An investigation of the effects of lead on children's cognitive abilities

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A thesis submitted in fulfilment of the requirements for
the degree of Doctor of Philosophy

19th August, 2011

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Rachel Earl (1106650) – 27.10.11

Amendments to Thesis

- On page 7, changed "plumbumb" to "plumbum".
- Page 13, changed second "summer" to "winter".
- Page 14 – deleted "but non-nutritive ingestion is viewed as the primary source of Pb exposure for both adults and children".
- Page 19- included mention of x-ray fluorescence as a measure of bone lead.
- Corrections made to Table 30 – gravidity and mode of delivery corrected to add to 100%.
- Page 275 added: "The likelihood that speed of information processing is important as demonstrated by these psychometric evaluations is also supported by previous investigations of the associations between nerve conduction velocity and Pb exposure (Araki & Honma, 1976; Feldman, Haddow, Kopito & Schachman,1973; Landrigan, Baker Jr., Feldman, Cox, Eden, Orenstein, et al.,1976)."
- Page 110 added: "Firstly, it is noted that in Australia primary Pb exposure pathways are likely to have changed since the collection of Donovan and Anderson's (1996) data due to the eradication of leaded petrol. Regrettably no national evaluation of Pb exposure in Australia was conducted before or subsequent to Donovan and Anderson's (1996) work. In the absence of updated data, estimates of numbers of population affected by Pb exposure are crude."

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Acronyms and abbreviation

AAIDD	American Association on Intellectual and Developmental Disabilities
ABS	Australian Bureau of Statistics
AEDI	Australian Early Development Index
APS	Australian Psychological Society
ACHIV	Achievement standard score
ADHD	Attention-Deficit Hyperactivity Disorder
ANZSCO	Australian and New Zealand Standard Classification of Occupations
BAS	British Ability Scales
BDI-II	Beck Depression Inventory - Second Edition
BoD	Burden of Disease
BOM	Australian Government Bureau of Meteorology
B-OTMP	Bruininks-Oseretsky Test of Motor Proficiency
BSID	Bayley Scales of Infant Development
BWRT	Burt Word Reading Test
CDC	The United States Centers for Disease Control and Prevention
CHC	Cattell-Horn-Carroll model of intelligence
CI	Confidence Interval
CLS	Cincinnati Lead Study
CNS	Central nervous systems
Cp	Process Capability
CPM	Raven’s Coloured Progressive Matrices
CPT	Continuous Performance Test
DAS	Dyadic Adjustment Scale
DNA	Deoxyribonucleic acid
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition.

DSOP	Daniel's Scale of Occupational Prestige
EFC	Plasma-extracellular fluid
EPA	United States Environmental Protection Agency
FSIQ	Full Scale IQ
FWS	Filtered Word Subtest
g	General intelligence
Ga	Auditory processing
Gc	Crystallised intelligence
GCI	General Cognitive Index
Gf	Fluid reasoning
Glr	Long-term storage and retrieval
Gs	Speed of information processing
Gsm	Short term memory
Gv	Visuo-spatial ability
HOME	Home Observation for Measurement of the Environment Inventory
IT	Inspection Time
ITPA	Illinois Test of Psycholinguistic Abilities
K-ABC	Kaufman Assessment Battery for Children
KBIT	Kaufman Brief Intelligence Test
KEDI-WISC	Korean Educational Development Institute – Wechsler Intelligence Scales for children
KID	Kent Infant Development Scale
K-TEA-BF	Kaufman Test of Educational Achievement – Brief Form
K-X-ray	K line X-ray fluorescence
MC HOME	Middle child Home Observation for Measurement of the Environment Inventory
MDI	Mental Development Index

MFC	Mother, Father and Child triple
MMR	Mild mental retardation
MPC	Mental Processing Composite standard score
MR	Mental retardation
mRPM	Modified Raven's Progressive Matrices
MSCA	McCarthy Scales of Children's Abilities
N	Sample size
n	subsample size
NHANES III	The third National Health and Nutrition Examination Survey
NHMRC	National Health and Medical Research council
NICU	Neonatal Intensive Care Unit
NMDA	N-methyl-D-aspartate
NONVB	Nonverbal standard score
OCS	Obstetrical Complication Scale
OR	odds ratio
Pb	Lead
PbB	Blood lead
PbD	Dentine lead
PbH	Lead in hair
PCS	Postnatal Complication Scale
PDI	Psychomotor Development Index
PIQ	Performance IQ
PO	Perceptual Organization
PPVT	Peabody Picture Vocabulary Test
PPVT-S	Peabody Picture Vocabulary Test-Spanish Version
PRDB	Parental Report of Predelinquent and Delinquent Behaviour
PRI	Perceptual Reasoning Index

PSI	Processing Speed Index
RBC	Red blood cells
RLE	Recent Life Events Questionnaire
RMSEA	Root Mean Square Error of Approximation
RPM	Raven's Progressive Matrices
RT	Reaction Time
SBIS	Stanford–Binet Intelligence Scale
SCAN	Screening Test for Auditory Processing Disorders
SD	Standard deviation
SE	Standard error
SEQ	Sequential Processing standard score
SES	Socio economic status
SICD	Sequenced Inventory of Communication Development
SIM	Simultaneous Processing standard Score
SOA	Stimulus onset asynchrony
SPM	Standard Progressive Matrices – Classic Version
SRD	Self-reported Delinquency scale
TAFE	Technical and Further Education
USA	United States of America
VC	Verbal Comprehension
VCI	Verbal Comprehension Index
VIQ	Verbal IQ
WAIS	Wechsler Adult Intelligence Scale
WAIS-R	Wechsler Adult Intelligence Scale- Revised
WAIS-S	Wechsler Adult Intelligence Scale- Spanish Version
WAIS-III	Wechsler Adult Intelligence Scale-Third Edition
WCST	Wisconsin Card Sorting Task

WHO	World Health Organization
WISC	Wechsler Intelligence Scale for Children
WISC-IV	Wechsler Intelligence Scale for Children- Fourth Edition
WISC-R	Wechsler Intelligence Scale for Children – Revised
WISC-S	Wechsler Intelligence Scale for Children – Spanish
WISC-RM	Wechsler Intelligence Scale for Children – Revised, version for Mexico
WJ-III	Woodcock Johnson-Third Edition Tests of Cognitive Abilities.
WMI	Working Memory Index
WPPSI	Wechsler Preschool and Primary Scale of Intelligence
WPPSI-R	Wechsler Preschool and Primary Scale of Intelligence-Revised
WRAT-R	The Wide Range Achievement Test - Revised

Abstract

This study explores the relationship between children's cognitive abilities and lead (Pb) exposure within the theoretical framework provided by the Cattell-Horn-Carroll (CHC) taxonomy of cognitive abilities. An abundance of research has centered upon the environmental neurotoxicant Pb and the outcomes of severe Pb poisoning (like brain damage and coma) are undisputed. Whilst people in industrialised societies have 500-to-1000 times more Pb in their bodies than their prehistoric ancestors, successful abatement programs have meant that Pb levels in humans are currently their lowest in 50 years. Paradoxically, questions have emerged about the effects of even these low levels of Pb exposure on children's cognitive abilities. Indeed, research (Lanphear, Hornung, Khoury, Yolton, Baghurst, Bellinger et al., 2005) has suggested that lower levels of Pb exposure may have a more deleterious impact on children's cognitive abilities than exposure at higher levels.

This study investigates the relationship between low-level Pb exposure (mean blood lead (PbB) concentration = 4.97 µg/dL, standard deviation (*SD)* = 3.52, range = 1.0 – 19.3) and child outcomes in two Australian communities (Port Pirie and Broken Hill) where Pb derived from ore bodies through mining and smelting remains a source of exposure. One hundred and six children (mean age = 7.96 years, *SD* = 0.59) were assessed using a battery measuring broad factors delineated in CHC theory by supplementing Wechsler IQ (Wechsler Intelligence Scale for Children-Fourth Edition**;** WISC-IV) scores with measures of CHC abilities (e.g., subtests from the Woodcock Johnson-III Tests of Cognitive Abilities). Information about parental cognitive functioning and a range of potential demographic, familial, psycho-social and environmental and pre- and post-natal variables was also collected.

In unadjusted analyses, moderate, inverse significant associations were identified between PbB levels and performance on the WISC-IV and CHC factor scores. The shape of the curve of the association between PbB levels and WISC-IV Full Scale IQ (FSIQ) and the *g* factor, respectively, was non-linear. In covariate adjusted analyses (controlling for maternal

IQ (Wechsler Adult Intelligence Scale-Third Edition), birth weight, Middle child Home Observation for Measurement of the Environment Inventory (MC HOME) scores, number of stressful life events, annual combined family income, smoking during pregnancy and duration of breast-feeding), consistent findings emerged that suggested that low-level Pb may detrimentally impact children's speed of information processing capabilities (across the three measurement approaches used in this study: WISC-IV Processing Speed Index, the Speed of Information Processing factor and Gs Invaders). When the PbB terms were added to models of WISC-IV Working Memory Index and the Woodcock Johnson-III Tests of Cognitive Abilities (WJ-III) Long-term storage and retrieval factor, these PbB variables contributed significantly to variance in children's memory performance above and beyond the variance already explained by variables considered to impact cognitive development. The variables that consistently explained the most variance in cognitive performance, aside from PbB level, were incidence and duration of breastfeeding and family income level. Higher PbB levels were significantly associated with lower paternal cognitive ability, parental education, combined family income and quality of the home environment, larger family size and later birth order.

This research supports the assertion that there is no safe level of paediatric Pb exposure and therefore contributes to the ongoing debate about whether the intervention level for childhood PbB levels should be reconsidered. In addition, this thesis discusses the confounding effects of socio-cultural and environmental factors that influence children's cognitive abilities.

Thesis Declaration

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Rachel Earl

Signed: ..... Date: 19/8/2011

Acknowledgments

I would like to take the opportunity to thank and acknowledge the help and support of a number of people in the completion of this doctoral thesis.

I am very grateful to my supervisory panel – Associate Professor Nicholas Burns, Professor Ted Nettelbeck and Associate Professor Peter Baghurst – I have valued the guidance that each of you have offered me over the course of my doctoral thesis. I also extend my thanks to each of you for the opportunity to be part of a research endeavour which married my interests in child development and cognitive psychology and subsequently fostered my emerging passion for public health.

My mother, Mary, father, Phillip and brother, Ben, have offered unwavering understanding and support of my educational choices over the many years that have culminated in the finalisation of this doctoral thesis. In particular I appreciate my mum's patience and understanding and my dad's genuine interest in this study and his ability to ask questions that challenged my decision-making. To my brother thank you for being a source of humour and for being one of the people I admire most. I would also like to acknowledge my maternal and paternal grandmothers, Agnes Faulkner and Patricia Earl, respectively; two women whom I respect for their strength, who have influenced my evolving interests and whom, I think of daily.

To my friends – I thank you for listening and making me laugh. In particular, I would like to thank Pépé for always encouraging me and only a couple of times, frustratedly asking – *um* when is this all going to be done?

I have shared my postgraduate experience with numerous Higher Degree Research and Clinical Masters students – it has been rewarding to be part of a cohort of students who are so passionate about their studies in Psychology and I have been inspired by the various academic and clinical directions these new graduates have taken. In particular I would like to thank my long-time officemate, Dr Jordan Bell for her wise, level headed approach and for her support in enabling me to envisage the end of this thesis.

I would also like to acknowledge the researchers, academics and colleagues who have inspired me over the course of my postgraduate studies; Professor Caroline Crowther, Professor Deborah Turnbull, Professor David Bellinger and Dr Claudia Stein. Each of these individuals has enabled me to conceptualise and envisage a career in the health sector which can be multidimensional, collaborative and can contribute to policy and best-practice – your examples have been a source of motivation.

I would like to acknowledge that this project was made possible through funding received from the National Health and Medical Research Council. The study would not have been possible without the valuable contributions of our research assistants including Ms Trudi Manfield, Ms Melinda Glisson-Gladman and Ms Lyn Campigli. In particular I would like to thank Trudi, who committed to this project from the very beginning – I have personally appreciated the warmth that Trudi has extended towards our participants and the dedication and patience she has shown. I would also like to thank Ms Georgia Antoniou for helping with questionnaire scanning and statistical analyses.

In addition, I extend my thanks to the primary schools in Port Pirie and Broken Hill for allowing us to approach their families through the school infrastructure.

Most of all I extend my gratitude to the families that participated in this research and invested their time in our work; this thesis would not exist without each of your valuable contributions.

Preface

The physical properties of lead (Pb) have made the heavy metal amenable to a variety of uses, so that humans have had close contact with the trace element. With no known biological function, exposure to Pb can produce neurological, haematological, nervous, renal and gastrointestinal manifestations (Bernard, 2003; Dundar, Öktem, Arslan, Delibas, Baykal, Arslan et al., 2006), even at levels that have previously been considered safe.

Children are particularly vulnerable to Pb exposure due to behavioural tendencies like outdoor play and hand-to-mouth activities (Glorennec, 2006; Jacobs & Nevin, 2006; Jacob, Ritz, Heinrich, Hoelscher & Wichmann, 2000; Jarosinska, Peddada & Rogan, 2004), the ongoing long-term development of their central nervous systems (CNS; Gao, Li, Kaufmann, Jones, Wang, Chen, Zhau & Wang, 2001; Jacobs & Nevin, 2006) and increased gastrointestinal absorption (Jacob et al., 2000; Jarosinska et al., 2004). It is now widely recognised that children can have already absorbed Pb into their bodies *in utero* via maternal Pb exposure (Dietrich, Krafft, Bornschein, Hammond, Berger, Succop & Bier, 1987; Shannon & Graeg, 1982).

Coinciding with the eradication of Pb-based paints and petrol, children's blood lead (PbB) levels have declined markedly over the last 50 years in Australia (Bernard, 2003). Nonetheless, in Australia, Pb derived from ore bodies through mining and smelting remains a dominant source of exposure for some communities (Gulson, Mizon, Davis, Palmer & Vimpani, 2004; Gulson, Mizon, Korsch, Howarth, Phillips & Hall, 1996). On a global front, exposure to Pb, via numerous pathways, remains a threat to population health, especially in developing countries.

The United States Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) define childhood PbB poisoning as occurring at a concentration of 10 micrograms per deciliter of blood (µg/dL) and above (Bar-on & Boyle, 1994) and since 1991 this has been the action level for poisoning intervention (Bernard, 2003) in the United States and Australia. In Australia, the National Health and Medical Research council

(NHMRC) in Australia endorse the 'action-level' of 10 µg/dL and state that "All Australians should have a blood lead level below 10 µg/dL" (NHMRC, 2009, p.1). Yet scientists, clinicians and public health advocates have recognised that, to date, there is no proven safe lower level of Pb in humans (Lanphear et al., 2005).

International discussions are currently taking place about the impacts of Pb upon human health and it is likely that significant reforms will follow for Pb-linked industries. For example, recently the Joint Food and Agriculture Organization of the United Nations/WHO Expert Committee on food additives (2010) withdrew the previously established provisional tolerable monthly intake of lead (25 micrograms per kilo body weight), believing it could no longer be considered health protective. In addition, in 2009, the German 'action level' was lowered to 3.5 µg/dL for children and 7 to 9 µg/dL for adults (Wilhelm, Heinzow, Angerer & Schulz, 2010). These moves foreshadow the probability that WHO and CDC will lower their endorsed lead exposure 'action level' in the near future.

It has been suggested that the effects of Pb may not be dichotomous ('all or none') but rather a continuum of adverse outcomes existing well below the cut-off for clinical poisoning. This view is a departure from the medical model of Pb poisoning and has been informed by two landmark studies that heralded an association between Pb and cognition and behaviour in children (Markowitz & Rosner, 2000). In Byers and Lord's (1943) clinical case studies, 95% of children in their sample of 20 exhibited difficulties in attention, impulse control and aggression (Hubbs-Tait, Nation, Krebs & Bellinger, 2005). This research showed that the cognitive impact of Pb existed even when sympotomology did not advance to the extremes of encephalopathy. The second study, Needleman, Gunnoe, Leviton, Reed, Peresie, Maher and Barrett (1979), used data from 158 children and found that children with the highest dentine Pb (PbD) exhibited undesirable behaviours, had longer reaction time (RT), lower intelligence scores (IQ) and slower auditory processing (Hubbs-Tait et al., 2005). The research of Byers and Lord (1943) and Needleman et al. (1979) instigated debate about the impact of low level Pb exposure (below 10 µg/dL) upon children, a level believed to be innocuous.

A number of cross-sectional and prospective studies commenced around the world in the late 1970's and early 1980's, with the charge of determining how much pre-natal and early childhood Pb exposure can be considered safe, if any at all (Dietrich, 1995). Studies have generally supported the CDC (2011) and WHO (2010) public health intervention level of 10 µg/dL (Bernard, 2003); however, in an analysis of pooled-data from seven international prospective studies (Baghurst, McMichael, Wigg, Vimpani, Robertson, Roberts et al., 1992; Bellinger, Stiles & Needleman, 1992; Canfield, Henderson Jr, Cory-Slechta, Cox, Jusko, & Lanphear, 2003; Dietrich, Berger & Succop, 1993; Ernhart, Wolf, Sokol, Brittenham & Erhart, 1985; Schnaas, Rothenberg, Perroni, Martínez, Hernández & Hernández, 2000; Wasserman, Staghezza-Jaramillo, Shrout, Popovac, & Graziano, 1998), Lanphear et al. (2005) suggested that PbB concentrations of 10 µg/dL or less, may not be safe. Lanphear et al. (2005) identified a steeper dependence of IQ on PbB concentration in the range 1 to 10 µg/dL than in the ranges above 10 µg/dL. This finding meant that the expected change in IQ points within the range 1 to 10 µg/dL doubled the expected change in the higher range 10 to 30 µg/dL (see Figure 1). This relationship between childhood PbB levels and cognition is an intuitively difficult and alarming finding and one that requires further investigation in this low-level range. Lanphear et al. (2005) summarised their research with the view that collectively, the pooled-data provided sufficient evidence to mount an aggressive campaign to eliminate childhood Pb exposure.

The effects of low-level Pb exposure remain highly controversial. Broken Hill and Port Pirie are mining and smelting communities, respectively, in Australia, where the Zinc-Pb industry has been established for over 100 years (Gulson et al., 1996). Abatement programs have been conducted and are ongoing in these communities. For example, under the *Tenby10* project the South Australian Government's Port Pirie Lead Implementation Program sought to reduce the PbB exposure levels of children (from birth to 4 years of age) to less than 10 µg/dL by the end of 2010; although targets were not fully realised. Whilst PbB levels exceeding 10 µg/dL are not unusual worldwide, these communities present higher child PbB levels than

non-industrial areas of Australia and other developed countries and hence offer an opportunity to study cognitive and behavioural outcomes in the exposure range up to and beyond 10 µg/dL.

