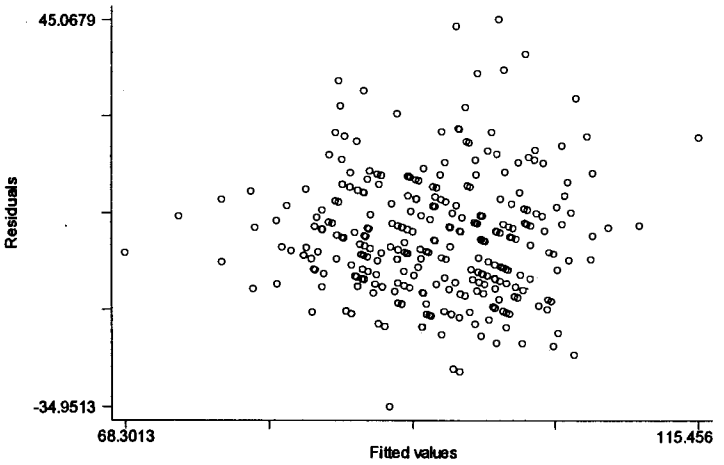
22. Cook's Distance values, assessing influential points



Interpretation: one potential influential point. Removal of suspect observation did not significantly change model outcomes.

Regression Diagnostics for Model 2e: WPPSI Verbal IQ

23. Residual vs. Fitted Value plot assessing consistency of error variance

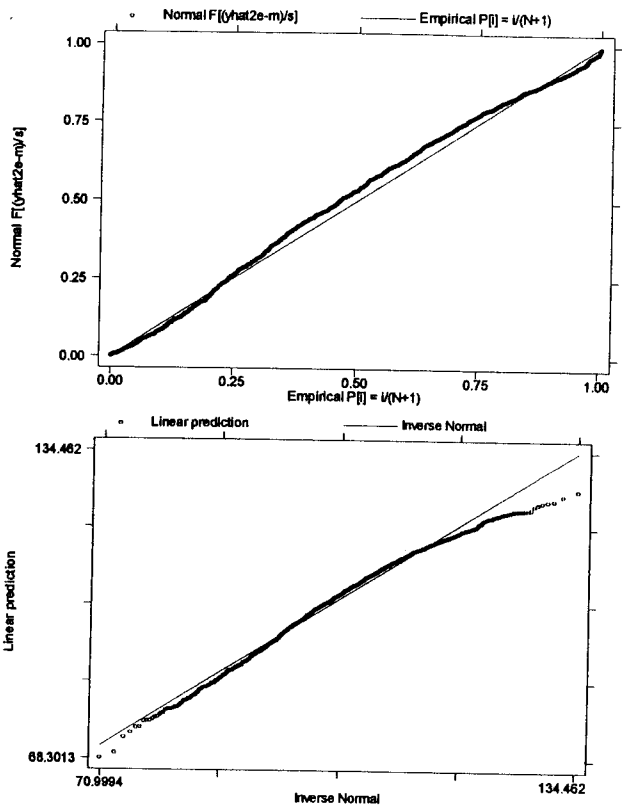


Interpretation: no clear trends in error variance. No observations with outlying residual values.

24. Residual vs. Predictor plot assessing linearity of relationship and consistency of variance

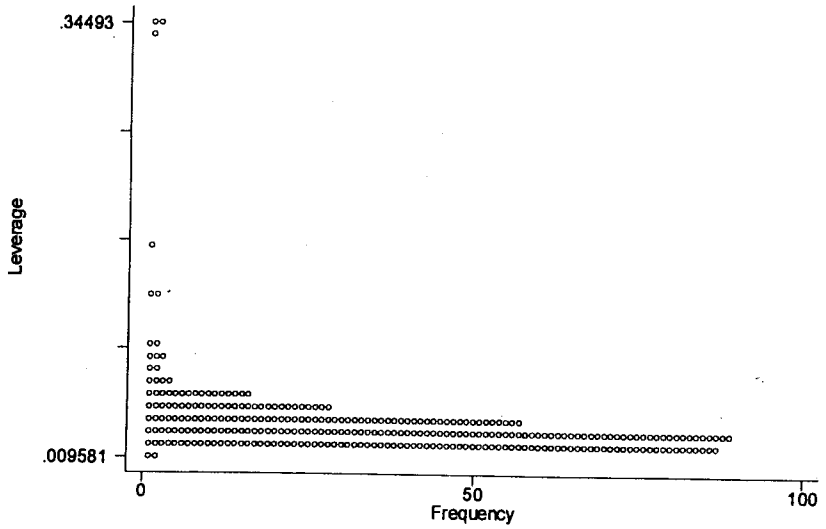
Interpretation: no trends indicating non-linear relationship. No clear trends in error variance. No observations with outlying residuals.

25. Normal probability plots



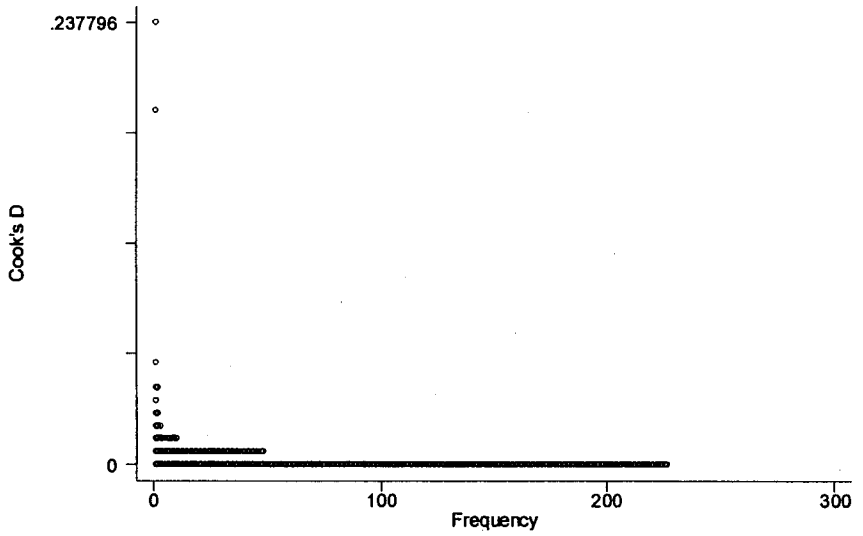
Interpretation: some minor departure form linearity, suggesting near-normality of prediction except perhaps at far tails.

26. Leverage values, assessing outliers



Interpretation: three moderate potential outlier identified. Removal of suspect observations did not significantly change model outcomes.

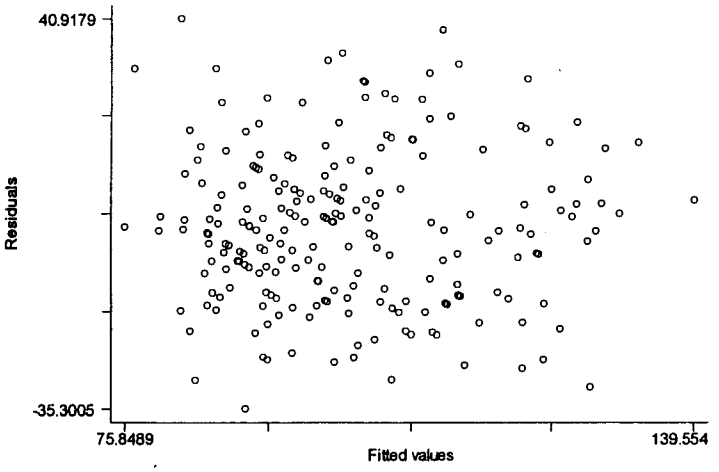
27. Cook's Distance values, assessing influential points



Interpretation: two potential influential points. Removal of suspect observations did not significantly change model outcomes.

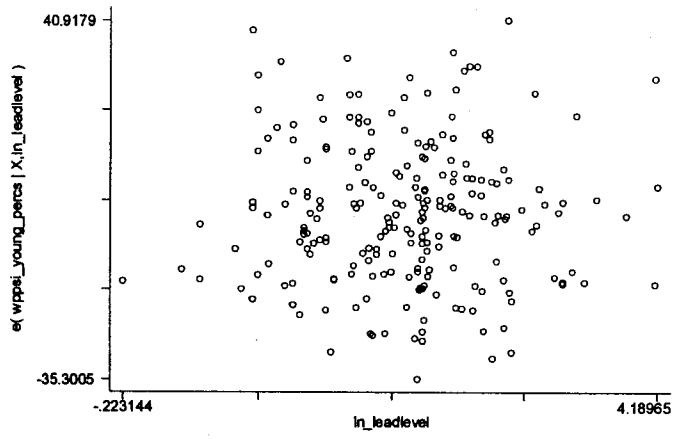
Regression Diagnostics for Model 2f: WPPSI Performance IQ

28. Residual vs. Fitted Value plot assessing consistency of error variance



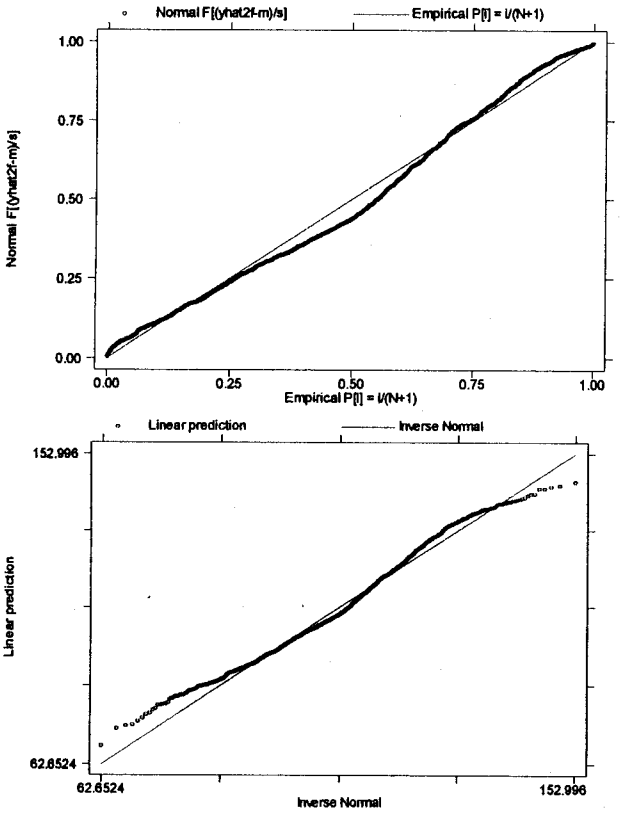
Interpretation: no clear trends in error variance. No observations with outlying residual values.

29. Residual vs. Predictor plot assessing linearity of relationship and consistency of variance



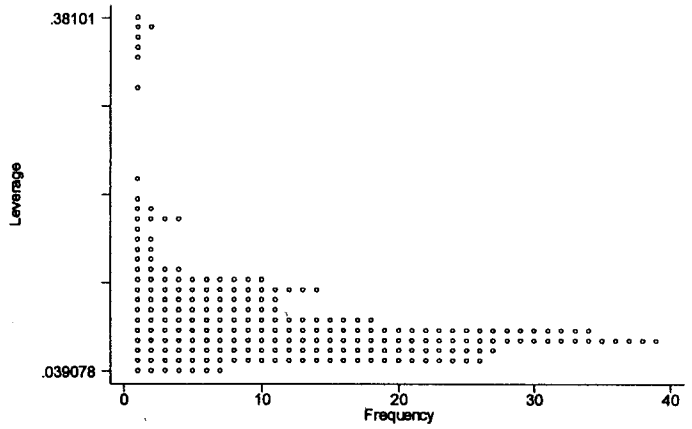
Interpretation: no trends indicating non-linear relationship. No clear trends in error variance. No observations with outlying residuals.