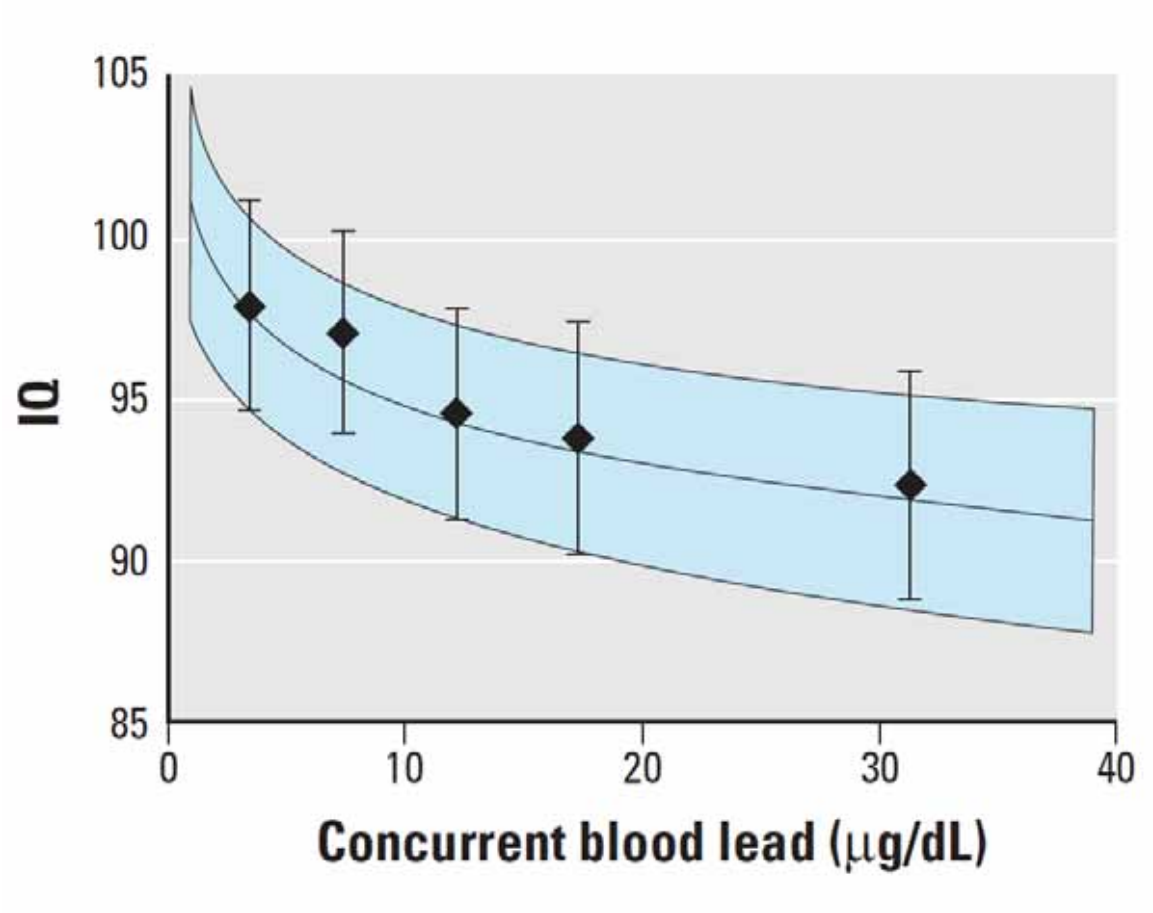

Figure 1

Log-linear model (95% Confidence Interval (CI) shaded) for concurrent PbB concentration, adjusted for Home Observation for Measurement of the Environment Inventory (HOME) score, maternal education, maternal IQ and birth weight (Lanphear et al., 2005, p. 898; Reproduced with permission from *Environmental Health Perspectives).*

Note: The mean IQ (95% CIs) for the intervals < 5 µg/dL, 5 - 10 µg/dL, 10 - 15 µg/dL, 15 - 20 µg/dL and > 20 µg/dL are shown (Lanphear et al., 2005, p. 898).

Thus, this study seeks to investigate the effects of Pb exposure on children's cognitive abilities in a low-dose exposure range within the Port Pirie and Broken Hill communities. The design of this study will seek to incorporate contemporary conceptualisations of intelligence and thorough treatment of relevant covariates into the study of Pb exposure and children's cognitive abilities.

The research proposed and presented via this thesis seeks to contribute to the ongoing debate about whether the intervention level for childhood Pb exposure should be reconsidered and lowered (Bernard, 2003).

INTRODUCTORY CHAPTERS

This study is designed to explore the impacts of lead (Pb) exposure on children's cognitive abilities. These introductory chapters seek to provide an overview of the research and knowledge base that precedes this study and informs the study design, aims and hypotheses.

Chapter 1: Lead in the environment and human body

Chapter summary

Chapter 1 provides an overview of human interactions with Pb and its uptake into the human biological system.

In particular Chapter 1 will provide an overview of the properties of Pb and a brief historical account of the uses of Pb. It will be evident that Pb has been a useful metal in the development of increasingly advanced human societies and hence human Pb exposure peaked when it was used as an additive to petrol and paint. Following considerable reforms, Pb is no longer used in petrol and paint in the majority of countries but is now a persistent metallurgic component of the human biosphere. Populations such as those in the Australian communities of Port Pirie and Broken Hill continue to be exposed to Pb through smelting and mining activities.

In addition, sources and pathways of childhood Pb exposure will be explored; Pb enters the human body through a range of pathways and it can be persistent in the human system as it settles in bone and blood.

Finally, approaches to the measurement of human Pb exposure will be discussed.

1.1 Lead: Properties and characteristics

Pb is a neurotoxin present in the earth's crust and biosphere. Neurotoxins are materials that can deleteriously impact the human nervous system and potentially play a role in behavioural change (Hubbs-Tait et al., 2005).

The chemical symbol for lead, 'Pb,' is derived from the Latin word for the metal, 'Plumbum.' Pb is amenable to a variety of uses due to its chemical properties; it has a relatively low melting point (327ºC; Rapp & Hill, 2006), is corrosion resistive, highly malleable and is a poor electrical conductor (Lewis, 1985).

Pb does not occur naturally in a metallic state and it must be derived from the smelting of Pb ore which allows it to be extracted from the other elements, metals and debris in which it is compounded. In fact, prior to human excavation of the earth's shell (Hubbs-Tait et al., 2005), Flegal and Smith (1992) estimated that the natural blood lead (PbB) levels of prehistoric humans were only in the order of 0.016 µg/dL. This means that contemporary views of "low level" exposure cannot be equated with "physiologically normal[ity]" (Hubbs-Tait et al., 2005, p. 62) - the current accepted safety level of 10 µg/dL is 625 times the level estimated in our human ancestors.

1.2 Human - Lead interactions

Lewis (1985) describes contemporary discussion about the toxicity of Pb and its suitable uses as a "mere footnote to centuries of controversy" (p.15) that continues to surround human-Pb interaction. Indeed human use of Pb has been dated back as early as the seventh millennium B.C.E in Turkey and its use has been documented in the cultures of the Ancient Romans and in the Middles Ages. This section will place current discussions about the toxicity of Pb into a historical context by exploring past uses of Pb and advances in human knowledge about Pb.

In the modern developed world, human contact with Pb and its derivatives shows two distinct historical peaks. The first peak aligned with the Industrial Revolution in the 18th

century. During this time Pb's malleability and low melting point made it a useful component of innovative production processes (Hubbs-Tait et al, 2005).

The second peak aligned with the identification of tetraethyl Pb, an organic form of Pb which became an anti-knock, octane-boosting additive to petrol (Hubbs-Tait et al. 2005; Lewis 1985). The use of Pb as a petrol additive enabled engines to perform more efficiently and for the automotive industry of the United States of America (USA) to market petrol-run vehicles globally. The insidious nature of leaded petrol was identified early in its use via the 'insanity' and eventual death of factory workers in proximal contact with leaded petrol (Lewis, 1985). In the 1970's the United States Environmental Protection Agency (EPA) set compulsory industry guidelines for the use of leaded petrol and Pb levels in petrol and the push to reduce levels of Pb in petrol and associated emissions was aided in 1975 when the automotive industry developed pollution-reducing catalytic converters fuelled by unleaded petrol. This technology has enabled the eventual banning of leaded petrol in Australia where it is now mandatory for all petrol-engine motor vehicles manufactured after 1 January 1986 to use unleaded petrol (Department of Environment and Conservation New South Wales, 2006); however, leaded petrol continues to be used for transportation in some developed and developing countries (Rahman, Maqbool & Zuberi, 2002; Kadir, Janjua, Kristensen, Fatmi & Sathiakumar, 2008) and in rural areas for farming equipment (Bryant, 2004).

As Berry and Garrard (1994) indicated "although background levels of lead in the environment are generally extremely low, people are exposed to lead sources virtually all the time" (p.24). General population sources of Pb exposure in the developed world are summarised in Table 1. Other researchers have linked Pb levels to environmental factors such as tarred roads, overcrowding, waste incineration, poor household hygiene (Nriagu, Jinabhai, Naidoo & Coutsoudis, 1992), number of siblings, carpeted flooring (Zejda, Grabecki, Król,

Panasiuk, Jedrzejczak, et al., 1997), consumption of contaminated food[1], water and passive smoking (Bryant, 2004; Department of Environment and Conservation, New South Wales, 2006; Glorrennec, 2006).

Table 1

Examples of common contemporary sources of lead exposure.

Domain	Use
Occupational	Lead mining and refining, mining waste dumps, plumbing and pipe fitting, auto repair, glass manufacturing, printers, battery manufacturing and recycling, construction work, plastic manufacturing
Environmental	Lead paint, soil or dust near roadways or persistent lead-painted homes, plastic window blinds, plumbing leachate (from pipes or solder), ceramic ware, lead-core candle wicks, leaded water pipes
Hobby/lifestyle	Glazed-pottery making, target shooting at firing ranges, lead soldering, stained-glass making, painting, car or boat repair, folk remedies, petrol sniffing, costume jewellery, cosmetics

Note. Adapted from Sanborn, Abelsohn, Campbell & Weir (2002, p.1288) and Maharachpong, Geater & Chongsuvivatwong (2006).

[1] Although several authors (Gulson et al., 1999; Gulson, Mizon, Korsch, Howarth & Hall, 1996; Manton, Angle, Stanek, Reese & Kuehnemann, 2003) have dismissed diet as a statistically significant contributor to PbB levels, the portion of Pb that can be attributed to food and diet is currently under consideration by the WHO Initiative to Estimate the Global Burden of Foodborne Disease (WHO, 2007). This WHO Initiative follows from the work of Fewtrell, Kaufmann and Prüss-Üstün (2003) and seeks to estimate the contribution of dietary Pb to PbB and to estimate the burden of disease from food for different regions based on PbB (WHO, 2007).

Indeed, important Pb sources in modern times have been via Pb-based paint and Pb plumbing. The consumption of Pb contaminated drinking water can be the product of corrosion of Pb water pipes, pipe fittings, solder, fluxes and Pb sediment (Bryant, 2004). Buildings constructed before 1930 frequently had Pb pipes and up till the mid 1980s Pb soldering was the method of choice for plumbing (Bryant, 2004). Recently Bryant (2004) collected drinking water samples from 292 schools in Philadelphia, USA and it was noted that over half (57.4 %) of these schools had drinking water Pb levels that exceeded 20 µg/g, the EPA action level. In summary, Hubbs-Tait et al. (2005) indicated the systematic exposure of humans to Pb has been facilitated by unknowingly coating entire homes with Pb, emitting Pb into the air and by using Pb to carry essential water supplies.

Coupled with reductions (and eradication) of leaded petrol in the developed world, distinct declines in Pb levels can also be linked to increases in public awareness, screening and prevention techniques, reduction in workplace exposure, and bans on Pb use in paint, food cans and water plumbing (Kaufmann, States & Matte, 2003). However, despite the huge gains that have been made, the global environmental Burden of Disease (BoD) work conducted by Fewtrell, Kaufman and Prüss-Üsten (2003) estimated that, in the year 2000 although fewer than 10% of children worldwide had PbB concentrations exceeding the WHO level of concern, 10 µg/dL, 99% of these children lived in developing countries (WHO, 2010). While Pb exposure is a global public health concern, detriments linked to Pb exposure contribute to the health inequality faced by populations in developing countries.

1.2.1 Lead mining and smelting communities: Port Pirie and Broken Hill

Australia has grown into the largest producer and exporter of Pb ore concentrate worldwide and a dominant Pb refiner amongst the developed countries (Department of Environment and Conservation, New South Wales, 2003). Following from Table 1 where Pb mining and refining is recognised as major occupational sources of Pb exposure, Pb becomes an environmental contaminate for communities that live in proximity to Pb mines and

smelters. These communities are high-risk groups because they are situated in pollution 'hotspots' (Fewtrell et al, 2003). Two such Australian industrial communities have been identified as the locations of this study exploring Pb and childhood outcomes; Port Pirie, situated on the eastern Spencer Gulf in South Australia (Figure 2), approximately 240 kilometres (kms) north of the capital city of South Australia, Adelaide (33.17 °S, 138.01 °E; Australian Government Bureau of Meteorology; BOM, 2011) and Broken Hill in western New South Wales (31.88 °S, 141.59 °E; BOM, 2011a; see Figure 2).

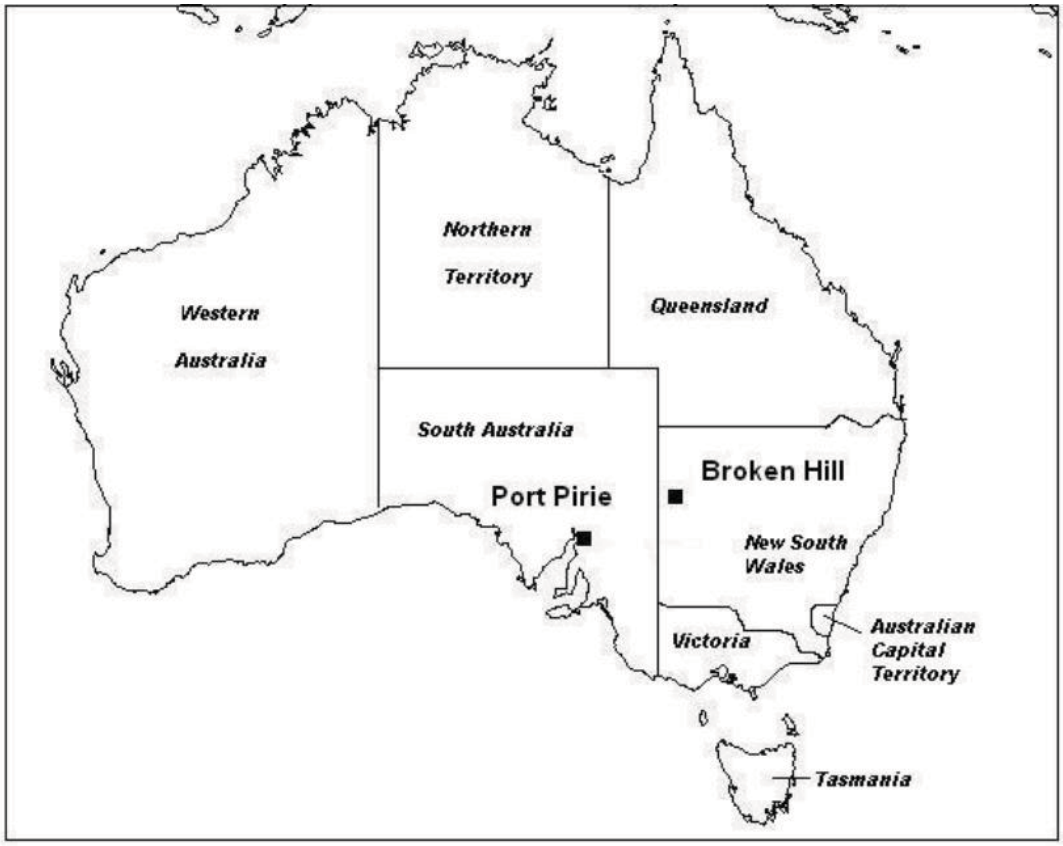

Figure 2

Location of study areas in Australia; Port Pirie in South Australia and Broken Hill in New South Wales.

A silver-Pb-zinc field was discovered in Broken Hill in 1883 (Broken Hill Associated Smelters, 1971) and the mining industry was quickly established around the deposit, the remnants of which continue to be mined to this day. Port Pirie was the nearest seaport to

Broken Hill at an approximate distance of 400 kms and hence it was a natural centre for what would become the largest Pb-Zinc smelter in the Southern Hemisphere. The smelter, located on the northern periphery of Port Pirie has provided employment and industry to residents of Port Pirie for over a century.

Hence, dust and fumes have been deposited in and around Broken Hill and Port Pirie for over 100 years via widely dispersing and environmentally persistent particulate materials that are by-products of the burning, sanding, scraping and cutting of Pb ore bodies (Department of Environment and Conservation, New South Wales, 2003) undertaken in the smelting and mining industries (Berry & Garrard, 1994; Esterman & Maynard, 1998). This means that residents of Port Pirie and Broken Hill are not only vulnerable to present day contamination of regional air and soil but also historically persistent contamination (White, van Leewen, Davis, Maddaloni, Hogan, Marcus & Elias, 1998). In addition, emission and effluent by-products of Pb smelting are released into the human environment, including sulphur dioxide, arsenic, cadmium, copper, mercury, zinc, iron and other particulates (World Bank Group, 1998).

Thus communities like Port Pirie (population estimate: 13,000 people; Australian Bureau of Statistics; ABS, 2007) and Broken Hill (population estimate: 18,500 people; ABS, 2007a) are particularly vulnerable to the deleterious impact of Pb exposure because there is more Pb in their environment. Specifically, Glorennec (2006) estimated that for a 2-year-old living in proximity to a mine, the exposure dose per kilogram of body weight that can be expected is 5.5 microgram per kilogram (µg/kg; Glorennec, 2006). Another investigation by Boreland and Lyle (2006) showed that the levels of Pb dust on windowsills and floors in Broken Hill homes exceeded the levels of concern for Pb on internal surfaces set by the EPA (2001) on at least one windowsill in 75% of homes and on 24% of internal floors. While remediation efforts in Boreland and Lyle's (2006) study significantly reduced Pb levels in homes and children over a 13 month period, this work illustrates the heightened exposure risk for children in these communities.

From a climatic viewpoint, some researchers (Laidlaw, Mielke, Filippelli, Johnson & Gonzales, 2005) have argued that contaminated Pb material may disperse more widely and readily during the warmer months of the year and in hotter climates. Port Pirie and Broken Hill are located in arid regions of Australia (see Figure 2) where the mean maximum temperature across the year is very similar; ranging from approximately 32ºC in summer to between 15ºC and 16ºC in winter (BOM, 2011; 2011a). Hence climatic conditions may further exacerbate the Pb exposure vulnerability of residents of Port Pirie and Broken Hill.

According to reports from the State of Public and Environmental Health Report 2009-2010 (Department of Health, Government of South Australia, 2010), the greatest decreases in childhood PbB levels were observed in the period 2006 – 2008 and are linked to 'major capital works' undertaken at the Pb Smelter. The trend in reduction in Port Pirie PbB levels and increase in numbers of children with PbB levels below 10 µg/dL is represented in Figure 3.

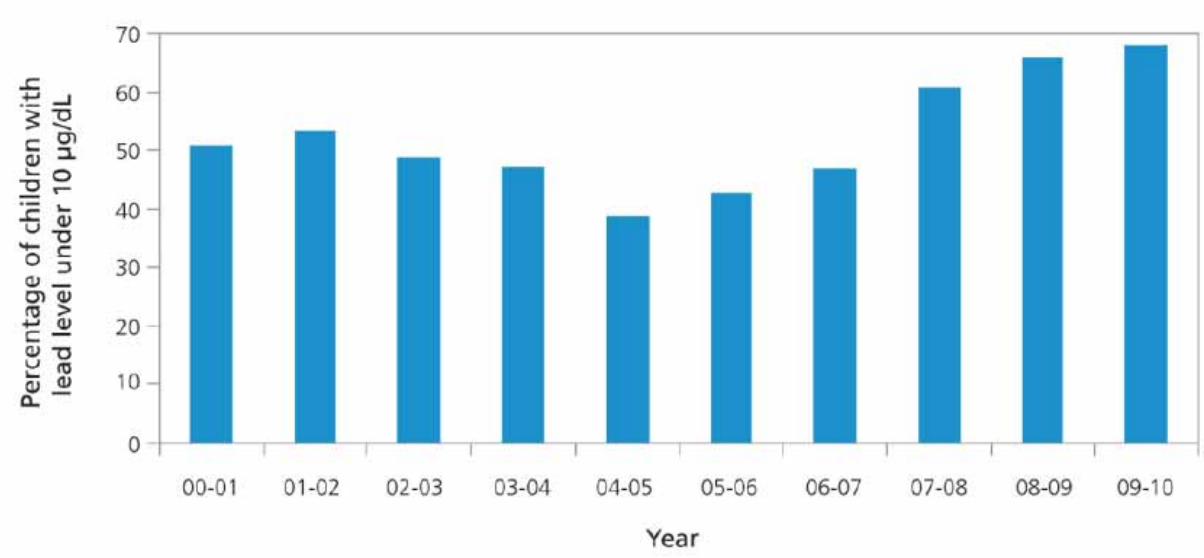

Figure 3

Port Pirie children's blood lead levels from 2000–01 to 2009–10 (Department of Health, Government of South Australia, 2010, p. 53; Reproduced with permission from the Department of Health, Government of South Australia).

Note. Data used for this graph are children's *maximum* PbB level test results, which represent the worst outcome a child may suffer and do not include surrogate maternal PbB level test results.