30. Normal probability plots



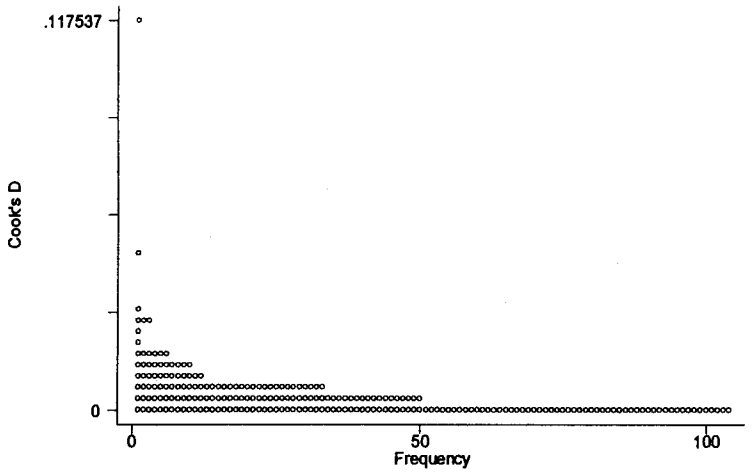
Interpretation: some minor to moderate departure form linearity, suggesting near-normality of prediction.

31. Leverage values, assessing outliers



Interpretation: seven moderate potential outliers identified. Removal of suspect observations did not significantly change model outcomes.

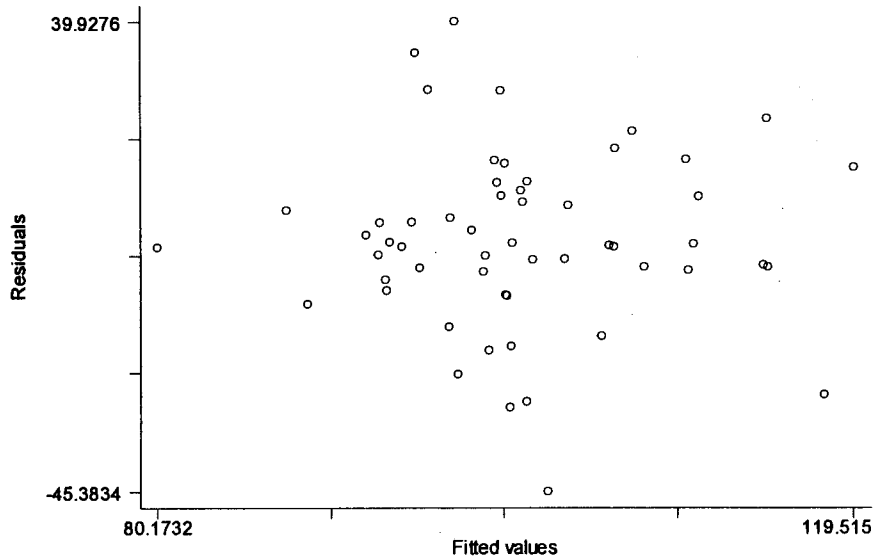
32. Cook's Distance values, assessing influential points



Interpretation: one potential influential point. Removal of the suspect observation did not significantly change model outcomes.

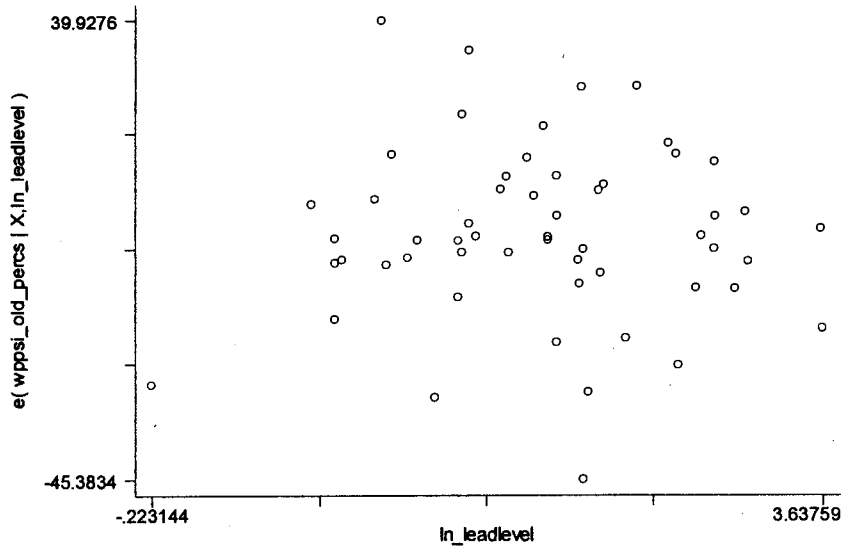
Regression Diagnostics for Model 2i: WPPSI Old Performance IQ