In Broken Hill, Balding and Reddan (1997) credits government initiatives, coupled with industry efforts to reduce emissions as responsible for declines in childhood PbB levels which saw the average PbB levels of children under 5 years of age decline from 18.4 µg/dL in 1991 to 10.8 µg/dL in 1996. More recent data (Population Health Division, New South Wales Government, 2008) estimate that the percentage of children with PbB levels less than or equal to 10 µg/dL in Broken Hill has increased from 14% in 1991 to 74.9% in 2007. See Appendix A for an overview of initiatives that have been undertaken in Port Pirie and Broken Hill to reduce children's PbB levels.

1.3 Exposure pathways – paediatric acquisition of lead

Pb is a multi-media contaminant because it can be found in soil, dust, water, food and the air (Bryant, 2004; Glorrenec, 2006; Gulson, Mizon, Korsch & Taylor, 2006) and it can enter the human body via skin absorption, ingestion, inhalation (Hulka & Wilcosky, 1988; White et al., 1998) and by crossing the placenta *in utero* (Department of Environment and Conservation, New South Wales, 2003). The multi-media nature of Pb means that source attribution[2] can, at times, be a challenge for remediation and exposure management programs.

Pb uptake occurs when Pb that has entered the body is transferred to blood plasma (White et al., 1998) and is circulated throughout the body, subsequently settling in bone and soft tissue (Dorsey et al., 2006). Individuals vary in Pb exposure level even if there is a common source of environmental exposure and this is due to "differences in behaviour, household characteristics and individual patterns of lead uptake and biokinetics" (White et al., 1998, p.1515).

White et al. (1998) developed the Integrated Exposure Uptake Biokinetic Model for Pb in children to capture the multiple and complex pathways for paediatric Pb exposure (see Figure 4). As illustrated in Figure 4, the gut and lungs are the main entry points for Pb into the human body. From the gut and lungs, Pb is transferred to blood plasma and central plasma-

[2] Source attribution seeks to identify the route or pathway of environmental Pb exposure.

extracellular fluid (EFC) and is subsequently circulated widely to blood, bone (trabecular and cortical), the kidneys, liver and the other soft tissue. Some of the original Pb intake is excreted from the body via urine, sweat, skin, hair and faeces.

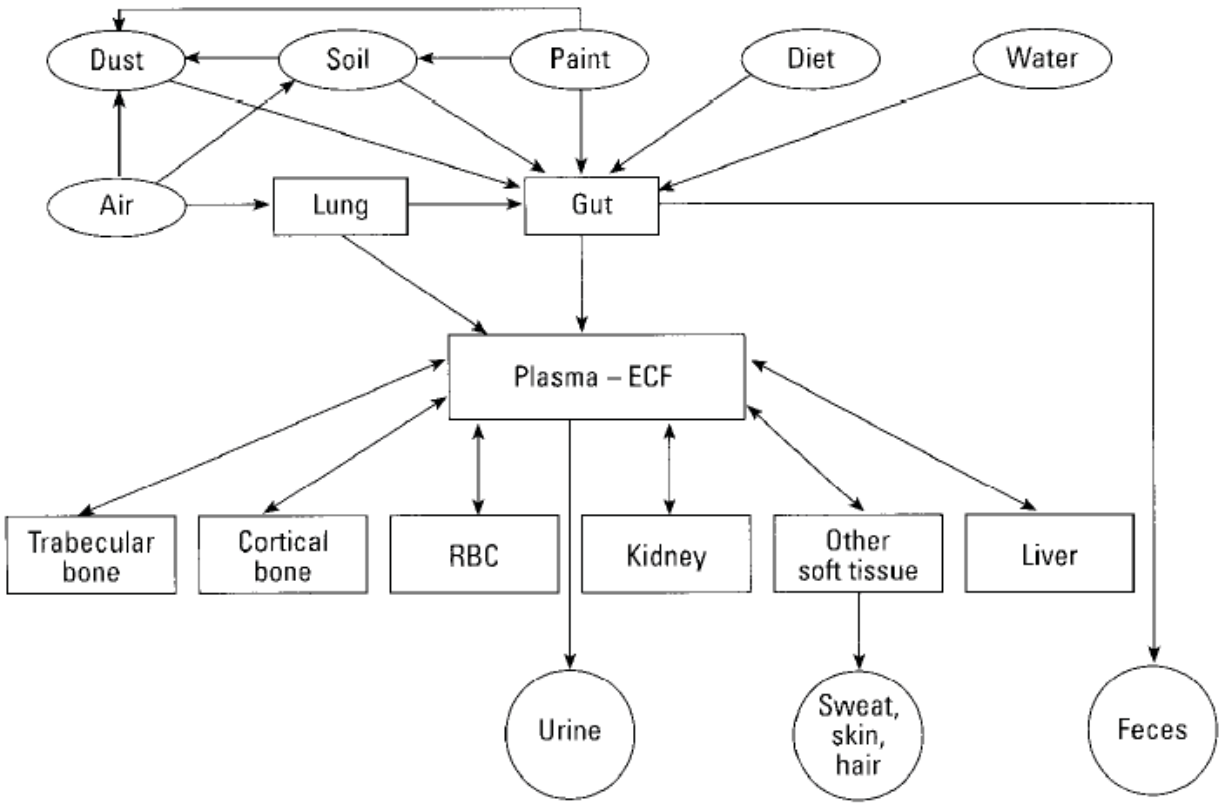

Figure 4

Conceptual diagram of the movement of environmental lead into and through the human body. Oval shapes represent environmental media and pathway uptake (White et al, 1998, p. 1515; Reproduced with permission from *Environmental Health Perspectives).*

Note. Rectangular boxes represent biokinetic components; the large rectangle is blood plasma, which mediates distribution of Pb throughout the body. Circles represent elimination outlets (White et al, 1998, p. 1515). RBC is Red Blood Cells and EFC is central plasma-extracellular fluid.

Children are particularly vulnerable to Pb exposure for a variety of behavioural, social, environmental and biological reasons:

- Breast milk is a potential source of Pb exposure which is unique to infancy and it contributes to a child's initial body Pb burden which is acquired from their mother *in utero*. Levels of Pb in breast milk represent the mother's current levels of Pb burden as well as all previous exposures, because bone Pb is mobilised during pregnancy and lactation, and subsequently released into blood and lactated milk.[3]
- Children explore their world through developmentally appropriate hand-to-mouth behaviour and geophagia (eating earthly matter such as clay or chalk; Glorennec, 2006), which places them at heightened risk of Pb exposure due to ingestion of contaminated soil, dust, or persistent Pb paint chips (Bryant, 2004).
- Additionally, children who engage in pica (the habitual eating of non-food objects) are at heightened risk of exposure; Department of Environment and Conservation, New South Wales (2003) estimate that children generally ingest 60 - 100 µg/day of soil and this increases to 20 grams/day with pica. Greene, Ernhart and Boyd (1992) confirmed an association (r = 0.30) between pica and PbB levels at 2 years of age.
- Further exacerbating the impact of children's hand-to-mouth behaviour, is evidence that 50% of all ingested Pb is absorbed into children's developing gastrointestinal tract compared with 10 - 15 % absorption in adults (Department of Environment and Conservation, New South Wales, 2003).
- Children also eat, drink and breathe comparatively more per unit body weight than adults, increasing their Pb intake (American Academy of Pediatrics Committee on

[3] Recent studies have called for universal screening of Pb levels for breastfed infants due to evidence that average Pb levels in breastmilk can vary from between 2.5 µg/dL and 10.8 µg/dL dependant upon maternal exposure pattern (Lozoff et al., 2009) and that duration of breastfeeding (sole milk source) correlated with Pb concentration (r values = 0.14 to 0.57; p values = 0.06 to < 0.0001). Despite the possibility of exposure to Pb and other toxins or disease via breast milk, consumption of breast milk is considered the most efficient form of nutrient delivery for infants and remains optimal even despite the possibility of neonatal and infant Pb intake (Ettinger et al., 2004). Indeed, WHO recognises a small number of maternal conditions that can warrant the permanent or temporary cessation of breastfeeding and at this time, Pb toxicity has not been named among these conditions (WHO, 2009).

Environmental Health, 2003, cited in WHO, 2010). At 2 years of age, children are estimated to inhale 6 cubic metres (m^3) of air per day (which gradually increases to 15 m^3/day by adulthood, Department of Environment and Conservation, New South Wales, 2003) and their inhalation zone is more proximal to the ground than for adults.

- Children spend the majority of their time in a single environment such as the home where Pb can accumulate (WHO, 2010) as evidenced by the work of Boreland and Lyle (2006) in Broken Hill.
- Children have limited autonomy over their surroundings (WHO, 2010); they are reliant upon caregivers to understand environmental threats to their health and wellbeing and to safeguard them.
- There is an increased likelihood of nutritional deficiencies in early childhood which can lead to increased Pb absorption (WHO, 2010).
- From a preventative public health perspective, children have many years of life ahead of them and time for absorption and accumulation of Pb; early life exposure may set them up for a lifetime of consequences (WHO, 2010).
- Children's developing biological system is highly susceptible to Pb exposure because its growth is rapid, complex and delicate (WHO, 2010). This is especially true in the developing brain where neurological damage attributed to Pb is "irreversible and untreatable" (WHO, 2010, p. 22).
- The field of epigenetics explores the impact of environment and lifestyle factors on the expression of genes and there is evidence that early life Pb-exposure may reprogram genes (WHO, 2010) impacting life-course development, disease incidence and vulnerability and potentially impacting subsequent offspring.
- WHO (2010) also link low-level Pb exposure to deficits in immune system development which can diminish the integrity of the immune system during periods of stress over the life course.

Hence, it is evident that children represent a subset of the population who are especially vulnerable to Pb exposure and thorough and ongoing efforts to understand how Pb impacts children's functioning is warranted and necessary.

1.4 Measurement of Lead Exposure

Although the brain is the organ of most interest when investigating the impact of Pb upon childhood cognitive abilities, measurements of Pb levels in the brain cannot be obtained *in vivo*. Rather, laboratory procedures enable identification of toxins in body tissues and fluids as internal dose markers (Hulka & Wilcosky, 1988). These internal dose markers are imperfect measures that can approximate levels of Pb in humans. Once Pb enters the human body, it settles in bone, blood, soft tissue (Dorsey et al., 2006) and hair (Pb in hair; PbH: Pb estimates taken from hair have been used as a marker of Pb exposure in the literature; Minder, Das-Smaal, Brand & Orlebeke, 1994); these sites can be sampled in order to estimate Pb exposure level. However, estimation of Pb exposure level using internal dose markers is complicated because:

- Pb is metabolised differently in each area of the body limiting the suitability of some samples;
- Pb levels in the body require continuous recalculation and single measures can only be viewed as a cross-sectional measure of exposure.

In consideration of a Pb marker suitable for clinical decision-making and research, Hulka and Wilcosky (1988) offer a number of cautionary considerations. Primarily, it is important to recognise that markers are limited in generalisabilty because normative data sets (by age and gender) are not available. Further, measures should be used that do not require "extraordinary collection or transportation procedures en route to [the] laboratory" (Hulka & Wilcosky, 1988, p.88); that is, samples that are not highly invasive to obtain and that retain their characteristics whilst being stored. In sum, where resources permit, it would be ideal for research studies in this field (either cross-sectional or prospective in nature), to use a mixed

marker approach to the assessment of Pb exposure, to acknowledge the limitations of each marker and provide the most comprehensive body-Pb burden picture for each child.

Dentine Pb (PbD) and PbB levels are particularly important internal dose markers and will be discussed in greater detail.

1.4.1 Measurement of Pb in human bone

Measurement of Pb in human bone represents an accumulation of Pb from all previous exposure. This is because 90% of Pb is stored in bone, with a half life ranging from years to decades (Ettinger et al., 2004).

Pb levels in bone have been non-invasively estimated via measurements taken from shed deciduous teeth and through x-ray fluorescence. Measures of bone lead alleviate some problems of causal inference because data are a more accurate representation of total body-Pb burden.

The collection and analysis of measures of bone lead levels and, in particular PbD, is beyond the resources of the current study, however PbD is a measurement approach used consistently in the research literature and studies using PbD will be further discussed in Chapter 2.

1.4.2 Measurement of Pb in human blood

The half-life of Pb in blood is approximately 30 days (Dorsey et al., 2006) and so PbB level is viewed as a transient marker of exposure (Hulka & Wilcosky, 1988) because it offers a cross-sectional picture of dose rather than a view of total body-Pb burden (Hubbs-Tait et al., 2005).

PbB measurements are limited by variation in individual behaviour patterns and biological process:

- Due to the metabolisation of Pb in the blood stream, PbB does not offer insight into total body-Pb burden of a child. Hence, the use of PbB as a marker of Pb exposure

may underestimate the amount of Pb impacting and interacting with the developing child's brain and body.

- Due to developmental patterns, ages 2-to-3 years are periods of heightened PbB levels (PbB levels tend to decline steadily from 2-to-3 years of age onward), coinciding with a child's locomotive and exploratory patterns, which bring them into increased contact with environmental Pb (Whaley, 1990). Thus measurements taken from 7 or 8 year olds do not necessarily capture the peak in PbB levels that a child may have experienced several years earlier. As Hubbs-Tait et al. (2005) summarised, "[if] one was to find that children with blood-lead levels at about 10 µg/dL perform significantly worse than with children at levels less than 5 µg/dL, one cannot conclude that a level of 10 produced the damage" (p.65).
- Fleming, Chettle, Webber and O'Flaherty (1999) reported that Pb has a greater affinity with the plasma component of blood, rather than the red blood cells, the erythrocytes. This is important because it is believed that concentration of blood plasma can influence the degree to which Pb is transported around the body, producing additional inter-individual variation.
- PbB is responsive to "evanescent environmental change" (David, Wintrob & Arcoleo, 1982, p. 147) and therefore can be unstable across even short periods of time.
- PbB levels may not be in a range of 'concern' even when there are toxic implications for the organism, or when toxicity has occurred recently, because uptake of Pb into the human body is highly variable and associated detriments are likewise variable; a Pb exposure level which is inconsequential for one child may be vastly deleterious for another based on their bodies' biokinetics and their risk factors.

Despite these limitations, the general consensus is that the limitations of PbB do not detract from its "manifold usefulness" (David et al., 1982, p. 147) as an easily obtainable, valid measure of Pb exposure when it is extracted and analysed using standardised methods (Tong, 1995).

In this study, PbB will be used as a marker of childhood Pb exposure through capillary blood sampling, which is considered a valid alternative to venous sampling which can be more intrusive and time consuming to collect (Parsons, Reilly & Esernio-Jenssen, 1997; Schlenker, Johnson, Mark, Layde, Linke, Murphy & Matte, 1994). However, it is noted that Binns, Campbell & Brown (2007) observed incongruence between simultaneously sampled capillary and venous PbB samples (estimated between 10 and 15µg/dL) but Schlenker et al. (1994) quantify these as, on average, at less than 1 µg/dL difference. Binns et al. (2007) report that the sensitivity and specificity of capillary PbB sampling for levels below 10µg/dL is yet to be examined by evaluative research efforts, hence this approach could limit the accuracy of Pb estimation.

Having discussed the characteristics of Pb, how humans come into contact with Pb and its uptake and measurement in the human body, Chapter 2 of this thesis will discuss the associations between Pb and children's cognitive abilities.

Chapter 2: Lead exposure and children's cognitive abilities: cross-sectional research

Chapter summary

Turning to the relationship between Pb and cognitive abilities, this chapter will chronologically review the knowledge gains made to date from cross-sectional research efforts:

The contributions of early research findings and animal studies. Byers and Lord (1943) observed that children recovering from overt Pb poisoning showed pervasive cognitive and behavioural deficits. In addition animal studies provided empirical evidence of neurological changes that may be linked to Pb exposure.

Cognitive deficits in the absence of classical poisoning. Extending from Byers and Lord (1943), Needleman et al. (1979) and other authors provided evidence that detriments to children's cognition and behaviour could be observed in the general population at relatively low-levels of Pb exposure.

Efforts to establish the nature of the relationship between Pb and children's cognitive abilities. Cohort studies initiated following Needleman et al. (1979) consistently identified a deleterious impact of Pb exposure on childhood cognitive abilities, but these investigations were not able to unequivocally identify an ability that was susceptible to Pb exposure. Nevertheless the cross-sectional research efforts identified new research gaps and agendas which heralded the establishment of prospective studies in the field.

2.1 Lead exposure and children's cognitive abilities

Knowledge of Pb toxicity is well established (Fewtrell et al., 2003) and both acute and chronic Pb exposure has been linked to a number of adverse physiological outcomes in humans;[4] CDC (2011) state that Pb deleteriously impacts virtually every biological system of the human body and Fewtrell et al. (2003) estimate that mild mental retardation (MMR; defined by Fewtrell et al., (2003) as IQ scores between 51 - 70)[5] and poor cardiovascular outcomes (due to increases in blood pressure) associated with Pb exposure, amounted to almost 1% of the global burden of disease, with the highest burden in developing regions.

For the developing child, Pb exposure in the range 100 - 150 µg/dL can cause death and exposure levels in the vicinity of 80 - 100 µg/dL may produce childhood encephalitis[6] (Hubbs-Tait et al., 2005). The incidence and devastation of Pb related encephalitis serves as evidence for the highly toxic impact that Pb has upon the juvenile brain.

The extreme impacts of Pb upon the human brain have long been observed and recognised but the more subtle detriments and nuances of damage have only been recognised more recently. Specifically, understandings of the impact of Pb upon neurocognition were advanced in the 1940s when Byers and Lord (1943) observed changes in child behaviour in the absence of what would have been considered 'high' Pb levels, 'clinical poisoning;' or the syndrome 'plumbism' (Needleman, Schell, Bellinger, Leviton & Allred, 1990). This observation marked an important departure from the dichotomous medical viewpoint of either

[4] For example, anaemia in children and adults, gastrointestinal symptoms in children, cardiovascular disease in adults, effects on the reproductive health of both men and women (increased incidence of miscarriages, still and preterm birth, decreased sperm count and sperm abnormalities; Fewtrell et al., 2003), changes in growth, pubertal development and endocrine function in females (Euling, Selevan, Pescovitz & Skakkebaek, 2008), variance in childhood height, weight and chest circumference (Schwartz, Angle & Pitcher, 1986) and reduced thyroid function (as measured by tests of free thyroxin) in adolescent males (Dundar et al., 2006).

[5] While Fewtrell et al. (2003) included the outcome variable of MMR in children in their Global Burden of Disease estimation, typically 'loss of IQ points' would not be conceptualised as a disease and hence overlooked by purist policy-makers and epidemiologists. Fewtrell et al. (2003) recognised 'IQ loss' as a marker for neurocognitive damage and the use of psychometric as useful communicators of the impact of Pb to the global public health community. Indeed, a move from the bipolar medical viewpoint has required the engagement of allied health and research fields, such as psychology, and more subtle neurological effects of Pb exposure have since been quantified through the use of psychometric tools and research paradigms.

[6] Encephalitis is characterised by edema, blood hemorrhaging or increased intracranial pressure and presenting as a loss of consciousness, seizure, persistent vomiting and ataxia (Hubbs-Tait et al., 2005), hyperirritability, tremor, optic disks, hyperactive reflexes, bulging fontanel, cerebral palsy, optic atrophy, hyperactivity, mental retardation (Rummo, Routh, Rummo & Brown, 1979).

‘poisoned’ or ‘unpoisoned’ children and hence lead to a shift in understandings of the impact of Pb on the developing human brain.

The knowledge gains that have heralded the current discussion about low-level Pb exposure are extensive and this research base requires careful consideration. Discussions will commence with an overview of early findings, animal models and a thorough review of the landmark work of Needleman et al. (1979) - studies using varying methodologies, primary outcome variables and Pb exposure measures (PbD and/or PbB levels) will be discussed in unison. The remainder of the introductory chapters will be structured to review the literature investigating the relationship between cognitive abilities and Pb exposure in chronological order of the main research questions that have emerged:

1. What is the nature of the relationship between Pb and cognitive abilities?
2. Does increased Pb exposure precede or result from neurodevelopmental deficits?
3. Is there a non-linear relationship between Pb and cognitive abilities?

2.2 Early findings

The toxic repercussions of Pb exposure were first noted scientifically when Gibson, Love, Hardine, Bancroft and Turner (1882) reported ten cases of Pb induced colic in Australian children. Gibson (1904) later concluded that Pb poisoning was a preventable condition prevalent in Australia due to the domestic use of Pb-based paint. At the time, Pb poisoning was believed to be exclusively seasonal (heightened prevalence in warmer months) and it was understood that children were at heightened risk due to developmental hand-to-mouth activity.

At the turn of the twentieth century, Pb related illness was considered to be an Australian phenomenon because the findings of Gibson and colleagues were only replicated in a few American studies (Mudge, 1996). This can be explained by the conceptualisation of the impacts of Pb that dominated that period – obvious encephalography was linked to Pb poisoning, whereas acute Pb poisoning went ‘under the radar’ because symptoms such as

lethargy, nausea, vomiting and gastro-intestinal disturbance were interpreted as the symptomology of other illnesses (Mudge, 1996).

In 1943, the seminal work of Byers and Lord documented children's recovery from overt Pb poisoning. The children enrolled in this study (sample size (*N)* = 20) were hospitalised for Pb poisoning with hallmark clinical symptoms (including Pb lines on their gums). Byers and Lord (1943) noted that at 2 to 8 years follow-up, 95 % of the sample (i.e., 19 of 20 children), presented behavioural difficulties such as impulsivity, distractibility and aggression. At this time, Byers and Lord (1943) observed that clinical Pb poisoning produced ongoing and pervasive cognitive and behavioural deficits in children who were understood to have recovered from the clinical syndrome.

In the 1950's, the advent of chelation agents that aided the recovery of the poisoned child meant that childhood Pb-related mortality decreased, whilst the morbidity associated with recovery from Pb poisoning and exposure increased (Mudge, 1996). This was illustrated by Perlstein and Attala (1966), who sampled 425 recovered encephalopathic Pb poisoned children ranging in age from 9 month to 8 years. Perlstein and Attala (1966) found that 40% of these children presented ongoing neurological dysfunction, in particular intellectual disability and pervasive neurological seizures.

2.3 Animal Models and Lead related cognitive deficits

Animal studies have been conducted in parallel to research looking directly at human populations and are a valuable source of information about the physiological impacts of Pb on living organisms. In particular, animal studies allow inferences to be made about the biological repercussions that Pb may have on the human physiological system because the regulations governing experimental models for human participants would not authorise intrusive *in vivo* or *in vitro* research, which may be conducted with animals. As Bellinger (2004) described "[animals] are literally a captive audience from whom cooperation and

consent for repeated testing is not required and who do not need to miss work or school to participate" (p.1019).

In addition, animal studies and models have played an important role in developing understandings of the impact of Pb because threats like confounding can be reduced and managed. This is achieved by random assignment to exposure groups, which is typically not possible in human environmental exposure research; and control of genetic and environmental factors within the laboratory setting (Bellinger, 2004; Hubbs-Tait et al., 2006). Animal studies in the field of Pb toxicity tend to utilise rodents and non-human primates. Due to the toxiokinetics of these species, the general consensus is that functional changes can be observed between groups at Pb levels commencing at 10 to 15 µg/dL, although there is no consensus that this is the threshold level (Cory-Slechta, 2003). Pb exposure and animal outcomes has been studied in the context of physiological changes to the brain, learning abilities, memory and attention.

Rodent studies have suggested that Pb induced cognitive deficits relating to spatial and memory performance may be linked to disruption of components of the hippocampus. Specifically, animal studies exploring changes to *neurological mechanisms* suggest that acute Pb exposure can inhibit hippocampal neuronal activities *in vitro* (Altmann, Lohmann & Wiegand, 1998). Likewise, there is evidence from animal models that Pb exposure disrupts Deoxyribonucleic acid (DNA) binding in the cerebellum and the hippocampus (Basha, Wei, Brydie, Razmiafshari, & Zawia, 2003), two parts of the brain that are important for appropriate CNS development and subsequent gene expression. Research has also established that Pb inhibits N-methyl-D-aspartate (NMDA), a key receptor for learning (Hubbs-Tait et al, 2005). There is also evidence of Pb-linked deficits to peripheral nervous system nicotinic cholinergic receptors which play a key role in learning and memory (Hubbs-Tait et al., 2006). This has been illustrated by Zhou and Suszkiw (2004) who found that rats that were Pb exposed had offspring exhibiting significant deficits in spatial reference memory acquisition and working memory performance as measured by the Morris water maze.

Animal studies have also played a role in accumulating evidence about the impacts of Pb upon *cognitive processes*. For animals, cognition tends to be inferred and explored through associative learning and observed difficulties in the "capacity to respond to changing or novel environments and selective failure to make necessary adjustments to shifting reward or punishment conditions" (Hubbs-Tait et al., 2005, p. 68). Cory-Slechta and Thompson (1979) and Cory-Slechta, Weiss and Cox (1983), have reported increased fixed interval schedule food reinforcement responding rates for rats exposed to Pb acetate in water (50 µg/g concentration resulting in PbB levels ranging from 20 to 30 µg/dL) directly after weaning. This work illustrated differentiation of the learned response to environmental circumstances between Pb exposed rats and controls. This finding has been further reinforced by Cory Slechta, Weiss & Cox, (1985) who similarly exposed male rats to 25 µg/g Pb acetate (mean PbB = 15 - 20 µg/dL; mean brain Pb = 0.07 µg/g) and compared their performance on an extensive (90 experimental sessions) behavioural training schedule, to controls. Cory-Slechta et al. (1985) found that over the first 40 experimental sessions, the exposed group's behavioural activity tended to be higher due to an increased frequency of 'shorter interresponse times' and faster running rates. The authors concluded that behavioural change could be observed in rats exposed to low-level Pb concentrations. Hubbs-Tait et al. (2005) explain that such behavioural changes are indicative of changes to learning processes and response regulation, rather than motor deficits.

Animal models have provided important insights into the neurological changes that may be linked to Pb exposure and this knowledge base compliments the extensive work with human populations that will be summarised in subsequent sections.

2.4 Cognitive deficits in the absence of clinical symptomology: Needleman, Gunnoe, Leviton, Reed, Peresie, Maher and Barrett (1979)

The research of Needleman et al. (1979) became an important turning point in conceptualisations of Pb toxicity because the study introduced the idea that low-level Pb exposure may detrimentally impact children's cognitive abilities.

Needleman et al. (1979) administered the Wechsler Intelligence Scale for Children - Revised (WISC-R[7]) to a sample of 158 Bostonian children[8] with either high PbD (*n* = 58, mean PbD > 20 µg/g, mean age = 7.3 years, standard deviation (*SD)* = 7.7 months) or low PbD levels (*n* = 100, mean PbD < 10 µg/g, mean age = 7.6 years, *SD* = 8.4 months). Both the high and low PbD groups performed in the average range on the WISC-R. In addition, Needleman et al. (1979) collected data relating to 39 possible covariates; of these, father's Socioeconomic Status (SES; educational level and occupational prestige), maternal age at birth, number of pregnancies, mother's educational attainment and parental IQ all significantly differed between the low and high PbD groups and were controlled in analyses.

Needleman et al.'s (1979) analyses showed that children with lower PbD levels performed significantly higher on Full Scale IQ (FSIQ; mean difference = 4.5 IQ points), Verbal IQ (mean difference = 4.6 IQ points), Information (mean difference = 1.1 scaled score points), Vocabulary (mean difference = 1.0 scaled score points), Digit span (mean difference = 1.3 scaled score points) and on the performance measure Picture Completion (mean difference = 0.9 scaled score points), than children with higher PbD levels.

Needleman et al.'s (1979) neuropsychological battery also collected data measuring concrete operational intelligence (Piagetian number conservation, substance and continuous quantity), academic achievement (using the Peabody assessments of mathematics, reading

[7] The WISC-R consists of 13 subtests which yield three summary scores (Jensen & Reynolds, 1982): (1) Full Scale IQ; (2) Verbal IQ; and (3) Performance IQ. The WISC-R has a mean of 100 and *SD* of 15 and it is designed for use with children aged 6 to 16 years.

[8] Children were excluded based on their medical history (birth weight below 2500 grams, prolonged hospital stay after birth, head injury, a diagnosis of Pb poisoning) and if English was not their native language.

recognition and comprehension), auditory and language processing (using Sentence Repetition, Token Test, Seashore Rhythm Test and Wepman Auditory Discrimination), visual motor competence (Visual Motor Integration Test and Frostig Test), attentional performance (RT and cognitive control battery) and motor co-ordination (selected subtests from the Halstead-Reitan Battery). Significant differences, where high PbD level children performed more poorly than their low PbD level counterparts, were identified for the Seashore Rhythm Test, Sentence Repetition, and for RT. Some years later, Bellinger and Needleman (1983) reanalysed Needleman et al.'s (1979) original data, correcting for only maternal IQ. This reanalysis supported the conclusion that as PbD level increased, child IQ decreased.

Bellinger, Needleman, Bromfield and Mintz (1984) followed-up the cohort (n = 141) as fifth graders. Seventy-two participants exhibited 'elevated' PbD levels (≥ 20 parts per million), 71 had 'midrange' levels (10.0–19.9 parts per million), and 48 had 'low' levels (< 10 parts per million). The researchers noted that associations between 1st grade PbD level and 5th grade outcomes were such that children with higher PbD levels had lower IQ, tended to require special education support and were more likely to repeat a grade (Needleman et al., 1990; Scientific Group on Methodologies for the Safety Evaluation of Chemicals, 1997). In summary, Bellinger et al. (1984) concluded that "the pattern of results suggests a consistent, though weak relationship between children's dentine lead levels and elementary school performance" (p. 207).

Needleman et al. (1990), followed-up a subsample of the original cohort (n = 132) at a mean age of 18.4 years. Needleman et al. (1990) note that this follow-up population was not representative of the original sample; follow-up adults had marginally lower PbD levels and higher IQ, SES, maternal IQ, better teacher ratings and fewer head injuries. Using data from 122 participants, with no childhood indicators of plumbism, Needleman et al. (1990) regressed adult outcomes onto PbD levels collected in childhood. In multiple regression (controlling for child's age, gender and birth order, family size and SES, mother's age at birth, neonatal stay in hospital, mother's education, IQ and current alcohol usage), Needleman

et al. (1990) found that higher childhood PbD levels were significantly associated with lower academic success (Needleman et al., 1979) as measured by highest year level completed at school, lower reading proficiency (Woodcock Reading Mastery Test), lower class rank, lower grammatical reasoning and vocabulary, slower finger tapping, longer RT using preferred hand and poorer hand-eye coordination. Hence, Needleman et al. (1990) provided evidence of long-term neurocognitive deficits in children without Pb poisoning.

Bellinger, Hu, Titlebaum and Needleman (1994) also followed-up the cohort as young adults (19 to 20 years of age). At follow-up the cohort's (n = 79) mean PbD level was estimated at 13.7 µg/dL (SD = 11.1) and bone Pb levels were measured as 5.4 µg/g in the tibia and 9.2µg/g in the patella. Bellinger, Hu et al. (1994) systematically explored the cohort's attentional functioning using the theoretical grounding of Mirsky et al.'s (1991) four domain conceptualisation of the components of attention; sustained attention (maintenance of attention over time), focus-execute attention (the ability to identify and react to critical information), shifting attention (executive function; the ability to switch attention between competing stimuli) and encoding (working memory; effective processing of auditory information).

Bellinger, Hu at al.'s (1994) adjusted analyses (adjusted for parent IQ using Peabody Picture Vocabulary Test (PPVT), mother's age at child's birth, maternal education, social class, gender, birth order and current cigarette smoking, illicit drug and alcohol use) revealed that higher PbD levels were significantly associated with lower performance on tests assessing focused-execute attention (measured by Talland Cancellation, Trail-making Test (which provides information on visual search, scanning, speed of processing, mental flexibility, and executive functions; Tombaugh, 2004), Stroop Test and Wechsler Adult Intelligence Scale- Revised (WAIS-R) Digit Symbol) and shifting attention (measured by Wisconsin Card Sorting Test; WCST) but significance was not reached for sustained and encoding attentional factors. Reading ability (measured by the Passage Comprehension scale of the Woodcock Reading Mastery Test) was also inversely associated with PbD levels.

Participant self-reported mood levels were not significantly related to PbD levels in this study. Bellinger, Hu et al. (1994) summarised their follow-up of Needleman et al.'s (1979) cohort by commenting that Pb exposure may target "executive/regulatory functions, often considered to depend on the frontal or prefrontal regions of the brain" (p. 103).

In summary, the research of Needleman et al. (1979) coupled with reanalysis by Bellinger and Needleman (1983) and follow-up by Bellinger et al. (1984), Needleman et al. (1990) and Bellinger, Hu et al. (1994), was controversial (Yule, Urbanowicz, Lansdown & Millar, 1984) and certainly seminal in the field of neurotoxicology - long-term cognitive deficits were noted in children with PbD levels lower than those deemed necessary to produce clinically recognised sequelae. In particular, the impacts of Pb upon generalised ability (IQ) and attention, warranted further systematic investigation. Indeed, the combined research efforts of Needleman and associates pointed to the possibility that early Pb exposure played a significant role in the lifetime trajectory of human cognition, quality of life and behaviour (Hubbs-Tait et al., 2005).

Needleman et al.'s (1979) research agenda was paralleled in the same year by Rummo, Routh, Rummo and Brown (1979). Rummo et al. (1979) sought to explore the neurological function, intelligence and hyperactivity of children with clinical Pb encephalopathy and those exposed to Pb both short and long-term but exhibiting no recognisable clinical sequelae. Rummo et al. (1979) conducted a control study comparing 45 children with abnormally high Pb levels (with encephalopathy: N = 10: mean PbB = 64.1 µg/dL, SD = 3.4; with long-term exposure, N = 20: mean PbB = 55.7 µg/dL, SD = 7.7; with short-term exposure: N = 15: mean PbB = 50.2 µg/dL, SD = 8.5) and children with considered to have low exposure levels (mean PbB = 21.2 µg/dL, SD = 6.0). The researchers confirmed that children with Pb encephalopathy differed significantly from controls neurologically, behaviourally and psychologically. However, analyses also showed that children with short-term exposure did not differ significantly from the 'no exposure' control group on the neurological index, auditory RT, two-plate tapping and stereognosis. This research confirmed the distinct impact

of encephalopathy on heavily poisoned children, as compared to lower level exposure, but failed to identify distinctions in cognitive abilities between children at lower levels of exposure. This may be accounted for by the relatively high levels of exposure for the entire study sample.

At the end of the 1970's, important knowledge gains had been made regarding the impact of Pb on neuropsychological functioning of children; the pervasive and severe impacts of encephalopathy from Pb poisoning were established and new questions were raised about potential cognitive deficits associated with symptom-free exposure, including attentional dysfunction. The research agenda for subsequent studies had been set.

'Attention' is a construct that has been prominent in the Pb literature and it has been identified as a part of a 'behavioural signature' (Chiodo, Jacobsen & Jacobsen., 2004) which is adversely affected by Pb. Generally, attentional dysfunction has been conceptualised and measured in two ways:

1. *As a quantifiable cognitive ability measured through neuropsychological tasks.* The measurement of attention in this approach has, at times, been guided by Mirsky and colleagues, Four Factor (later Five Factor) conceptualisation of attention (Mirsky, Anthony, Duncan, Ahearn & Kellam, 1991).
2. *As an observable and ratable behavioural outcome.* In this approach, attention has been captured in summary behavior measures such as the Child Behaviour Checklist (CBCL). However, other researchers have also sought to quantify the clinical syndrome associated with attentional dysfunction - Attention Deficit Hyperactivity Disorder (ADHD; Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition (DSM-IV), 1994) characterised by "deficient response inhibition and impaired sustained attention that generally presents with unknown etiology" (Morgan, Garavan, Smith, Driscoll, Levitsky & Strump, 2001, p. 519). Generally, understandings of the prevalence of ADHD and other attentional dysfunctions have been bound to the accuracy of reporting and observations offered by parents and teachers.

In order to manage the breadth of approaches to the measurement of attentional dysfunction and given a focus on quantifiable cognitive abilities, this thesis will include performance-based measures of attention. Studies which capture attention through behavioural and diagnostic rating scales are beyond the scope of this thesis and will not be discussed.

2.5 Establishing the nature of the relationship between Lead and cognitive abilities

Cross-sectional studies initiated in the years following the publication of Needleman et al. (1979) were part of worldwide inquiry to further explore the idea that Pb may deleteriously impact childhood cognitive abilities in the absence of clinical signs of Pb poisoning. All studies sought to investigate and quantify the impact of Pb upon the neurocognitive functioning of children. Variations in methodology and research questions enabled a rich tapestry of data and evidence for the deleterious impact of Pb on cognitive abilities to be established. However, there was no consistent finding of a specific effect of PbB or PbD levels on cognitive function across these studies.

The main strengths and weakness of cross-sectional research are summarised in Table 2. A notable limitation of cross-sectional research is that causality cannot be inferred from results. Hence, when an inverse correlation is identified between neurocognitive outcomes and Pb level, it is questionable as to whether neurocognitive outcomes preempted Pb levels or vice versa. For example, a low functioning child may heighten their Pb levels by engaging in pica and further exposing themselves to Pb. Alternatively, Pb exposure may deleteriously impact a child's developing cognitive abilities in the first instance. Cross-sectional research cannot clarify whether Pb exposure is heightened by a child's behaviour patterns, which may reflect a developmental lag and the window of data gathered only offers a current view of function and exposure. As Chen, Dietrich, Ware, Radcliffe & Rogan (2005) pointed out, a cross-sectional study with school aged children may reflect latent physiological damage that occurred at 2 years of age but can only be functionally measured in school aged children.

Table 2

Strengths and weakness of cross-sectional research investigating childhood Pb exposure and cognitive abilities.

NOTE:
This table is included on page 34
of the print copy of the thesis held in
the University of Adelaide Library.

Note. Adapted from Tong (1995).

The studies summarised in this section (see Appendix B for a tabular overview) were based in various countries (USA, Germany, New Zealand, United Kingdom, Taiwan, Netherlands, Slovakia, Mexico, Pakistan Canada and the Republic of Korea), focused on children aged (5.5 - 16 years) and differed in sample size and the range of covariates addressed. Two exposure measures were favoured; PbD (mean PbD levels ranged from 2.5 - 202.1 µg/g) and PbB (mean PbB levels ranged from 1.9 - 11.85 µg/dL). Minder et al. (1994) also estimated Pb exposure using analysis of hair samples. In terms of the evolution of the conceptualisation of 'Pb poisoning' and 'safe' levels of exposure, the PbB levels represented through these studies are relatively low.

Studies also varied in the primary outcome measure used, reflecting different conceptualisations of cognitive abilities and intelligence that were circulating. Some studies (Calderón et al., 2001; Chiodo et al., 2004; De la Burde & Choate, 1975; Kim et al., 2009; Lanphear, Dietrich, Auinger, & Cox, 2000; Pocock, Ashby and Smith, 1987; Sovcikova, Ursinyova, Wsolova, Rao & Lustik, 1997; Winneke, Kramer, Brickhaus, Ewers, Kujanek, Lechner & Janke, 1983) sought to measure psychometric intelligence, or IQ (Eysenck, 1988; IQ score follow a normal distribution with a mean of 100 and standard deviation of 15 points: Fewtrell et al., 2003) as represented by the use of the Wechsler scales.

Other researchers measured cognitive abilities using constructs that may be conceptualised as impacting on IQ or reflecting IQ: Reaction Time (Hunter, Urbanowicz, Yule, & Lansdown, 1985; Minder et al., 1994), Raven's Progressive Matrices (Rabinowitz, Wang & Soong, 1991; Rahman et al., 2002), measures of educational attainment (Wang, Chuang, Ho, Yang, Tsai, Wu et al., 2002), neurophysiological measures (Després et al., 2005; Minder et al., 1994), and other general ability measures (Davis, Chang, Burns, Robinson & Dossett, 2004; Fulton, Raab, Thomson, Hunter, Raab, Laxen et al., 1987; Hu, Téllez-Rojo, Bellinger, Smith, Ettinger & Hernández-Avila, 2006).

Discussions about the approach of each cross-sectional research group will be structured according to the primary outcome measure or construct that was favoured; Wechsler scales, Reaction Time, British Ability Scales, Raven's Progressive Matrices, Selected tests from the Neurobehavioural Evaluation System, Class Ranking, Kaufman Brief Intelligence Test and Puzzle-Matching Tasks and Bayley Scales of Infant Development.

Wechsler scales

While studies favouring the Wechsler scales have identified negative correlations between Pb and IQ, they have failed to consistently link the Pb related deficit to FSIQ, subscale scores or individual subtests (notice these represent a hierarchy of measures).