33. Residual vs. Fitted Value plot assessing consistency of error variance



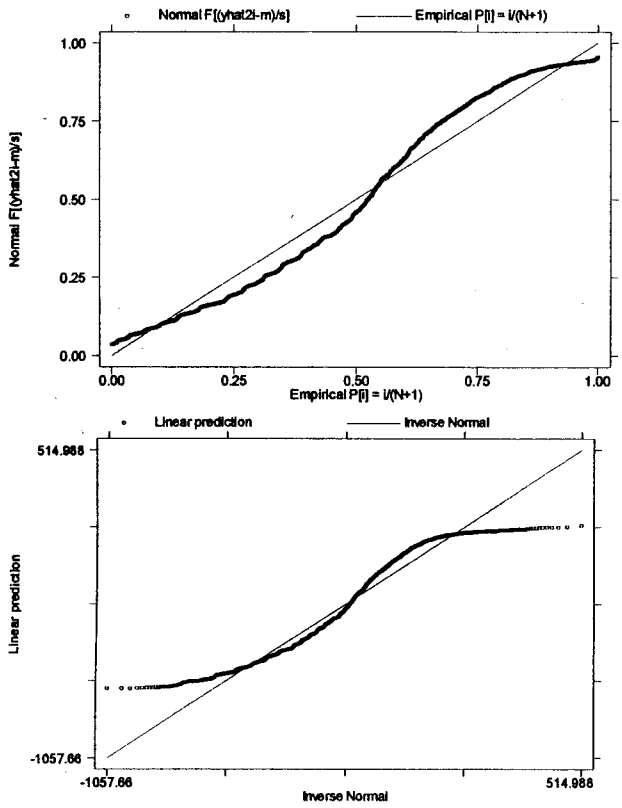
Interpretation: no clear trends in error variance. No observations with outlying residual values.

34. Residual vs. Predictor plot assessing linearity of relationship and consistency of variance



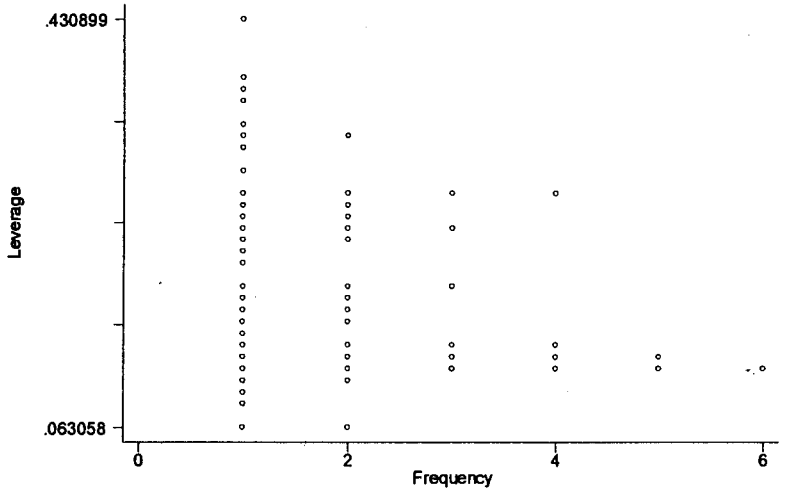
Interpretation: no trends indicating non-linear relationship. No clear trends in error variance. No observations with outlying residuals.

35. Normal probability plots



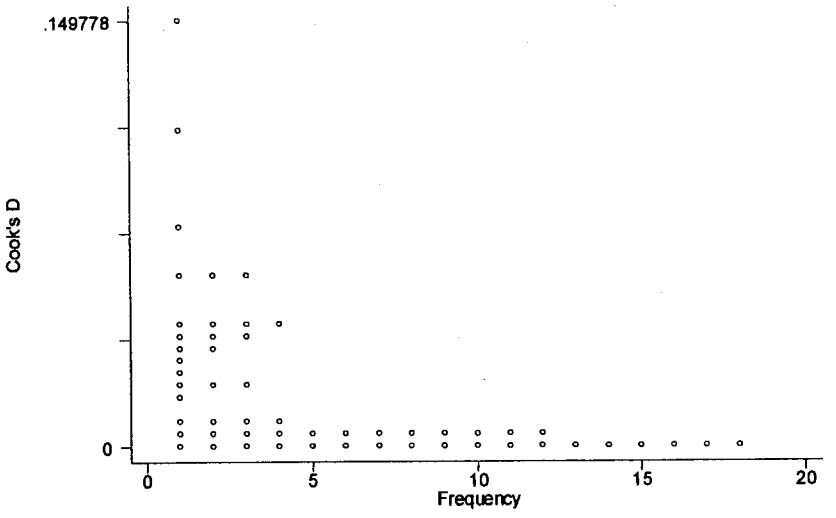
Interpretation: moderate to significant departure form linearity, calling into question the normality of the prediction.

36. Leverage values, assessing outliers



Interpretation: No major outliers identified.

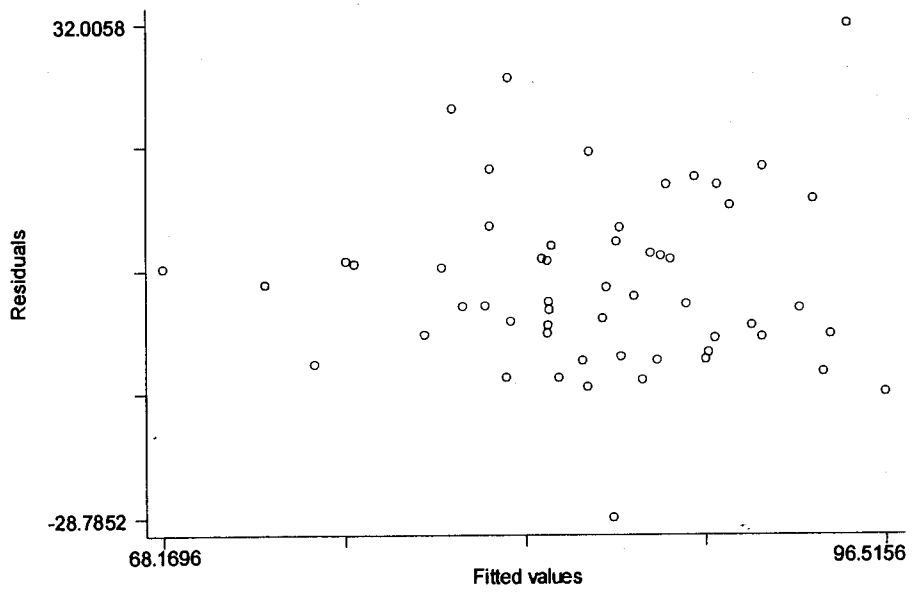
37. Cook's Distance values, assessing influential points



Interpretation: one or two potential influential points. Removal of the suspect observations did not significantly change model outcomes.