De la Burdé & Choate (1975) contributed to the discussion by noting a statistically significant difference between the Wechsler Intelligence Scale for Children (WISC)[9] FSIQ scores of 7 year olds (*N* = 137) for elevated PbD children (mean PbD = 202.1 µg/g; FSIQ = 86.6, *SD* =10.4) and 'control' children (mean PbD = 111.6 µg/g; FSIQ = 90.1, *SD* = 7.7), but the difference was not significant for Verbal IQ (VIQ) or Performance IQ (PIQ). This research followed-up with children enrolled in a child development study in Virginia, USA and compared children with a history of early life (1 - 3 years) pica (eating plaster and paint) in the absence of clinical sequelae, with children with no apparent unusual interactions with Pb. At 7 years of age a neuropsychological assessment was conducted with a battery of tests including the WISC, Bender Gestalt test (which provides information about perceptual maturity and neurological function; Koppitz, 1964), Wide Range Achievement Test (a measure of reading, spelling, and mathematics computation; Robertson, 2010), Goodenough-Harris draw-a-person, auditory-vocal association subtest of the 1961 Illinois Test of Psycholinguistics (ITPA); tactile finger recognition from the Reitan Indiana Battery and a behaviour profile. Significant differences between the two groups were also noted for the Bender and the auditory-vocal association subtest of the ITPA, where significantly more Pb-exposed children performed in the 'suspect or abnormal range.'

Winneke et al. (1983) identified a negative correlation (*r* = - 0.05) between WISC VIQ and PbD levels (geometric mean = 6.2 µg/g, range: 1.9 - 38.5 µg/g) which approached significance, so that as PbD levels increased, VIQ scores decreased. Winneke et al.'s (1983) study included 115 children (mean age = 9.4 years) from the Pb smelting community, Stolberg, Federal Republic of Germany. PbD levels were collected and supplemented with capillary PbB concentration data for 83 children (geometric mean PbB = 14.3 µg/dL, range: 6.8 – 33.8 µg/dL). The WISC (German adaptation) was administered, along with an unpublished behavioral measure, a cancellation test, and data was collected that measured 52

[9] The WISC consists of 12 subtests which yield three summary scores (Ohta, 1987): (1) Full Scale IQ; (2) Verbal IQ; and (3) Performance IQ. The WISC has a mean of 100 and *SD* of 15 and it is designed for use with children aged 5 to 15 years.

child, family, social environmental and medical variables. Analyses suggested that Pb and IQ levels may be related to a variable deemed 'socio-hereditary background,' comprised of parental occupational status and school attended by the child. Significant or near-significant association was established between PbD levels and visual motor integration (Göttinger Formreproduktionstest) performance, reaction-performance (false reactions) and four behavioural dimensions as rated by the mothers (namely distractibility, restlessness, lack of information and wasting of time); however, the proportion of explained variance never exceeded 6% (Winneke et al., 1983). To further explore the data, participants were classified as high PbD (mean = 15.7µg/g) and low PbD levels (mean = 3.1 µg/g), although there was no statistical difference between the IQ performances of the two groups, the low PbD level group had IQs which were 4.6 points higher than the high PbD group.

Pocock et al. (1987) studied the correlation between PbD levels (low: 2.5 µg/g, medium: 5.0 µg/g and high: 8.0 µg/g) and the intelligence (WISC-R) of 6-year-olds (N = 402) based in London. In unadjusted correlations, a highly significant inverse association was identified between log PbD levels and FSIQ (r = - 0.16, p < 0.01). Pocock et al.'s (1987) methodology thoroughly addressed a range of confounding variables by collecting data on child gender, social class, family size, birth order, length of gestation, birth weight, length of hospital stay after birth, mother's IQ (Wechsler Adult Intelligence Scale; WAIS), quality of marital relationship, family characteristics, mothers' mental health, social background, parental education, parental attitude, and parental interest. Regression modelling was conducted to assess the relationship between children's cognitive abilities and Log PbD levels. In the regression model, the optimality criterion process capability (Cp) reached its minimum when 11 variables were entered, and the standardised regression coefficient for log PbD in this optimal model was not statistically significant. Maternal IQ was identified as the most important statistical determinant of child IQ. Another observation was a significant correlation between PbD level and the child's gender (female: N = 220; mean IQ = 103.6, standard error (SE) = 0.9, geometric mean PbD = 4.02; male: N = 182, mean IQ = 108.2, SE =

1.1, geometric mean PbD = 3.98). Specifically, a significant (p = 0.01) negative association was identified between male children's PbD levels and cognitive abilities when covariates were controlled, but a positive and non-significant association between PbD levels and cognitive abilities was identified for female children. The authors concluded that moderate elevations in PbD play only a minor role in children's cognitive development in comparison to parental and socio-environmental factors, but that the weak negative correlation between PbD levels and children's cognitive abilities should not be dismissed.

Sovcikova et al. (1997) recruited 395 children aged 9 - 10 years in Bratislava, Republic of Slovakia, a region with strong links to the mining and smelting industry. Mean PbB concentration of the sample was 3.65 µg/dL (SD = 1.62). A comprehensive battery was designed utilising Comprehension and Digit Span from the WISC, Raven's Progressive Matrices (RPM), Bender Gestalt Test, Benton Visual Retention Test (a short term memory and retention test which assess the capacity to discriminate the direction of lines; Benton, Varney & Hamsher, 1978), Vienna Determination Test (Reaction to 6 coloured light stimuli) and SRT. Spearman rank correlations indicated statistically significant inverse associations between PbB concentration and RPM and Benton Test performance. With covariate control (gender of child, childhood illness, mother's educational level, parental assistance with homework, smoking habits of parents, car ownership, proximal residency to large petrochemical plant in Bratislava), multivariate analyses identified a moderate, statistically significant inverse association between PbB levels and RPM and Benton Test scores. Associations indicated that subtle increases in Pb exposure (Sovcikova et al., 1997) implicated general intellectual ability, abstract reasoning, short term memory and memory retention.

Although Calderón et al. (2001) failed to identify significant associations between PbB levels and FSIQ, VIQ or PIQ, in an analysis of Wechsler Intelligence Scale for Children - Revised, version for Mexico (WISC-RM) subscales, PbB was significantly negatively associated with a 'sequential' factor, comprised of arithmetic, digit span and coding. This

research suggested that Pb exposure may differentially impact various domain abilities or 'intelligences.' Calderón et al.'s (2001) study population consisted of 80 children, aged 6 to 9 years, living in proximity to a metals smelter in Sau Luis Potosi, Mexico. Two community groups were targeted; the Morales village (N = 41; geometric mean PbB = 8.98 µg/dL) living within 1.5 kms of the smelter and the Martinez village (N = 39; geometric mean PbB = 9.73 µg/dL) located within 7 kms of the smelter. Both groups were also exposed to an unquantified amount of arsenic. In conjunction with the administration of the WISC-RM, data were collected about SES, clinical history, neurological examination, nutritional status and iron levels.

Chiodo et al. (2004) investigated Pb exposure in 246 African American children in the USA with mean age of 5.5 years and mean venous PbB levels of 5.4 µg/dL. The study was carried out as a component of a larger research project (N = 337) investigating pre-natal alcohol exposure (maternal alcohol consumption prior to and at the time of conception). Children were assessed using the WISC-III[10], which was supplemented with an extensive battery of measures targeting information processing (Sternberg Short-Term Memory task, Mental Rotation, Magnitude Estimation, Colour Naming Task), attention (Continuous Performance Test; Continuous Performance Test (CPT; child observes a stream of letters and must only respond when target stimuli is presented), the Talland Digit Cancellation, WCST, Tower of London, the Verbal Fluency task from the McCarthy Scales of Children's Abilities (MSCA)[11] and the Seashore Rhythm Test), memory and learning (Wide Range Assessment of Memory and Learning), visual-motor integration and fine motor skills (the Grooved Pegboard Test, the Corsi Test, the Matching Familiar Figures Test, Beery Test of Visual–Motor Integration), and behaviour rating scales. The relationship between child PbB levels and

[10] The WISC-III yields FSIQ, VIQ and PIQ as well as four subscales: the Verbal Comprehension, the Perceptual Organization, the Freedom from Distractibility and the Processing Speed (Wasserman, Liu, Lolacono, Factor-Litvak, Kline, Popovac et al.,1997). It has a mean of 100 and *SD* of 15 and it is designed for use with children aged 6 to 16 years.

[11] The McCarthy Scales of Children's Abilities (MSCA) produces two indices; the General Cognitive Index (GCI), a mental development measure and comprised the verbal, perceptual-performance and quantitative subscales, and the Motor Score. The GCI is normed to a mean of 100 and standard deviation of 16, whereas the Motor Score is normed to a mean of 50 and standard deviation of 10.

neurological outcomes was investigated using multiple regressions, controlling for potential covariates.

In summary, Chiodo et al.'s (2004) study identified neuropsychological deficits linked to Pb exposure across the range of abilities measured:

- *Wechsler IQ:* In adjusted analyses (adjusted for SES, maternal education, number of children in the family, total scores on the Home Observation for Measurement of the Environment Inventory (HOME), maternal IQ, child's gender, parity and Family Environment Scale) a significant inverse association existed between PbB levels and FSIQ, VIQ and PIQ. Some differential specificity of Pb upon IQ was suggested in that PbB levels were significantly associated with the Verbal Comprehension and Perceptual Organisation subscales and not the Freedom from Distractibility or Processing Speed subscales.
- *Processing speed as measured by reaction time:* Although there was no significant association between PbB levels and WISC-III Processing Speed, deficits were noted in speed of processing as measured by RT tasks. Specifically, when controlled for covariates, Pb exposure was significantly associated with slower RT on the Sternberg Task 'yes' condition, mental rotation, magnitude estimation and colour naming; but was not significantly correlated with number of correct responses on RT tasks.
- *Attention including executive function:* Chiodo et al. (2004)'s battery was designed to measure attention as in Mirsky et al's (1991) four domain conceptualisation of attention; sustained attention (CPT), focused attention (The Talland Digit Cancellation and Coding subscale from the WISC-III), shifting attention or executive functioning (WCST, Tower of London and the Verbal Fluency task from The McCarthy Scales of Children's Abilities) and encoding or working memory (The Seashore Rhythm Test and Arithmetic and Digit Span subscales from the WISC-III). A range of associations, in both the positive and negative directions, were identified. On the whole the

associations identified indicated that as PbB exposure increased, attentional performance decreased.

- *Memory and learning:* Negative correlations were identified between performance on the Verbal Learning and Story Memory subtests of the Wide Range Assessment of Memory and Learning and PbB levels, although these associations did not reach significance when covariates were controlled.
- *Visual–motor integration and fine motor skills:* When covariates were controlled, Chiodo et al. (2004) identified negative correlations between Pb exposure levels and performance on the Beery Visual-Motor Integration and the number of correct items of the Matching familiar figures task. A positive correlation (with covariate control) was identified between PbB levels and the number of pegs dropped on the Pegboard task. The negative correlations identified between PbB levels and Corsi Spatial Span task performance, did not reach significance when confounders were controlled

Chiodo et al.'s (2004) study contributed to the knowledge base about deleterious Pb effects by sampling a low-level Pb group and designing a thorough battery of tests targeting neurocognition and covariates. Their research identified neuropsychological deficits across the range of abilities measured and no apparent threshold level free from the impact of Pb was identified.

Lanphear et al. (2000) explored Pb and intelligence using data from the third National Health and Nutrition Examination Survey (NHANES III; 1988 - 1994), which was designed to provide national estimates of the health and nutritional status of the American population aged from 2 months and above (Stone & Reynolds, 2003). Cognitive data were available for children aged 6 to 16 years (N = 4,853) from subtests of the WISC-R (Digit Span and Block Design) and the Wide Range Achievement Test-Revised (WRAT-R; Arithmetic and Reading). Participant's geometric mean PbB level was 1.9 µg/dL and just 172 children (2.1%) had PbB levels exceeding 10 µg/dL. Statistical adjustment was applied for gender, race/ethnicity, poverty, geographical region, parent or caregiver's educational level, parent or

caregiver's marital status, serum ferritin level and serum cotinine level. With adjustment, Lanphear et al. (2000) identified inverse relationships between PbB concentration and scores on four measures of cognitive functioning; Arithmetic, Reading, Block Design and Digit Span. In adjusted analyses participants were also grouped on the basis of their PbB level:

- PbB levels < 10 µg/dL (*n* = 4,681): Significant inverse associations were identified between PbB concentrations and performance on Arithmetic, Reading, Block Design and Digit Span.
- PbB levels < 7.5 µg/dL (*n* = 4,526): Significant inverse associations were identified between PbB concentration with performance on Arithmetic, Reading, Block Design and Digit Span.
- PbB levels < 5 µg/dL (*n* = 4,043): Significant inverse associations were identified between PbB concentration and performance on Arithmetic and Reading.
- PbB levels < 2.5 µg/d*L* (*n* = 2,467): A significant inverse association was identified between PbB concentration and Reading performance.

Lanphear et al. (2000) concluded that it was possible to quantify Pb-linked deficits in cognitive and academic skills associated with PbB concentrations lower than 5 µg/dL.

The research of Lanphear et al. (2000) has been criticised due to the use of the complex NHANES III data, and, indeed, their analyses have been described as devoid of external validity (Stone & Reynolds, 2003). Particular methodological complaints summarised by Stone and Reynolds (2003) were that NHANES III was marred by data collection errors that undermined the integrity of the sample and cognitive data, that key confounding variables were not considered (birth weight, the home environment and parental IQ) and a large amount of data was missing. Stone & Reynolds (2003) cautioned that "[n]either policy nor scientific problems related to cognitive and other neurodevelopmental problems should be considered using the NHANES III Youth dataset" (p.242).

Recently, Kim et al. (2009) recruited 267 children (mean age = 9.05 years, *SD* = 0.72 years) from schools in a number of Korean cities in order to investigate neurocognition and

Pb exposure. Kim et al.'s (2009) study was designed with a similar research agenda to the current study; to investigate cognitive performance in the low level PbB range (mean PbB = 1.73 µg/dL, *SD* = 0.80). Kim et al. (2009) used a battery based upon the abbreviated form of the Korean Educational Development Institute – Wechsler Intelligence Scales for Children (KEDI-WISC; mean FSIQ = 110.4, *SD* = 14.9), supplemented with CPT, the Children's Colour Trails Test and the Stroop Colour–Word. In multivariate analyses, controlled for age, gender, maternal education, paternal education, yearly income, maternal smoking during pregnancy, indirect smoking after birth, birth weight, and mother's age at birth, PbB levels showed a significant linear relationship with FSIQ and VIQ, but not PIQ. Kim et al. (2009) noted that their analyses were limited because the home environment and parental IQ were not directly measured and hence important environmental and genetic influences could not be ruled out. However, recent views in the field posit that some environmental and genetic factors may increase susceptibility to neurotoxins and over control may cloud the ability to identify an effect (Bellinger, 2008).

In additional analyses with Kim et al.'s dataset, Cho, Kim, Hong, Shin, Yoo, Kim et al. (2010) focused upon the impacts of low level Pb exposure upon neurocognitive domains such as attention, inhibitive control, sustained attention, sequencing and cognitive flexibility and processing speed. KEDI-WISC IQ was used as a confounding variable which was statistically controlled. Hence, in controlled multivariate analyses (controlling for age, gender, educational level of the father, maternal IQ, child IQ, residential area and birth weight), Cho et al. (2010) identified a significant inverse association between PbB concentration and the Commission errors component of the CPT. Cho et al. (2010) align this finding with Nigg, Knottnerus, Martel, Nikolas, Cavanagh, Karmaus et al. (2008) theory that Pb is detrimental to cognitive control abilities.

Other measures of cognitive abilities

Reaction Time

Historically, measures like RT (the time taken to lift the finger of the preferred hand off a button on detecting the stimulus) have been used to estimate nervous system function, stemming from the assumption that "parameters of the response to a simple stimulus might reveal some key limitations of nervous system functioning that contribute variance to psychometric test performance" (Deary, Der & Ford, 2001, p. 389). RT has also been favoured because it is believed to be a test of neurological functioning that is relatively free from educational and social biases (Minder et al., 1994).

According to Hunter et al. (1985), the primary explanatory argument of Needleman et al. (1979) was that children's ability to sustain their attention was most affected by Pb exposure. Using Shakow's RT paradigm (four blocks of varying delay conditions in the order: 3 second delay, 12 second delay, 12 second delay, 3 second delay; Rodnick & Shakow, 1940), Needleman et al. (1979) noted a significant difference between children with high and low PbD levels under the 12 second delay conditions (a delay condition refers to the time delay between a warning signal, such as 'ready' and the onset of the stimulus); low PbD level participant's had significantly shorter RT than high PbD level participants. Likewise, for the Block IV, 3 second delay condition, low PbD level participants had significantly shorter RTs than the high PbD level participants. Needleman et al.'s (1979) statistical analysis revealed that these effects could not be accounted for by a range of 39 demographic and social variables collected about the children. This finding was also supported by Needleman et al. (1990) with 11 year follow-up on the original Needleman et al. (1979) cohort where higher childhood PbD levels were associated with longer early adulthood RT.

The early findings of the impacts of Pb upon children's RT were later supported by Hunter et al. (1985). Hunter et al. (1985) recruited 302 children (mean age = 9 years, 11 months, *SD* = 26.1 months; mean PbB = 11.85 µg/dL, range = 5.0 – 26.0 µg/dL) who lived in proximity to Pb works in Leeds, UK. Recognising inter-tester variability as a limitation of

standard measures of cognitive measures, Hunter et al. (1985) sought to establish the utility of a CNS test, like RT (as measured by Shakow's paradigm), which was independent of tester bias. Hunter et al. (1985) identified a significant positive relationship between age-adjusted RT and log PbB concentration for all four RT trial blocks, but this relationship accounted for only approximately 1% of the total variance.

Minder et al. (1994) explored the relationship between Pb exposure and neuropsychological functioning, with an emphasis upon attentional deficits. Their sample, of 43 children was drawn from the special educational system in Amsterdam, the Netherlands. Participants were males, aged 8 to 12 years (mean age = 10.2 years). The children in the cohort were identified for participation in the study by school doctors and principals and the key inclusion criteria was that the child's IQ was in the range 80 - 130 IQ points (mean IQ for the sample was 100). Pb levels were measured through hair sampling and the mean PbH levels of the sample was 1.26 parts per million (*SD* = 1.09 µg/g). Attentional functioning was measured using a battery of 11 tests taken from the Neurobehavioural Evaluation System (Baker & Letz, 1986: Hand Eye Coordination, Simple RT, Choice RT) and the WISC-R (Mazes, Digit Span, Coding), as well as Underlining, Stroop Test, Trail Making Tests A and B, Beery Test, Dichotic Listening. Information pertaining to 27 covariates was collected and included WISC-R (the child's IQ was collected as a covariate), SES, school, history of pica, passive smoking, environmental noise, television viewing habits, sleeping habits, emotional functioning, restless behaviour, allergies, birth order and family size.

Correlational analyses identified significant correlations between PbH levels and performance on simple RT ($r = 0.37$, $p = 0.01$), Trail Making A ($r = 0.29$, $p = 0.03$) and Trail Making Test B ($r = 0.40$, $p = 0.004$). After statistical correction for covariates (Age, SES, child IQ and incidence of pica), significant correlations were identified between PbH levels and RT and speed of Trail Making Test B, respectively. The authors observed that as PbH levels increased, RT increased and performance on Trail Making Test B decreased. With

correction for RT, performance on Trail Making Test B was still significantly correlated with PbH level.

In terms of simple RT, it was found that PbH level explained 8.35% of the variance in performance. With correction for age, SES, IQ and pica, the variance in Trail Making Test A was not significant. However, significance was reached for Trail making Test B, where PbH levels explained 11.7% of the variance. When correction for RT was applied hair Pb still explained 9.9% of variance in Trail Making Test B.

Minder et al.'s (1994) research mirrored the findings of Needleman et al. (1979) and Hunter (1985) through the identification of an increase in length of RT accompanied by an increase in hair Pb. Significant positive associations were also identified between PbH levels and slower performance on Trail Making Tasks. Noting that RT itself may be a factor in level of performance on Trail Making Tasks, Minder et al. (1994) controlled for the confounding of RT and still noted significant associations between Trail Making Task performance and PbH levels. The authors interpreted this as an indication that attention "was less flexible in children with higher hair lead levels" (p.397).

British Ability Scales

Fulton et al. (1987) studied children aged 6-to-9 years from 18 primary schools across central Edinburgh, Scotland, a city with a plumbsolvent water supply. The students had a geometric mean PbB level of 10.4 µg/dL. A stratified sample (N = 501) was identified consisting of the top quartile of PbB exposure levels and a random subsample of remaining students. The main outcome measure was the British Ability Scales (BAS) and a range of covariates were measured (including maternal IQ, school experiences, household characteristics, SES, number of occupations, parent mental health, pre- and post-natal factors, and family environment). Using multiple regression, Fulton et al., (1987) identified a strong negative correlation between PbB levels and performance upon the BAS combined score (mean = 112.0, SD = 13.4), number skills and word reading, taking into account 33 potentially

influential variables. The authors concluded that "[l]ead at low levels of exposure probably has a small harmful effect on the performance of children in ability and attainment tests" (p.1221).

Raven's Progressive Matrices

Rabinowitz et al. (1991) recruited 515 Taiwanese children who donated incisor teeth for analysis. Children who attended school near a Pb smelter (6.3 µg/dL, *SD* = 3.3) and those very proximal to the smelter (mean = 13.0 µg/dL; *SD* = 4.4) had higher mean PbD levels than those children recruited from Taipei City (4.3 µg/dL, *SD* = 3.7). The Raven's Coloured Progressive Matrices (CPM) was administered to the children as a measure of fluid intelligence and their parents completed a questionnaire compiling information on a range of confounding variables (their age, education, employment, family composition, areas lived, language usage, pregnancy events, delivery, and maternal and children health). Rabinowitz et al.'s (1991) analyses showed that CPM scores were significantly negatively correlated with Pb levels. This association was particularly marked for female children and for children whose parents reported lower levels of educational attainment versus those whose fathers were college graduates. Rabinowitz et al. (1991) found that the correlation between CPM and PbD levels could be lowered by controlling for risk factors like parental education but the association was not entirely abolished.

Rahman et al. (2002) administered the RPM (mean IQ calculated as 87.7, *SD* = 13.61) to a sample of 138 children aged 6 to 10 years (mean age = 8.4 years) in Karachi, Pakistan. Pb levels were estimated through the collection of PbD (mean = 5.68 µg/g, *SD* = 4.10) and PbB levels (mean = 16.08 µg/dL, *SD* = 6.29). The authors comment that 88% of their sample had PbB levels exceeding 10 µg/dL, the CDC and WHO level of concern and, further, that 205 participants had PbB levels greater than 20 µg/dL, double the level of concern. For Rahman et al. (2002) this cross-sectional data further quantified the ongoing exposure challenges for people living in developing countries, even in sample such as this that

was recruited from both industrial and residential exposure communities and both poor and affluent precincts. After adjustment for height-for-age and haemoglobin levels, Rahman et al. (2002) found the association between PbB concentration and RPM performance remained significant.

Class Ranking

Wang et al. (2002) investigated the association between class ranking (as a proxy for academic achievement) and PbB levels in 934 children recruited from Kaohsiung City, Taiwan (mean age = 8.9 years, *SD* = 0.41 years; mean PbB = 5.50 µg/dL, *SD* = 1.89). Class raking was used to infer learning achievement and, after controlling for father's SES and maternal education, the authors found that PbB levels significantly correlated with class ranking in the subject areas of Chinese language, mathematics, history and science. These findings supported the notion that academic achievement is inversely associated with environmental Pb exposure. The authors suggested that the strong impact of Pb on Chinese language skills reflected Pb's deleterious impact on the ability to memorise information, rather than other skills like calculation, theorised to be relevant to the less affected mathematical course performance.

Kaufman Brief Intelligence Test and Puzzle-Matching Tasks

Davis et al. (2004) recruited 57 children living in Louisville, Kentucky, USA, whose families received financial support under the United States Federal Poverty Guidelines. Davis et al.'s (2004) central research question was whether attentional performance differed between Pb exposed children (*N* = 24; mean age = 4.59 years, *SD* = 0.44 years; mean PbB = 15 µg/dL, *SD* = 5.16 µg/dL) and non Pb exposed (*N* = 33; mean age = 4.64 years, *SD* = 0.45 years; mean PbB = 4.42 µg/dL, *SD* = 1.3). While Davis et al. (2004) described their 4.42 µg/dL group as 'non Pb exposed,' this description reflects their categorisation of participants as either having PbB levels above or below 10 µg/dL, the CDC action level. Participants were

administered the Kaufman Brief Intelligence Test (KBIT; Kaufman & Kaufman, 1990) which is a generalised ability measure, assessing verbal ability and matrices performance producing a composite IQ. Davis et al. (2004) found a 4.21 IQ point difference favouring the low exposure group, but this did not reach statistical difference due to a lack of power.

Davis et al. (2004) also utilised two puzzle-matching tasks[12] developed by Wertsch, McNamee, McLane and Budwig (1980) which collect information about attention-allocation patterns and puzzle-matching performance. In terms of attention, Davis et al. (2004) found that the Pb exposed group tended to perform significantly worse on the puzzle-matching task both when working with their parent and individually. In summary, Davis et al. (2004) concluded that lower Pb exposure children tended to spontaneously develop performance strategies characterised as "a mature, self-regulated attention allocation pattern" (p.829) that meant that they performed better than the Pb exposed children both when working with a parent and individually.

Neuromotor abilities

Després et al. (2005) sought to evaluate the neuromotor impacts of mercury, Polychlorinated biphenyls and Pb in 6 year old (N = 110) Inuit children in northern Quebec, Canada and to differentiate pre-natal and childhood exposures. The geometric Pb mean of the sample was 4.1 μg/dL (SD = 3.7), a level that was considered very low amongst research studies at the time. The authors found that gross motor development and neurological examination were not statistically impacted by neurotoxicant exposure. However, fine motor skills and higher Pb levels were significantly associated as was Pb and longer RT. Significant

[12] Wertsch et al.'s (1980) puzzle-matching tasks were: (1) Parent–Child puzzle-matching condition: Parent-child dyads are seated separately but each given a copy of the same puzzle. The child's task is to reassemble the cargo after an initial viewing so that it looks like their parent's intact model. Two superfluous pieces of puzzle are given to the child to increase the difficulty of the task. The child can seek as much help as they require from their parent and the session is tape recorded. The development of the task is based on the theoretical view that the development of attention is inextricably linked to adult interaction (Davis et al. 2004), (2) Child alone puzzle-matching condition: The child is required to work independently to reassemble a puzzle. Like in the previous condition some distracting irrelevant puzzle pieces are given to the child to increase task difficulty. The second task is administered to the child one week after the Parent–Child puzzle-matching condition and the child's approach is video recorded.

associations were also identified between Pb and preclinical alterations, or neuromotor functioning, like alternating movements, pointing movements and sway oscillations. These relationships were maintained with covariate adjustment (demographic and familial characteristics, pre-natal neurotoxicant exposure (alcohol, tobacco) and the child's nutrient levels (selenium and Omega-3 polyunsaturated fatty acids)).

Bayley Scales of Infant Development

Hu et al. (2006) sought to investigate the impact of pre-natal Pb exposure upon neurodevelopment. Exposure data were collected from 146 pregnant women in Mexico City via PbB samples taken during each trimester of their pregnancy (First trimester: mean = 7.0 µg/dL, *SD* = 5.1; Second trimester: mean = 6.0 µg/dL, *SD* = 3.2; Third trimester: mean = 6.8 µg/dL, *SD* = 4.2), at delivery (mean = 7.3 µg/dL, *SD* = 4.3), from cord blood (mean = 6.2, *SD* = 3.8) and when the child was 12 months (mean = 5.2 µg/dL, *SD* = 3.4) and 24 months (mean= 4.8, *SD* = 3.7). Neurocognitive function was measured at 24 months using the Bayley Scales of Infant Development (BSID)[13].

Single-trimester multivariate linear regression models for the Mental Development Index (MDI) were run to explore the influence of Pb exposure markers measured at different times. Analyses indicated negative coefficients for each trimester PbB measure, cord blood and early childhood Pb (i.e., 12 and 24 months). Significant relationships were identified between MDI and first trimester plasma PbB and whole PbB levels. In conclusion, Hu et al. (2006) found that levels of Pb exposure in early pregnancy (first trimester) were "predictive of adverse neurodevelopment later in life, with an effect that was independent from that of postnatal lead exposure" (p. 1734).

[13] The BSID provides a three part assessment with a standardised population mean and SD of 100 ± 16 (Baghurst et al., 1992; Dietrich, Succop, Bornschein, Krafft, Berger, Hammond et al., 1990). The BSID is comprised of: (1) The Mental Development Index (MDI: 163 items) assessing sensorimotor coordination, perceptual acuities, objective and visual-spatial relations, imitation, prelinguistic and linguistic behaviours, and memory; and (2) The Psychomotor Development Index (PDI: 81 items) designed to measure coordination of the large body muscles and finer manipulatory skills of the hands and fingers.

2.6 Summary of cross-sectional research

Cross-sectional research studies undertaken over the last 40 years have consistently identified a deleterious impact of Pb exposure on childhood cognitive abilities. Despite this consistent finding, efforts to identify abilities that are most susceptible to Pb exposure have not been unequivocal. Studies utilising the Wechsler family of scales have identified significant negative correlations between Pb exposure and FSIQ (de la Burde et al., 1975; Chiodo et al., 2004, Kim et al., 2009), VIQ (Winneke et al., 1983; Chiodo et al., 2004, Kim et al., 2009), PIQ, Perceptual Organisation (PO), and Verbal Comprehension (VC; Chiodo et al., 2004) and subscale scores (Digit Span and Block Design: Lanphear et al., 2000; Digit Span, Block Design and Arithmetic: Calderón et al. 2001). For studies utilising measures of other cognitive abilities, increasing Pb exposure level has tended to deleteriously impact functional abilities such as speed of information processing (Hunter, 1985; Needleman et al. 1979; Minder 1994), fluid ability (Rabinowitz et al., 1991; Sovcikova et al., 1997; Rahman et al., 2009 and Després et al., 2005), academic abilities (Wang et al., 2002; Lanphear et al., 2000) and generalised ability measures (Fulton et al., 1987; Hu et al., 2006).

Despite a lack of consensus about the specific impact of PbB concentration on cognitive abilities, a meta-analysis by Needleman and Gastonis (1990) lead to the view that the deleterious impact of low level Pb upon IQ was strongly supported by the accumulated research**.** This work investigated the relationship between low-level Pb exposure and IQ between 1972 and 1987 and used data from 12 cross-sectional studies (*N*s ranged from 75 to 724 participants) which conducted multiple regressions of IQ (majority of studies used WISC-R but variations included Stanford Binet IQ Scale, the British Ability Scale and the McCarthy Scale) on Pb, with covariate control. Studies were categorised according to type of Pb marker used – that is, PbB (*n* = 7; range = 2.9 – 23 μg/dL) or PbD levels (*n* = 5; range = 5.1 – 12.7 μg/g). The analyses provided confirmation that as Pb level (PbB and PbD) increased, FSIQ decreased. Specifically, the regression coefficient for Pb was negative in the majority (11 of

12 studies) of the studies included in the meta-analysis. For the PbB group combined *P* values were less than 0.001 and for PbD levels, the combined *P* values were less than 0.05.

Cross-sectional studies have played an important role in confirming the existence of Pb-related cognitive deficits and highlighting research gaps to take the field forward. A question emerging from the early cross-sectional studies was one of causality – does increased Pb exposure precede or result from neurodevelopmental deficits? Subsequently, co-ordinated prospective studies were initiated seeking to systematically address the causal links between Pb and cognitive abilities and to further delineate a 'signature' cognitive deficit linked to Pb exposure; these studies will be discussed in Chapter 3.

Chapter 3: Lead exposure and children's cognitive abilities: prospective research and pooled analyses

Chapter summary

Chapter 3 provides an overview of the prospective research efforts that sought to address questions of causality – does increased Pb exposure precede or result from neurodevelopmental deficit? The prospective studies failed to clearly delineate the nature of the relationship between Pb and childhood outcomes or to identify a period of development during which children were maximally susceptible to the confirmed deleterious impact of Pb exposure.

However, some prospective studies (Canfield et al., 2003) suggested that there may be a non-linear relationship between Pb and children's cognitive abilities and this was further supported by pooled analyses and further investigations, which suggested, somewhat counter-intuitively, that low-level Pb exposure (< 10 µg/dL) could, in fact, be more detrimental to the developing brain and children's cognitive abilities, than higher levels of exposure.

At the end of Chapter 3 the individual and population-level implications of a Pb-linked deficit to cognitive ability are considered in the context of Fewtrell et al. (2003)'s efforts to calculate the disease burden from Pb-related loss of IQ points (using data from the Schwartz, 1994 meta-analysis); specifically, Fewtrell et al. (2003) considered how many people on the cusp of the 'intellectual disability' threshold would be in the MMR range through Pb-linked loss of IQ points? The closing message of Chapter 3 is that while the quantified detriments associated with children's low-level Pb exposure are relatively small, for vulnerable children, Pb-linked IQ loss can significantly impact their trajectory of development with wider community and policy implications.

3.1 Does increased lead exposure precede or result from neurodevelopmental deficits?

In the 1980's prospective studies were established in seven cities, in four countries around the world, making this a watershed decade in the study of child cognitive abilities and Pb exposure. The longitudinal collection of data was initiated in order to map levels of Pb and cognitive ability, investigate a window of vulnerability, and to address the question:

"Does increased [Pb] exposure precede or result from neurodevelopmental deficits?" (Hubbs-Tait et al., 2005, p.65).

In addressing this question, researchers sought to identify and differentiate effects that could be attributed to pre-natal versus post-natal/early childhood exposure (Cooney, Bell, McBride & Carter, 1989).

Studies in the core 'group of seven' were located in Boston, Cincinnati, Cleveland, Kosovo, Mexico City, Port Pirie, and Sydney. Research groups co-ordinated their study designs (assessment ages, outcome variables and covariate measures), so that all 'group of seven' studies included measures of the child's social environment (home environment and maternal IQ), collected venous or capillary PbB levels and utilised age-appropriate Wechsler Scales as an outcome measure of IQ (except Cleveland). Participants were recruited prenatally and follow-up assessments were carried out at varying intervals in the first year of life and in some studies even into early to mid adolescence (Bellinger et al., 1992; Tong, Baghurst, McMichael, Sawyer, Mudge, 1996) and late adolescence (Ris, Dietrich, Succop, Berger, & Bornschein, 2004) in some studies. A distinct strength of this research program was the diversity of each cohort's route of Pb exposure, ethnicity and socioeconomic standing.

Despite some differences in study design, consistent findings emerged. After adjustment for covariates, an inverse relationship (the magnitude of the association ranged from moderate to strong) was identified between PbB levels and IQ, or other cognitive tests, in Boston, Cincinnati, Port Pirie, Kosovo and Mexico City. Consistent findings relating to the

relationship between PbB concentration and outcome measures were not found in Cleveland and Sydney.

The findings of the prospective studies are qualified by a range of methodological limitations that are summarised in Table 3. Notable threats to the integrity of prospective studies are issues of sample attrition and the possibility that children and families lost to follow-up differ on socioeconomic, familial or cognitive factors. As Schnaas et al. (2006) indicated, in the prospective studies attrition "reduced the possibility of detecting subtle effects and increased the possibility of instability of model coefficients" (p.795).

An aim of the prospective studies was to determine a 'critical window' in child development when children may be more susceptible to the supposed deleterious impact of Pb. An age range vulnerability was not conclusively agreed upon but suggestions ranged from 1 to 3 years of age in Boston (Bellinger et al., 1992), through to views from Cincinnati (Dietrich, Succop, Berger & Keith, 1992) and Port Pirie (Tong et al., 1996) that the most recent exposure was the most influential, and to Kosovo (Wasserman, Graziano, Factor-Litvak, Popovac, Morina, Musabegovic et al., 1992) where the impacts of PbB levels were seen irrespective of age. In addition, analyses of maternal antenatal blood also did not associate significantly with IQ (Pocock, Smith & Baghurst, 1994) bringing the theorised impact of pre-natal Pb exposure into question.

In terms of exploring the shape of the dose-effect relationship in the range of 10 µg/dL or below, the prospective studies included relatively few children within this range due to the widespread prevalence of Pb-based petrol and paint for these cohorts of children. Participants tended to have Pb levels that exceeded those of children in urban communities today, and even current day Port Pirie and Broken Hill residents where environmental contamination is evident.

The cohort studies also failed to identify a specific 'lesion' in the development of intelligence as measured by the tools available at the time. In general, verbal and performance IQs were all similarly (inversely) associated with Pb exposure. Thus, little information was

obtained about the developmental ‘effects’ in the lower exposure range (1 – 10 µg/dL) and the direction of the causal relationship could not be estimated.

Table 3

Strengths and weakness of prospective research investigating childhood Pb exposure and cognitive abilities

NOTE:
This table is included on page 56
of the print copy of the thesis held in
the University of Adelaide Library.

Note. Adapted from Tong (1995).

The ‘group of seven’ cohort studies are summarised here (in alphabetical order; Boston, Cincinnati, Cleveland, Kosovo, Mexico City, Port Pirie and Sydney) in addition to other notable prospective research independent of this initial research group (New York City, Glasgow, New Zealand, Denmark and multicentre USA). The summaries provided here will not exhaustively explore the findings of each study but rather seek to characterise the contributions of each research group, with particular emphasis placed on analyses undertaken in middle childhood.

3.1.1 Group of Seven

Boston

The first prospective study was headed by D. Bellinger and investigated the impact of Pb levels upon cognitive functioning (Bellinger, Sloman, Leviton, Rabinowitz, Needleman & Waternaux, 1991) and academic achievement (Bellinger et al., 1992) in metropolitan Boston, USA, in a cohort recruited from birth and followed until 10 years of age. The sample is described as comprising mainly Caucasian, middle and upper-class children, exposed to environmental Pb (Bellinger et al., 1991). At one month of age 249 infants were enrolled in the Boston study and they were stratified according to cord PbB concentration; low PbB (n = 5, mean = 1.8 µg/dL), mid-range PbB (n = 88, mean = 6.5 µg/dL) and high PbB levels (n = 76, mean = 14.6 µg/dL). The covariate and PbB concentration data are presented in Table 4.

Table 4

Study design and sample characteristics for the Boston prospective study.

Boston (*N* = 294)[a] Middle, upper class population.				
Age	PbB [b] (*SD*) (µg/dL)	Cognitive Measures[c]	Key covariates	Notable findings
1 month	Cord PbB 6.5	BSID	Mother employment status, marriage status, number of siblings, parents' educational level, maternal age at birth, family stress index, birth weight, gestational age, child's gender.	• A significant negative adjusted coefficient was identified between PbB at 24 months and FSIQ (r = - 0.58, SE = 0.21, p = 0.01) and VIQ (r = - 0.63, SE = 0.22, p = 0.004). • 5.8 point FSIQ decline is associated with a 10 µg/dL increase in PbB at 24 months (95% CI: 1.7, 9.9 points, p = 0.01) and an 8.9 point decline in K-TEA battery composite scores (95 % CI: 4.2, 13.6 points, p = 0.0003) • The authors suggested that high pre-natal PbB children may have experienced a 'recovery of function' between 24 - 57 months.
6 months	6.7 (7.0)	BSID		
12 months	7.7 (6.5)	BSID		
18 months	7.8 (5.7)	BSID		
24 months	6.8 (6.3)	BSID: MDI = 115.6 (16.4)		
57 months (4.75 years)	6.4 (4.1) PbD = 2.8 µg/g.	MSCA: GCI =115.5 (14.5); Verbal = 59.7 (10.0); Perceptual Performance = 57.6 (8.7); Quantitative = 57.8 (8.0); Memory = 56.4 (9.0); Motor = 50.6 (8.5)		
10 years	2.9 (2.4)	WISC-R: FSIQ = 119.1 (14.8) VIQ = 118.1 (14.9) PIQ = 115.9 (14.2). K-TEA-BF: Composite = 118.8 (16.3); Maths = 122.1 (18.7); Reading =117 (14.0); Spelling = 113.5 (17.1). Range of additional cognitive measures.	Family Adaptability & Cohesion Evaluation Scales, Social Readjustment Rating Scale, Parenting Stress Index, Children's life events Inventory-Revised, Social Support, HOME, Maternal IQ, Social class, Medical & educational history.	• In covariate adjusted regression analyses significant negative associations identified between PbB at 24 months & 10 year old FSIQ (r = - 0.58, SE = 0.21, p = 0.01) & VIQ (r = - 0.63, SE = 0.22, p = 0.004); • Significant negative associations identified between 24 month PbB & K-TEA-BF total composite score (r = - 0.89, SE = 0.24, p = 0.0003), mathematics (r = - 0.91, SE = 0.29, p = 0.002) & reading (r = - 0.97, SE = 0.28, p = 0.001).