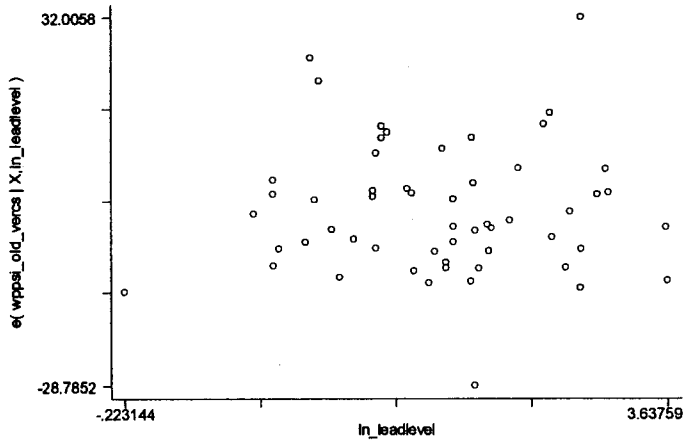
Regression Diagnostics for Model 2h: WPPSI Old Verbal IQ

38. Residual vs. Fitted Value plot assessing consistency of error variance



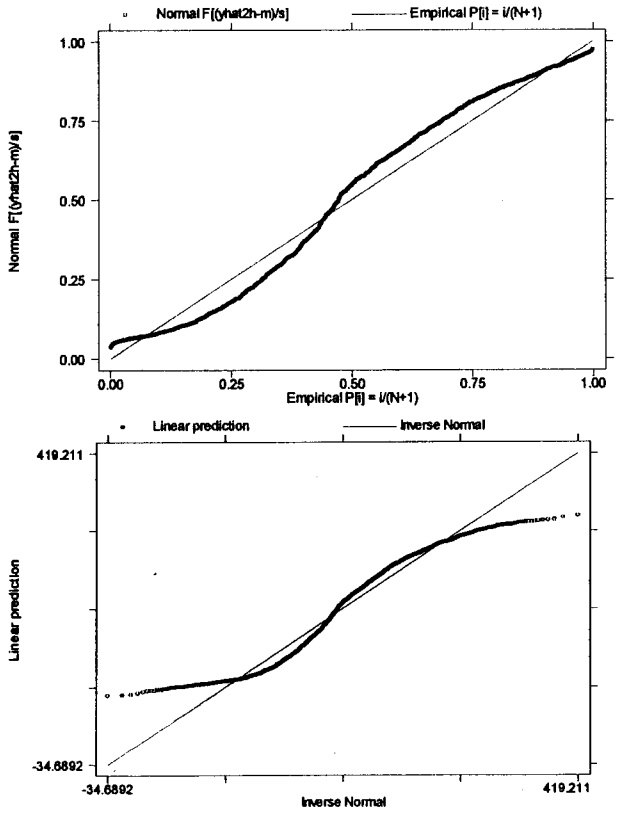
Interpretation: no clear trends in error variance. No observations with outlying residual values.

39. Residual vs. Predictor plot assessing linearity of relationship and consistency of variance



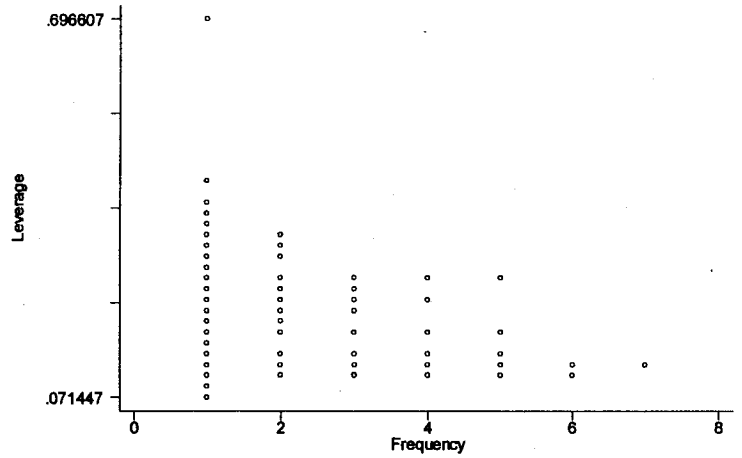
Interpretation: no trends indicating non-linear relationship. No clear trends in error variance. No observations with outlying residuals.

40. Normal probability plots



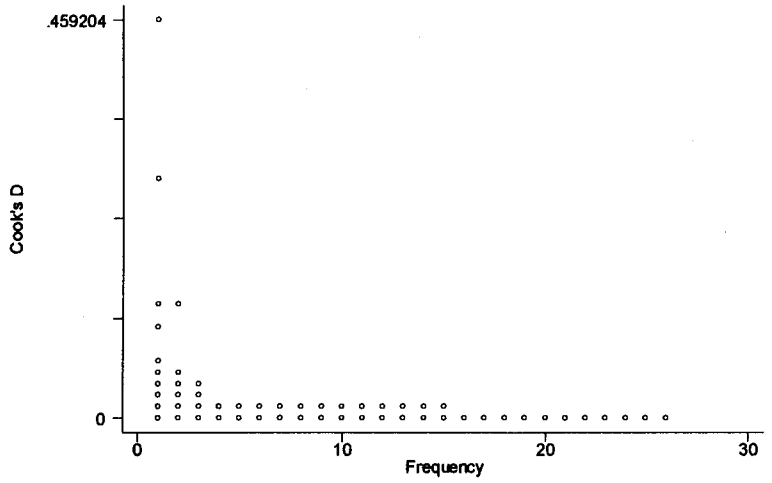
Interpretation: moderate to significant departure form linearity, calling into question the normality of the prediction.