Note. BSID: Bayley Scales of Infant Development; CI: Confidence interval; FSIQ: Full Scale IQ: GCI: General Cognitive Index; HOME: Home Observation for Measurement of the Environment Inventory; K-TEA-BF: Kaufman Test of Educational Achievement – Brief Form; MDI: Mental Development Index; MSCA: McCarthy Scales of Children's Abilities; *N*: sample size; PbB: blood lead; PbD: dentine lead; SE: Standard error; *SD*: standard deviation; VIQ: Verbal IQ; WISC-R: Wechsler Intelligence Scale for Children – Revised; µg/dL: microgram per deciliter; µg/g; microgram per gram.

[a] This figure represents the number of children enrolled at birth.

[b] Arithmetic mean PbB level.

[c] Mean (standard deviation) of cognitive ability measures are included where reported by research group.

Table 4

Continued.

Boston (*N* = 294)[a] Middle, upper class population.				
Age	Pb [b] measures	Cognitive Measures[c]	Key covariates	Notable findings
19 - 20 years (*n* = 79)	PbD = 13.7µg/g. mean tibia Pb = 5.4 µg/g. mean patella Pb = 9.2 µg/g.	Range of measures assessing Mirsky's four factor model of attention.	Parent IQ (PPVT), mother's age at birth, years of maternal education, family social class, gender, birth order, current cigarette smoking, illicit drug and alcohol use.	In adjusted analyses PbD levels significantly associated with factor scores for focus-execute and the shifting factors. Tibia Pb was significantly associated with the focus-execute factor.

Note. n: subsample size*; N*: Sample size; Pb: lead; PbD: dentine lead; PPVT: Peabody Picture Verbal Test; *SD*: standard deviation; µg/g; microgram per gram.
[a] This figure represents the number of children enrolled at birth.
[b] Arithmetic mean Pb level.
[c] Mean (standard deviation) of cognitive ability measures are included where reported by research group.

The BSID was administered at 6, 12, 18 and 24 months and scores were inversely associated with cord PbB levels at these times (Bellinger, Leviton, Waternaux, Needleman, & Rabinowitz, 1987). Children with high levels of PbB in their umbilical cords performed 4.8 MDI points (95% CI = 2.3, 7.3) lower than children with low levels of PbB in their umbilical cords. Children with high levels of PbB in their umbilical cords scored 3.8 MDI points lower (95% CI = 1.3, 6.3) than children with mid-range levels of PbB in their umbilical cords. Strong correlations were found between environmental Pb sources such as indoor air and gasoline Pb sales and the umbilical PbB levels of infants. Tap water Pb levels did not correlate with PbB concentration (Rabinowitz, Needleman, Burley, Finch & Rees, 1984).

At 24 months, Bellinger, Leviton, Rabinowitz, Needleman and Waternaux (1986) assessed the predictive power of five sets of variables in determining PbB levels. The five sets of variables were:

1. *Environmental Pb source*: seasonal collection of PbB samples (September - April vs. May - August), Pb content of dust collected in home, home refinishing activities during 6 months prior to PbB collection.
2. *Mouthing Activity*: ratings of thumb/finger sucking and mouthing of toys taken from the BSID at 18 and 24 months and parent ratings of mouthing and sucking at 18 and 24 months.
3. *Home Environment/Care-giving style*: Scales from the HOME (Emotional and Verbal Responsiveness of Mother and Maternal Involvement with the Child) and Nursing Child Assessment Teaching Scales at 18 months.
4. *Child development status*: MDI scores at 18 and 24 months.
5. *Sociodemographic factors*: Family social status, parental marital status, parental education, maternal intelligence, number of children in family, birth order and family stress levels at 18 and 24 months.

In terms of vulnerability to Pb exposure, the authors found that child developmental status (MDI scores at 18 and 24 months) was not significantly associated with PbB levels at 24 months. Significant positive associations were identified between PbB levels at 24 months and seasonality (PbB levels collected May - August), refinishing in the home, Pb in house dust, thumb/finger sucking behaviour and number of significant life events in the 12 - 18 month period. Bellinger et al. (1986) concluded by characterising the profile of a child at highest risk of elevated Pb exposure as “a young child who tends to engage in excessive oral activity, an overburdened mother who is unable to provide adequate care, and old urban housing with accessible leaded surfaces in poor repair” (p. 831).

The MSCA was administered at 57 months and the General Cognitive Index (GCI) score was significantly inversely associated with PbB levels at 24 months, with statistical adjustment for covariates (social class, maternal IQ, marital status, preschool attendance, HOME total, hours per week in childcare, number of residential changes, recent medication use, number of adults in household, gender, ethnicity, birth weight and birth order; Bellinger et al. 1991). No significant correlation was identified between cord PbB levels and developmental outcomes at 57 months. The identification of a statistically significant effect between PbB levels at 57 months and GCI was interesting given that no significant associations were identified between post-natal PbB levels and MDI at 24 months (Bellinger et al., 1986). Here the authors suggested that high pre-natal PbB levels children experienced a 'recovery of function' for between 24 - 57 months.

Further exploring the developmental changes occurring between 24 and 57 months, Bellinger, Leviton and Sloman (1990) found that children who had 'high' cord PbB levels at birth, presented a neuropsychological performance profile which considerably improved from 24 month to 57 month testing, at which point their development was inversely related to post-natal Pb exposure.

The Boston cohort was followed-up at 10 years of age (mean age = 9.9 years; Stiles & Bellinger, 1993), at which time the children and families assessed at 57 months were reapproached and 148 were available for participation. Bellinger et al., (1992) described the population at 10 years as consisting of predominately Caucasian children from high functioning, university educated, and intact families. Indeed, lifetime exposure of the cohort was relatively low (mean PbB = 2.9 µg/dL, *SD* = 2.4). A comprehensive assessment battery was administered (Stiles & Bellinger, 1993) including the WISC-R, Kaufman Test of Educational Achievement – Brief Form (K-TEA-BF), California Verbal Learning Test for Children (an assessment of verbal learning and memory skills), Story Recall (assessing immediate and delayed memory recall), WCST (assessing attention, abstract reasoning and

executive processes), Developmental Test of Visual-Motor Integration, Rey-Osterrieth Complex Figure (ROCF; assessment of visual perception), Finger Tapping and the Grooved Pegboard (measures of fine motor speed). When covariate adjusted (HOME sum of scales relating to active stimulation and family involvement in stimulating activities, child stress, maternal age, ethnicity, maternal IQ, HOME total score at 57 months, SES, gender, birth order, marital status, number of residential changes prior to 57 months of age) regression analyses were conducted between PbB concentrations measured at six intervals (6, 12, 18, 24, 57 months, 10 years), cord PbB levels and WISC-R FSIQ (mean = 119.1, *SD* = 14.8), VIQ (mean = 118.1, *SD* = 14.9) and PIQ (mean = 115.9, *SD* = 14.2), significant negative coefficients were identified between PbB levels at 24 months and 10 year old FSIQ and VIQ. Bellinger et al. (1992) reported a 5.8 point FSIQ decline was associated with a 10 µg/dL increase in PbB levels at 24 months and an 8.9 point decline in K-TEA battery composite scores. The addition of 24 month PbB levels to the covariate model accounted for an extra 3.2% of the variance. A small number of significant associations were also identified between 24 month PbB levels (and other PbB measures) and the other neuropsychological tests administered (Stiles & Bellinger, 1993), such that there was a positive association between PbB level and the amount of perseveration and perseverative errors, as well as inverse associations between 24 month PbB levels and organisation on the ROCF. Significant negative coefficients were identified between 24 month PbB levels and K-TEA-BF total composite score, mathematics composite and reading.

Bellinger, Titlebaum and Needleman (1994) also reported efforts to explore whether components of attention were adversely impacted by PbD levels (PbD = 13.7µg/g), current PbB levels (79.2% had PbB levels ≤ 5 µg/dL) and tibia (mean = 5.4 µg/g) and patella (mean = 9.2 µg/g) bone Pb measured by K line X-ray fluorescence (K-X-ray). Specifically, 79 participants from the cohort were followed-up at ages 19 to 20 years and they were administered a battery of measures based on Mirsky et al.'s (1991) model: encoding attention (Digit span and arithmetic from the WAIS-R), focused and executive attention (Talland Letter

Cancellation Test, Stroop Colour-Word Inference Test, digit-symbol from the WAIS-R and the Trail-making Test), sustained attention (visual CPT), shifting attention (number of errors on the WCST) and three additional tests (Passage comprehension from the Woodcock-Johnson Reading Mastery Test-Revised, L'Anthony Desaturated 15 Hue Test (a visual colour ordering task) and the Profile of Mood States). In adjusted analyses (parent IQ; PPVT), mother's age at birth, years of maternal education, family social class, gender, birth order, current cigarette smoking, illicit drug and alcohol use), PbD levels were significantly associated with factor scores for focus-execute and the shifting factors but not for the encoding and sustained attention factors. While tibia Pb was significantly associated with the focus-execute factor, no significant associations were identified between patella Pb and the four attentional factors.

Cincinnati

The Cincinnati Lead Study (CLS) commenced pre-natal recruitment in 1979 and continued until early 1985 and investigated the impact of Pb levels upon children's neurobehavioural development (Dietrich, Krafft, Bornschein, Hammond, Berger, Succop, & Bier, 1987), motor development (Dietrich, Berger & Succop, 1993) and delinquency (Dietrich, Ris, Succop, Berger & Bornschein, 2001). The catchment area of Cincinnati, Ohio, was chosen due to a history of high childhood PbB levels relating to Pb based paint and dust and poor housing conditions (Dietrich et al., 1987). The sample comprised mainly African-American, lower class, disadvantaged children living in deteriorated housing. The covariate variables and PbB concentration data are presented in Table 5.

Table 5

Study design and sample characteristics for the Cincinnati prospective study

Cincinnati (*N* = 305)[a] Disadvantaged population, 33% African American.				
Age	PbB[b] (*SD*) (µg/dL)	Cognitive Measures[c]	Key covariates	Notable findings
10 days	4.6 (2.8)	n.d	Birth weight, Gestation, OCS & PCS, Tobacco/alcohol consumption, maternal age, gravidity, parity, maternal iron-binding capacity, gender, race, number of siblings, birth order, 5 minute Apgar Score, shortened WAIS-R, HOME. *Other PbB Exposure Data:* 1st/2nd or 3rd trimester mean = 8.0 µg/dL, *SD* = 3.7; Cord blood mean = 6.3 µg/dL, *SD* = 4.5.	• 6 month MDI scores, with covariate adjustment - inversely associated with maternal PbB, 'maternal PbB and child gender' interaction variable & '10 day newborn and SES' interaction variable. • 24 month MDI and PbB exposure multiple regression failed to identify any significant relationships except a positive relationship between maternal PbB and 24 month MDI. Was a 'neurobehavioural catch-up' at play? • At 4 years, a significant correlation was identified between the interaction 'neonatal Pb and social class' and composite and subscale scores of the K-ABC. Do children from less advantaged environments express cognitive deficits at lower PbB levels? • At 5 years, statistically significant associations were identified between PbB measures and K-ABC subscales and measures of auditory processing, respectively. • At 6 years, assessments pointed to the value of motor development measures as markers for the impact of Pb upon children. • 16-17 years: the first study to report a significant association between low level pre-natal Pb exposure and adolescent outcomes.
3 months	5.9 (3.4)	BSID: MDI = 100.4 (9.91).		
6 months	n.d	BSID: MDI = 107.7 (16.28).		
12 months	15.85 (8.17)	BSID: MDI =111.9 (14.46).		
24 months	17.45 (9.16)	BSID: MDI = 88.08 (13.77).		
3 years	16.2 (7.6)	n.d		
4 years	14.0 (7.1)	K-ABC: MPC = 80.3 (10.40).		
5 years	11.9 (6.4)	K-ABC: MPC = 87.2 (10.7); SCAN.		
6 years	10.1 (5.6)	B-OTMP & WISC-R.		
6.5 years	B-OTMP & WISC-R			
15-17 years	SRD & PRDB; battery of cognitive measures.			

Note. 'n.d' is indicative of 'no data' and means that research papers did not collect data at this time point or did not report data that was collected. B-OTMP: Bruininks-Oseretsky Test of Motor Proficiency; BSID: Bayley Scales of Infant Development; HOME: Home Observation for Measurement of the Environment Inventory; K-ABC: Kaufman Assessment Battery for Children; MDI: Mental Development Index; MPC: Mental Processing Composite standard score; OCS: Obstetrical Complication Scale (Littman & Parmelee, 1978); *N*: Sample size; PCS: Postnatal Complication Scale (Littman & Parmelee, 1978); PbB: blood lead levels; PRDB: Parental Report of Predelinquent and Delinquent Behaviour; SCAN: Screening Test for Auditory Processing Disorders; *SD*: standard deviation; SES: Socioeconomic status; SRD: Self-Report of Delinquent Behaviour; WAIS-R: Wechsler Intelligence Scale for Adults- revised; WISC-R: Wechsler Intelligence Scale for Children – Revised; µg/dL: microgram per deciliter.

[a] This figure represents the number of children enrolled at birth.

[b] Arithmetic mean PbB levels unless otherwise stated.

[c] Mean (standard deviation) of cognitive ability measures are included where reported by research group.

The initial sample recruited 305 mother–child dyads. Strict exclusion criteria were enforced for mothers who were drug or alcohol dependent, diabetic, or neurologically, psychotically, or intellectually impaired. Likewise, infants with serious medical conditions and born at fewer than 35 weeks gestation or below 1500g birth weight were excluded. Using the Apgar scoring system (a method designed to capture the condition of a new born at delivery; Apgar, 1966), infants with Apgar scores exceeding 6 at five minutes were also excluded. The final sample has been described as comprised predominately African America, single-parent families receiving governmental support (Dietrich et al, 1993).

From Table 5 it is evident that venipuncture child PbB levels progressively rose from birth and steadily increased until peaking at 2 years of age (mean = 17.45 µg/dL, *SD* = 9.16). Dietrich et al. (1993) explained this peak as coinciding with developmentally appropriate locomotive and hand-to-mouth activity.

Neuropsychological assessment was carried out using the BSID at 3, 6 and 24 months of age. After adjustment for covariates (birth weight, gestational age, maternal age, child race and sex and SES), no significant correlations existed between fetal Pb exposure and Bayley Psychomotor Development Index（PDI) at 3 months; however, with adjustment maternal PbB and cord PbB levels were significantly inversely correlated with BSID MDI at 3 months**.** This equated to a 0.34 reduction in MDI points for each µg/dL increase in maternal PbB levels and a 0.60 MDI point reduction for each µg/dL increase in cord PbB levels (Dietrich et al., 1987).

For 6 month BSID data, adjusted (birth weight, gestation, maternal age, child sex and SES) analyses revealed:

- No statistically significant correlations identified between fetal Pb exposure and Bayley PDI at 6 months.
- For 6 month MDI scores, with covariate adjustment, inverse associations were identified for maternal PbB levels and 10 day newborn PbB levels. The associations were also inverse between 6 month MDI scores and cord and 3 month PbB levels, respectively, although they did not reach significance.

- A significant inverse association was also identified between 6 month MDI and the 'maternal PbB and child gender' interaction variable. For maternal PbB levels, dose-related deficits were most notable for males in the cohort at 6 months such that each µg/dL increase in maternal PbB levels was accompanied by a 0.84 decrement in MDI points. Likewise, a significant inverse association was also identified between 6 month MDI and the '10 day newborn and SES' interaction.
- Review of the data revealed that 10 day newborn PbB dose-related deficits were most pronounced for children from families with SES below the cohort median, such that each µg/dL increase in 10 day newborn PbB levels was accompanied by a 0.73 decrement in MDI points. Using the 3 and 6 month data, Dietrich et al. (1987) conducted structural equation modelling which suggested that neurobehavioural declines may be partly mediated by Pb-linked declines in birth weight and gestation.

Multiple regressions exploring the relationship between PbB levels (eleven PbB level variables, which were analysed both in µg/dL and transformed to their natural logarithms) and 24 month MDI failed to identify any significant relationships (with the exception of a positive relationship between maternal PbB levels and 24 month MDI). In fact, as in the significant maternal PbB levels and 24 month MDI association, many of the parameter estimates for these correlations were positive, rather than negative, as seen in the 3 and 6 month data. The association between MDI 24 month and the interaction variable 'high pre-natal' and 'high postnatal' PbB concentration was also found to be non significant. The only significant independent predictors of 2-year BSID MDI were gender (with females out performing males), birth length and maternal intelligence. Other covariates that were associated with 2-year Bayley MDI, but eliminated from the trimmed regression models, were birth weight, head circumference, gestational age, Postnatal Complication Scale score and HOME score.

At this point, Dietrich, Succop, Berger & Keith (1992) proposed that a 'neurobehavioural catch-up' was at play in the 24 month assessment whereby a damaged CNS had recovered from early Pb exposure. To explore this theory an exploratory analysis was

conducted whereby MDI raw scores were entered as a measure of 'behavioural growth' (Dietrich, Succop, Bornschein, Krafft, Berger, Hammond et al., 1990) because these scores represent the gross number of items passed by the participant in their first two years of development. Developing a ratio that expressed the percentage change in scores between 3 and 24 month MDI, Dietrich Succop, Bornschein, Krafft, Berger, Hammond et al. (1990) found that the mean percent MDI raw score increase from 3 to 24 months was 275.4% (*SD* = 72.5, range = 144.7 – 892.3). When this analysis was applied to PbB level variables and measures of fetal growth and development (pre-natal PbB concentration, birth weight, gestation, and head circumference), these perinatal variables were significantly correlated with the percent increase in MDI score. Thus, infants with the highest PbB concentration and smallest gestational age, head circumference and birth weight, were those presenting the most notable early life neurobehavioural 'catch-up' (Dietrich et al, 1990).

At 4 years of age the Kaufman Assessment Battery for Children (K-ABC) was administered. The K-ABC allows calculation of a Mental Processing Composite standard score (MPC; comparable to FSIQ from the Wechsler scales), a Sequential Processing standard score (SEQ; ordered problem slowing), a Simultaneous Processing standard Score (SIM; assimilation of information and problem solving by integrating contrasting stimuli into a coherent pattern), a Nonverbal standard score (NONVB; sequential and simultaneous information processing skills), and an Achievement standard score (ACHIV; learning from home and academic environments; Dietrich, Succop, Berger, Hammond, & Bornschein, 1991). After adjustment for covariates (birth weight, maternal cigarette use during pregnancy, maternal alcohol use during pregnancy, maternal marijuana use during pregnancy, child race, HOME score, maternal intelligence, and preschool attendance) a significant correlation was identified between the interaction 'neonatal Pb and social class' and MPC, SIM, NONVB and ACHIV. According to Dietrich et al. (1991) these analyses suggested that "children from less advantaged environments express cognitive deficits at lower PbB levels than do children from families of relatively higher socioeconomic status" (p. 210).

When the K-ABC was readministered to the cohort at 5 years of age (*n* = 259), adjusted analyses (for head circumference at birth, length at birth, cigarette consumption during pregnancy, social class, preschool attendance, maternal intelligence, HOME scores and maternal age) showed a statistically significant association between SIM and PbB levels at 4 years. Measures of central auditory processing were also collected at the 5-year cohort follow-up using a Screening Test for Auditory Processing Disorders (SCAN). A subtest of the SCAN, the Filtered Word Subtest (FWS) yielded adjusted (hearing screen, social class, HOME scores, birth weight, gestational age, obstetrical complications scale score, and alcohol consumption) statistically significant relationships between neonatal PbB levels and FWS left ear. Inverse significant relationships were also identified between FWS right ear and PbB levels at 3 years, PbB levels at 5 years and lifetime PbB levels. Dietrich, Succop, Berger and Keith (1992) rationalised that at 5 years of age, the absence of significant associations following covariate adjustment may be explained by the large degree of unaccounted confounding that occurs in epidemiological studies.