41. Leverage values, assessing outliers



Interpretation: one potential outliers identified. Removal of suspect observation did not significantly change model outcomes.

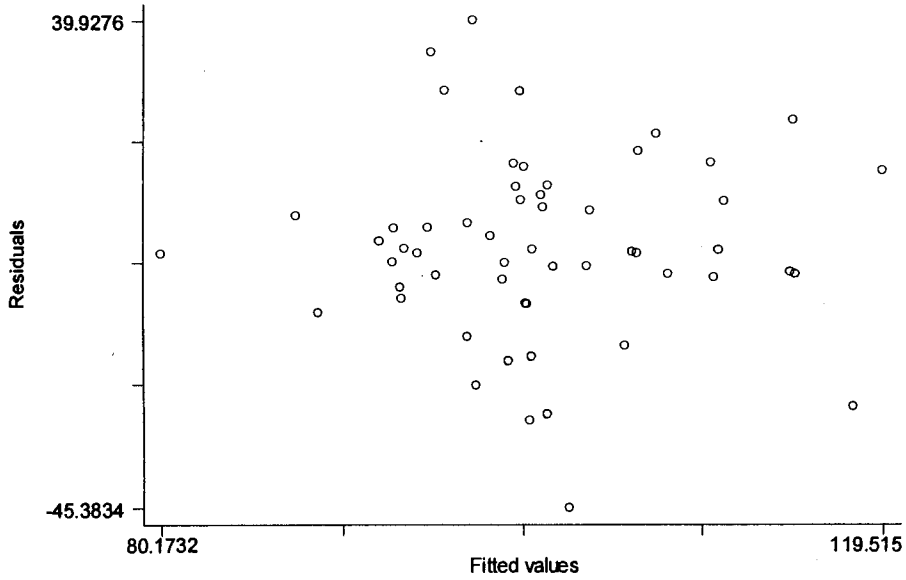
42. Cook's Distance values, assessing influential points



Interpretation: one or two potential influential points. Removal of the suspect observations did not significantly change model outcomes.

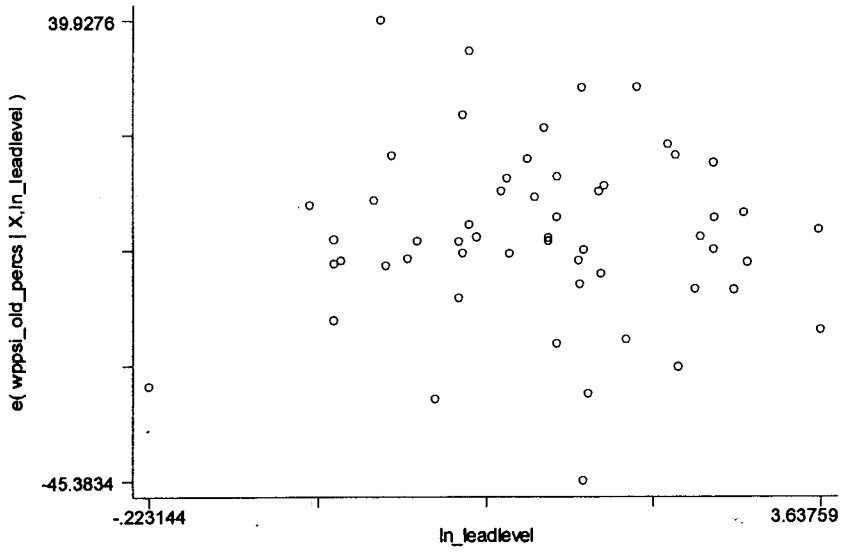
Regression Diagnostics for Model 2i: WPPSI Old Performance IQ

43. Residual vs. Fitted Value plot assessing consistency of error variance



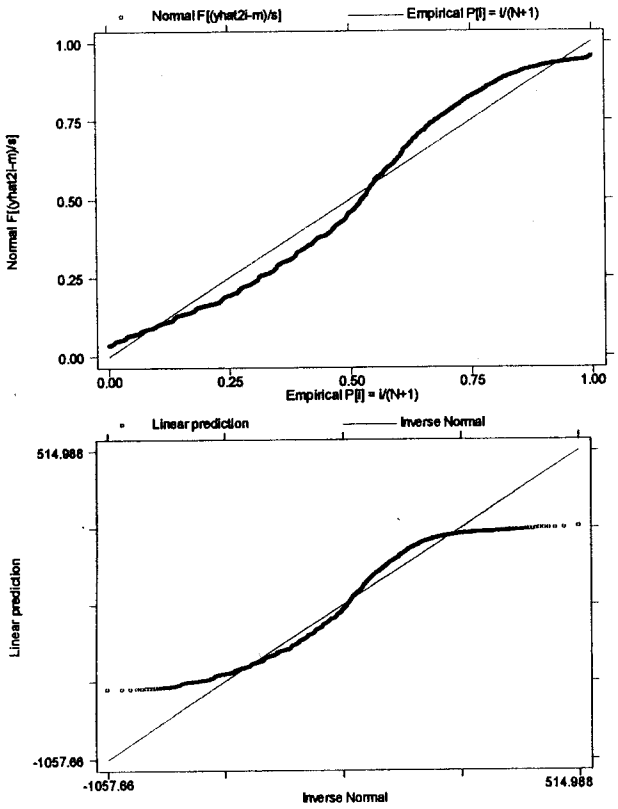
Interpretation: no clear trends in error variance. No observations with outlying residual values.

44. Residual vs. Predictor plot assessing linearity of relationship and consistency of variance



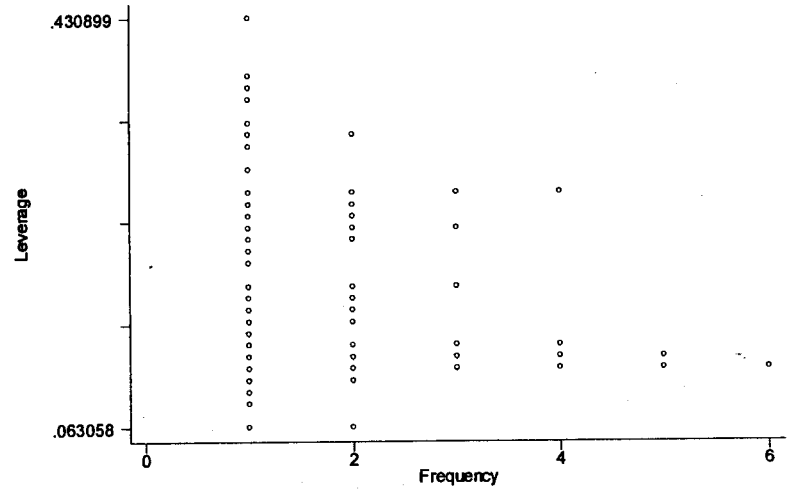
Interpretation: no trends indicating non-linear relationship. No clear trends in error variance. No observations with outlying residuals.

45. Normal probability plots



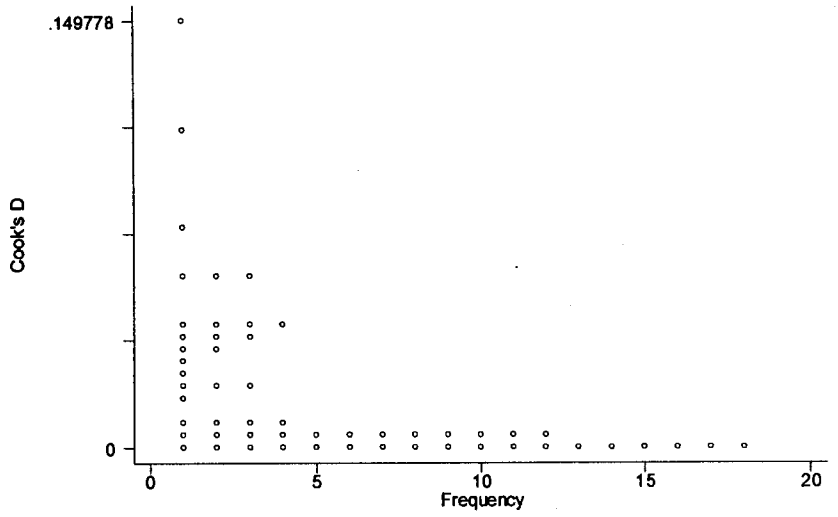
Interpretation: moderate to significant departure form linearity, calling into question the normality of the prediction.

46. Leverage values, assessing outliers



Interpretation: No major outliers identified.

47. Cook's Distance values, assessing influential points



Interpretation: one or two potential influential points. Removal of the suspect observations did not significantly change model outcomes.

APPENDIX 5: Review of the performance characteristics of the LeadCare® blood lead testing system.

Review of the Performance Characteristics of the LEADCARE® Blood Lead Testing System

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INTRODUCTION

Lead poisoning continues to be a major childhood health problem worldwide. A significant number of children acquire lead poisoning in their first year of life.[1] This harmful condition can be prevented or its effects reversed, but first it must be identified. According to recent national estimates, 1.7 million children had elevated blood lead levels. Only 25% of young children in the United States have been screened, only 33% of poor children who are most at risk have been tested and 37% of African-American children in large cities have elevated blood lead levels.[2] An effective method for preventing lead poisoning is the periodic measurement of blood lead.[3,4] In an effort to screen children more effectively and efficiently, the Centers for Disease Control and Prevention (CDC) made it a primary objective to stimulate the development of a blood lead test that can be performed at point of care. A portable blood lead analyzer for use in the physician's office laboratory (POL) is now available. It uses the same electrochemical technology that has been successfully used for blood lead testing for the past 20 years.

The LEADCARE Blood Lead Testing System (LEADCARE System) developed by ESA and ANDCARE, with partial funding by the CDC, was evaluated in multiple clinical trials. In one trial the LEADCARE System was compared to the ESA Model 3010B Lead Analyzer. The LEADCARE System was also compared to graphite furnace atomic absorption spectroscopy (GFAAS). Finally, a clinical trial was conducted using laboratory personnel in three physician office laboratories (POLs).

The comparison of the LEADCARE System with the Model 3010B Lead Analyzer and one of the GFAAS sites used blood from patients admitted to a lead poisoning referral clinic in Boston, MA. This clinic treats children found to have elevated blood lead concentrations through screening programs performed by private pediatricians, hospital outreach programs, and state and local screening efforts, and serves the entire New England region.

Another study (using GFAAS analyzed blood) was performed by a major lead outreach and referral clinic/hospital in New York City. The blood samples were analyzed using both the LEADCARE System and GFAAS.

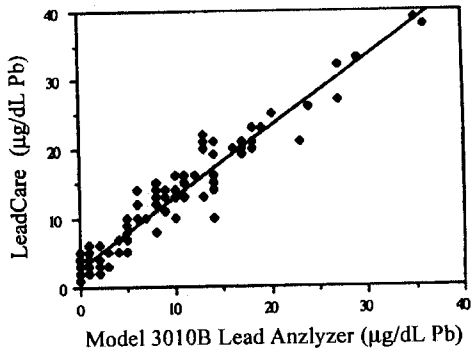
The third study included POLs located in different geographical regions of the Southeast. The POLs are in large pediatric practices and participate in the state lead screening program. The samples used in this study were capillary blood samples collected from finger stick punctures.

Only results that were less than 1.4 µg/dL (the sensitivity of the LEADCARE system) were discarded from the statistical analyses. In all cases, blood samples were obtained as part of routine care. Parents provided informed consent where appropriate. Studies were approved by the appropriate internal review boards.

ACCURACY

Clinical Laboratory Studies

97 venous whole blood samples were analyzed by both the LEADCARE System and the Model 3010B Lead Analyzer. A graph and statistics of the results are shown in Figure 1.

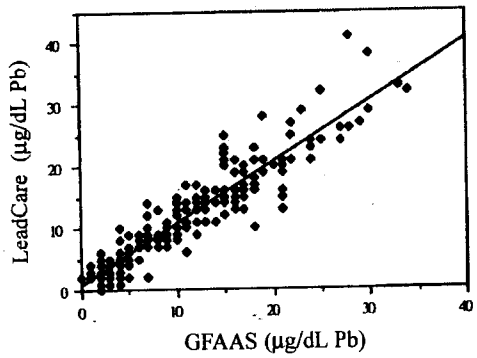


STATISTICAL PARAMETERS
LEADCARE System vs Model 3010B Lead Analyzer

Number of samples:	97
Slope:	1.023
Intercept:	2.67 µg/dL
Correlation coefficient (R):	0.97
Range:	1.6-39.3 µg/dL

Figure 1. Comparing results of the LEADCARE System and Model 3010B Lead Analyzer.

234 venous whole blood samples were analyzed by the LEADCARE System and the GFAAS method. A graph of the results and the pertinent statistical parameters are summarized in Figure 2.

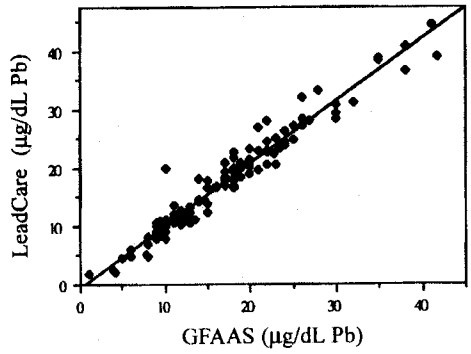


STATISTICAL PARAMETERS
LEADCARE System vs GFAAS Analytical Method

Number of samples:	234
Slope:	0.979
Intercept:	0.94 µg/dL
Correlation coefficient (R):	0.94
Range:	1.6-41.3 µg/dL

Figure 2. Comparing results of the LEADCARE System and GFAAS.

For the second comparion of results from the LEADCARE System and GFAAS method, 112 venous whole blood samples were analyzed. A graph of the results and the pertinent statistical parameters are summarized in Figure 3.



STATISTICAL PARAMETERS
LEADCARE System vs GFAAS Analytical Method

Number of samples:	112
Slope:	1.07
Intercept:	-0.57 µg/dL
Correlation coefficient (R):	0.97
Range:	1.8-44.6 µg/dL

Figure 3. Comparing results of the LEADCARE System and GFAAS.

Physician's Office Laboratory Studies

The range of capillary blood lead values collected by finger stick was 1.4 to 26 µg/dL using the LEADCARE method. Of the 179 samples analyzed, the LEADCARE System and GFAAS agreed on 170 samples at the 10 µg/dL lead decision point. This is an agreement of 95.0%. Six of the nine results that were not in agreement were false negatives. All six of the false negatives were on samples having GFAAS values less than 15 µg/dL lead, the action level recommended by the CDC. Despite the discrepancy in the results of the six samples, there would be no difference in medical intervention. Under CDC recommendations, the patient would be retested. The remaining three values that were not in agreement were false positives. These were all detected as >10 µg/dL lead by the LEADCARE System and would have been interpreted as requiring follow-up testing.

Comparison of the statistical results between the POL and clinical laboratory trials showed no significant differences. These results demonstrate that the LEADCARE Blood Lead Testing System operates in an effective manner when analyzing for lead in blood.

PRECISION

The precision of the LEADCARE System was determined at three POL sites and by trained personnel at the manufacturing site. In this study, users analyzed two blood-based lead control samples. One was a low blood lead control with a value of 5 µg/dL and the other, a high blood lead control with a value of 28 µg/dL. Testing of each sample at each of the four sites was performed in duplicate, 2 times per day for 10 days. The results of the precision study are shown in Table 1.

CONTROL	NUMBER OF TESTS	MEAN (µg/dL)	OVERALL SD (µg/dL)	OVERALL CV (%)
Low	170	5.35	0.77	14.4
High	169	28.5	2.83	9.95

Table 1. Precision data for the LEADCARE System.

CONCLUSION

These data prove that the new LEADCARE Blood Lead Testing System is an acceptable technical means for screening children with elevated blood lead levels. Instrument performance was evaluated by comparison to currently used laboratory methodologies. The LEADCARE System proved to be accurate, quick, and precise when used in the clinical laboratory or POL environment. "Lead poisoning is a common health threat to children around the world, and early detection and treatment are critical for preventing serious damage to the developing nervous system," stated Donna E. Shalala, Secretary of Health and Human Services.[5]

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3. Shannon M and Graef JW. (1992) Lead Intoxication in Infancy. *Pediatrics*, **89**: 87-90.
4. Shannon M and Rifai N. (1997) The Accuracy of a Portable Instrument for Analysis of Blood Lead in Children. *Ambulatory Child Health*, in press.
5. "FDA Approves Simpler, More Accessible Lead Poisoning Test Kit: New Device Has Big Potential for Overseas Use." *Food and Drug Admin.* HHN News Bulletin, September 10, 1997.

ACKNOWLEDGEMENT

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