At 6 years of age, the cohort (*n* = 245) was assessed using the Bruininks-Oseretsky Test of Motor Proficiency (B-OTMP), which calculates Gross Motor (Running Speed and Ability, Balance, Bilateral Coordination and Strength) and Fine Motor (Response Speed, Visual-Motor Control and Upper-Limb Speed and Dexterity) composite scores (Dietrich et al., 1993). The cohort performed in the average range in all B-OTMP subtests with the exception of Balance, Response Speed and Visual-Motor Control, leaving the Fine Motor Composite approximately 1.3 *SD* below the US mean. After adjustment for covariates (subtests of the HOME, maternal IQ, social class, child gender and race) Bilateral Coordination was significantly associated with lifetime Pb exposure and current PbB levels. Visual-Motor Control was significantly associated with current PbB levels. Upper-limb Speed and Dexterity was significantly associated with neonatal PbB, lifetime PbB and current PbB levels. Finally, the Fine Motor composite Score was significantly associated with neonatal

PbB, lifetime PbB and current PbB levels. This research points to the value of motor development measures as markers for the impact of Pb upon children.

Given the rich dataset accumulated in the CLS, the research group turned their attention to long-term follow-up of the cohort and managed to engage 195 participants from the original cohort now mean age 15.6 years (*SD* = 0.8 years). Ris et al. (1994) focused their follow-up investigation upon the associations between pre-natal maternal PbB, average childhood PbB (from the first 5 years), and 78 month PbB levels and a range of cognitive function domains. Since the CLS follow-up study was designed following the publication of findings from other seminal prospective studies, Ris et al. (2004) were able to target functional domains that had been flagged as being potentially vulnerable to the effects of Pb exposure in the other cohorts. Hence, Ris et al. (1994) designed their battery to assess executive function (Stiles & Bellinger, 1993), attention (Bellinger, Hu et al., 1994; Needleman et al., 1979), memory (Stiles & Bellinger, 1993), academic achievement (Needleman et al., 1990), verbal skills (Fergusson & Horwood, 1993), visuoconstructional skills (Dietrich et al., 1993 Stiles & Bellinger, 1993), and fine-motor coordination (Dietrich et al., 1993; Wasserman, Liu, Popovac, Factor-Litvak, Klines, Waternaux et al., 2000). Ris et al. (2004) found that with statistical adjustment (for maternal IQ, SES, total average HOME scores and adolescent marijuana consumption), significant relationships were identified between pre-natal PbB levels and, average childhood PbB and 78 month PbB levels and attention (as measured by the Continuous Performance Test). Significant associations were also identified between visuoconstruction (a factor comprised of Block design from the WISC-III and Rey-Osterrieth Complex Figure) and pre-natal PbB levels and fine-motor performance (factor comprised of Grooved Pegboard Test and Finger Tapping Test) and 78 month PbB levels. At the time of publication, this was the first study to report a significant association between low level pre-natal Pb exposure and later adolescent outcomes. Ris et al. (2004) conceptualised their final contribution from the CLS study as exploratory in nature and as adding to the knowledge base by providing some evidence of long-term associations

between early life Pb exposure and mid-adolescent outcomes, in particular in domains of sustained attention, visuoconstruction and fine-motor abilities. In sum, the CLS research group collected a rich dataset, the analyses of which point to:

- Detrimental impact of early life Pb exposure (*in utero*) and early outcomes;
- Possibility of a 24 month neurocognitive 'catch-up' for the infants with highest PbB levels and lowest birth growth measures;
- Role of gestational age and birth weight as mediators of the Pb – neurocognitive relationship;
- Relevance of a range of covariates; and
- Possible repercussions of early Pb exposure into adolescence.

Cleveland

Three hundred and fifty-nine mother-child dyads were recruited in Cleveland, Ohio, between January 1981 and March 1982 for a prospective study investigating the consequences of pre-natal and early childhood low-level Pb exposure. The population was considered disadvantaged and the primary Pb exposure routes were via deteriorated housing and the general environment. Cognitive deficit (confidence intervals indicate an average 2 IQ point decrement) related to maternal alcohol consumption in pregnancy had been documented previously (Greene, Ernhart, Ager, Sokol, Martier & Boyd, 1991). It is important to note that alcohol was reported as having been used during pregnancy by more than 50% of the Cleveland study mothers. The covariate variables and PbB concentration data are summarised in Table 6.

Table 6

Study design and sample characteristics for the Cleveland prospective study.

Cleveland (*N* = 359)[a] Disadvantaged population, 33% African American.				
Age	PbB[b] (*SD*) (µg/dL)	Cognitive Measures[c]	Key covariates	Notable findings
Maternal	6.5 (1.84)	n.d	Maternal alcohol & smoking behaviour, gestational age, maternal age at birth, race, gender, age, birth order, birth weight, HOME, maternal IQ, parental education, parity & social class.	• Up to 3 years - In adjusted analyses no significant associations between historical and concurrent PbB concentrations were identified and the directionality of all observed associations were inconsistent. Minimal support was delineated for the hypothesis that Pb may influence the development of language skills in the developmental window 3 year and below. • 4 years 10 months: Once covariate adjustment was applied statistical significance was not reached for correlations between any of the subscale components of the WPPSI and PbB measures (maternal, cord, preschool total, 6 months, 2 years and 3 years).
Cord	5.89 (2.10)	n.d		
6 months	9.99 (3.32)	BSID: MDI=112.1(8.6); PDI =111.8 (14.6); KID = 111.7 (13.8).		
12 months	n.d	MDI = 111.5 (15.1), SCID.		
24 months	16.70 (6.45)	MDI =101.8 (17.5); KID, SCID.		
3 years	16.70 (6.01)	Stanford-Binet = 89.7(15.5); Sequenced Inventory of Communication Development.		
4 yrs, 10 mths (*n* =260)	17.0 (n.d)	WPPSI: FSIQ = 87.5 (16.6); VIQ = 86.2 (14.4); PIQ = 92.4 (16.6).		

Note. 'n.d' is indicative of 'no data' and means that research papers did not collect data at this time point or did not report data that was collected. BSID: Bayley Scales of Infant Development; FSIQ: Full Scale IQ; HOME: Home Observation for Measurement of the Environment Inventory; KID: Kent Infant Development Scale; MDI: Mental Development Index; *N*: Sample size; *n*: subsample size; PbB: blood lead levels; PDI: Psychomotor Development Index; SCID: Sequenced Inventory of Communication Development; *SD*: standard deviation; VIQ: Verbal IQ; WPPSI: Wechsler Preschool and Primary Scale of Intelligence; µg/dL: microgram per deciliter;
[a] This figure represents the number of children enrolled at birth.
[b] Arithmetic mean PbB levels unless otherwise stated.
[c] Mean (standard deviation) of cognitive ability measures are included where reported by research group.

At birth, maternal PbB (mean = 6.5µg/dL, *SD* = 1.84) and cord Pb concentration (mean cord Pb= 5.89 µg/dL, *SD* = 2.10) were measured. Childhood PbB levels steadily rose from 6 months of age (mean PbB = 9.99 µg/dL, *SD* = 3.32), to 2 years (mean PbB = 16.7 µg/dL, *SD* = 6.45), then 3 years (mean PbB = 16.70 µg/dL, *SD* = 6.01) and at peaked at the final assessment aged 4 years, 10 months (mean PbB = 17.0 µg/dL). Developmental status was gauged at these times through various age-appropriate developmental measures such as the BSID, Kent Infant Development Scale (KID) and Wechsler Preschool and Primary Scale of Intelligence (WPPSI)[14].

The primary goal of all assessments conducted up to 3 years of age (Ernhart, Morrow-Tuck & Wolf, 1988) was to explore whether measures of cognitive development were significantly associated with pre-natal Pb level, early life Pb measures and concurrent Pb concentrations. In analyses adjusted for covariates (age, sex, race, birth weight, birth order, gestational exposure to other toxic substances, maternal intelligence and several indicators of the quality of the caretaking environment) and confounding risk factors (gestational exposure to alcohol and other toxic substances) no significant associations between historical and concurrent PbB concentrations were identified and the direction of observed associations were inconsistent.

At 4 years 10 months the WPPSI was administered to the cohort (Ernhart, Morrow-Tlucak, Wolf, Super & Drotar, 1989). To explore the possible neurocognitive repercussions of pre-natal PbB exposure, maternal and cord PbB concentration were analysed in conjunction with WPPSI scores. These analyses found that FSIQ and subscale WPPSI (VIQ and PIQ) scores were significantly negatively correlated with both maternal and cord PbB levels prior to applying adjustment for covariates. Once covariate adjustment was applied, associations were not significant. Similarly, when analyses were conducted exploring WPPSI subscale performance and childhood PbB levels (preschool total, 6 months, 2 years and 3 years)

[14] The WPPSI is a 12 test battery designed for use with children aged 4 to 6.5 years; it yields FSIQ, VIQ and PIQ (Yule, Gold & Busch, 1982). The WPPSI is normed at a mean of 100 and *SD* of 15. The original WPPSI has undergone a number of revisions in order to update the normative samples and revise the tests included in the battery.

statistically significant negative associations were identified prior to adjustment for covariates and these associations were no longer significant with covariate adjustment.

In sum, the Cleveland cohort study failed to identify a compelling relationship between early Pb exposure and verbal development but identified a significant inverse association between 4 year 10 month WPPSI scores and *in utero* and early life Pb exposure that withstood covariate adjustment.

Kosovo

The town of Kosovska Mitrovica, in the province of Kosovo, Yugoslavia, was pinpointed as a site to investigate Pb exposure, iron status and infant development, due to its industrial history of Pb smelting, refining and its battery production plant (Wasserman et al., 1992; Wasserman et al., 1998; Wasserman et al., 2000). Kosovska Mitrovica infants were compared with infants from Pristina, a relatively unexposed community 40 kilometres away. Seven hundred and six infants were identified for follow up from a prospective study of 1502 pregnant women in 1985 and 1986. Three year follow-ups were completed with families prior to the eruption of conflict in Yugoslavia in 1992 (Wasserman et al., 1998).

Venous blood samples were taken during mid-pregnancy (Kosovska Mitrovica: mean PbB = 19.9 µg/dL, *SD* = 7.7; Pristina: mean = 5.6 µg/dL, *SD* = 2.0), cord PbB levels (Kosovska Mitrovica: mean PbB = 22.2 µg/dL, *SD* = 8.1; Pristina: mean PbB = 5.5 µg/dL, *SD* = 3.3) at delivery and then at 6, 12, 18 and 24 months (Kosovska Mitrovica: mean PbB = 35.4 µg/dL; Pristina: mean PbB = 8.5 µg/dL) and at 3, 4, 5 and 7 years. The MDI of the BSID was administered at 6, 12, 18 and 24 months. The MSCA was administered at 3 and 4 years and then the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) and WISC-III at ages 5 and 7 respectively. The covariate variables and PbB concentration data are summarised in Table 7.

Table 7

Study design and sample characteristics for the Kosovo prospective study.

Kosovo (*N* = 706)[a] General population				
Age	PbB[b] (*SD*) (µg/dL)	Cognitive Measures[c]	Key covariates	Notable findings
Maternal	Kosovska Mitrovica: 19.9 (7.7) Pristina: 5.6 (2.0)		Ethnic group, birth order, birth weight, gender, maternal age, maternal education, weight, height, head circumference, & living in apartment.	• <u>At 24 months:</u> with covariate adjustments increases in PbB concentration from 10 to 30 µg/dL at each age, would result in decrements in MDI points ranging in magnitude from - 1.13 at 6 months to - 2.53 points at 2 years. • <u>At 5 - 7 years:</u> Following covariate adjustment regression analyses showed significant associations between accumulated lifetime PbB and FSIQ, PIQ and VIQ.
Cord	Kosovska Mitrovica 22.2 (8.1) Pristina: 5.5 (3.3)			
6 months	n.d	BSID		
12 months	n.d	BSID		
18 months	n.d	BSID		
24 Months	Kosovska Mitrovica: 35.4 (n.d). Pristina: 8.5 (n.d).	BSID: Kosovska Mitrovica: 104.6 (18.5) Pristina: 105.8 (17.6)		
3 - 4 Years	Kosovska Mitrovica: 40.9 (14.9). Pristina: 9.8 (3.4).	MSCA	Maternal IQ (RPM) & CBCL/2-3.	
5 – 7 years	n.d	WPPSI-R/ WISC-III	HOME.	

Note. 'n.d' is indicative of 'no data' and means that research papers did not collect data at this time point or did not report data that was collected. BSID: Bayley Scales of Infant Development; CBCL/2-3: Child Behaviour Check List for 2 - 3 year olds; FSIQ: Full Scale IQ; HOME: Home Observation for Measurement of the Environment Inventory; MDI: Mental Development Index; MSCA: McCarthy Scales of Children's Abilities; *N*: Sample size; PbB: blood lead levels; PIQ: Performance IQ; RPM: Raven's Progressive Matrices; *SD*: standard deviation; VIQ: Verbal IQ; WISC-III: Wechsler Intelligence Scale for Children – Third edition; WPPSI-R: Wechsler Preschool and Primary Scale of Intelligence-Revised; µg/dL: microgram per deciliter.

[a] This figure represents the number of children enrolled at birth.

[b] Arithmetic mean PbB concentration.

[c] Mean (standard deviation) of cognitive ability measures are included where reported by research group.

Wasserman et al. (1992) reviewed the relationship between PbB concentration and MDI performance when cohort participants reached 24 months of age. Prior to control for covariates no associations between PbB concentration and MDI were identified. In order to explore further the data, adjustments were made for birth weight, gender, maternal intelligence, maternal education, and maternal age at birth. When PbB concentration was added to the core model developed for 2 year MDI scores, it was observed that increases in PbB concentration from 10 to 30 µg/dL at each age would result in decrements in MDI points ranging in magnitude from - 1.13 at 6 months to - 2.53 points at 2 years. This decrement in MDI points, noted at 2 years, was a statistically significant decline and accounted for 1.0% of observable MDI variance.

At 5 - 7 years of age, 309 cohort members were administered the WISC-III. Following covariate adjustment, regression analyses showed significant associations between accumulated lifetime PbB concentration (up to 7 years) and FSIQ, PIQ and VIQ. After covariate adjustment, a change in lifetime PbB concentration from 10 to 30 µg/dL was associated with an estimated decrease of 4.3 points (95% CI = 3.4, 5.1) in FSIQ; corresponding estimated decreases for VIQ and PIQ were 3.4 (95% CI = 1.7, 5.0) and 4.5 points (95% CI = 2.7, 6.3), respectively. The relationship was further explored in terms of WISC-III factor scores and, with adjustment, significant correlations were identified between lifetime cumulative PbB concentration and Freedom from Distractibility, Perceptual Organisation and Verbal Comprehension.

Hence, the Yugoslavian research of Wasserman et al. (1992) indicated that as PbB concentration increased, detriments to MDI performance could be observed at 2 years of age. Lifetime PbB concentration was significantly inversely associated with WISC-III scales and subscales.

Port Pirie

The Port Pirie Cohort Study (PPCS) commenced in 1979 and sampled families living in proximity to a large Pb smelter in Port Pirie, South Australia, as well as some families living in rural communities in the general region who were assumed to be very much less likely to be exposed to effluent from the smelter. The study explored the effects of Pb on pregnancy outcomes (Baghurst, Oldfield, Wigg, McMichael, Roberston & Vimpani, 1985; Baghurst, McMichael, Vimpani, Robertson, Clark & Wigg,, 1987; Baghurst, Roberston, Oldfield, King, Mc Michael, Vimpani, et al., 1991; McMichael, Vimpani, Robertson, Baghurst & Clark, 1986), cognitive function (McMichael, Baghurst, Wigg, Vimpani, Robertson & Roberts, 1988; Wigg, Vimpani, McMichael, Baghurst, Robertson & Roberts, 1988; Baghurst et al., 1992; Tong, 1995; Tong, Baghurst, McMichael, Sawyer & Mudge, 1996; Tong, Baghurst, Sawyer, Burns & McMichael, 1998) and emotional and behavioural development (Burns, Baghurst, Sawyer, McMichael & Tong, 1999). The original sample included almost 90% of all births in Port Pirie and nearby townships from May 1979 to May 1982 and followed children until they were between 11 and 13 years of age.

Maternal venous PbB samples were collected between 14 and 20 weeks gestation, at 32 weeks gestation, from the umbilical cord at birth (Baghurst, McMichael, Vimpani, Robertson, Clark & Wigg, 1987; Baghurst, Robertson et al., 1987) and from the child at birth, 6, 15, 24 months, then annually until age 7 years (Baghurst et al., 1992) and between 11 and 13 years (Burns et al., 1999). For children, PbB levels increased from birth, 8.3µg/dL, to 21.2 µg/dL at 2 years of age and then declined to 7.9 µg/dL between 11 and 13 years (Tong et al., 1998). The child's cognitive status was gauged at 24 months using the BSID (Baghurst et al., 1985), at 4 years using the MSCA, at 7 years using the WISC-R (Baghurst et al., 1992) and between 11 and 13 years with the WISC-R (Burns et al., 1999). The covariate variables and PbB concentration data are summarised in Table 8.

Table 8

Study design and sample characteristics for the Port Pirie prospective study.

Port Pirie (*N* = 623)[a] Community located in proximity to lead smelter				
Age	PbB [b] (µg/dL)	Cognitive Measures [c]	Key covariates	Notable findings
Maternal (14-20 weeks)	9.1	n.d	Area /duration of residence, maternal alcohol /tobacco use, marital status, maternal age at birth, BMI, dietary practice (vitamin supplements) & social status. *From 6 months:* Parental level of education, parents workplace, parental relationship, child birth rank, oxygen use at birth, Apgar score at 5 minutes, neonatal jaundice, size for gestational age, mouthing activity @ 15 months, duration breast-feeding, season & rain water use. *Early childhood:* HOME at 3-4 years, WAIS-R at 3-4 years, CBCL at 4 and 5 years.	• <u>2 - 4 years:</u> the significant association between Pb exposure and cognitive functioning was maintained for girls (GCI: estimate of Pb-Gender term = - 7.58, *SE* = 3.54, *p* = 0.03) and for Memory (estimate Pb-Gender term = - 5.28, *SE* = 2.20, *p* = 0.02) but not for boys in the cohort. • <u>11- 13 years</u>: Pb exposure was inversely associated with cognitive measures at 2, 4, 7 and 11-13 years. • At ages <u>11 to 13 years</u> geometric mean lifetime PbB was 14.3 µg/dL for males and 13.9 µg/dL for females (Burns et al., 1999).
Cord	8.3	n.d		
Birth	8.3	n.d		
6 months	14.4	n.d		
15 months	6.5	n.d		
24 months	21.2	BSID		
3 years	20.9	WISC-R K-TEA-BF		
4 years	n.d.	MSCA.		
7 years	11.6	WISC-R = 104.7 (95% CI =103.5, 106.0)	*7 years* DSOP, HOME & maternal IQ WAIS-R.	
11-13 years	7.9	WISC-R = 100 (95% CI = 98.8, 101.2)	*11-13 years:* CBCL, HOME, General Health Questionnaire, WAIS-R & McMaster Family Assessment.	

Note. 'n.d' is indicative of 'no data' and means that research papers did not collect data at this time point or did not report data that was collected. BMI: Body Mass Index; BSID: Bayley Scales of Infant Development; CBCL: Child Behaviour Check List; CI: Confidence interval; DSOP: Daniel's Scale of Occupational Prestige; GCI: General Cognitive Index**;** HOME: Home Observation for Measurement of the Environment Inventory; K-TEA-BF: Kaufman Test of Educational Achievement – Brief Form; MSCA: McCarthy Scales of Children's Abilities; *N*: Sample size; PbB: blood lead levels; *SE*: standard error; *SD*: standard deviation; WAIS-R: Wechsler Adult Intelligence Scale- Revised; WISC-R: Wechsler Intelligence Scale for Children – Revised; µg/dL: microgram per deciliter

[a] This figure represents the number of children enrolled at birth and this figure declined to 375 participants by 11 – 13 years.

[b] Geometric mean PbB concentration.

[c] Mean (standard deviation) of cognitive ability measures are included where reported by research group.

McMichael, Baghurst, Vimpani, Robertson, Wigg, & Tong (1992) identified gender as an effect modifier in associations between PbB concentration and cognitive performance measures at 2 and 4 years, respectively. After adjustment for parental smoking, SES, HOME scores, maternal IQ, birth weight, infant feeding style and number of siblings in the household, the association between Pb exposure and neurocognitive measures was more pronounced and significant for girls for the GCI and for Memory. When data were stratified, the significant association between Pb exposure and cognitive functioning was maintained for girls and for Memory but not for boys in the cohort. Specifically, McMichael et al. (1992) estimated that for GCI, increases in PbB in the range from 10µg/dL to 30µg/dL, would be accompanied by estimated covariate-adjusted decrements of 8.3 points for girls and 0.8 points for boys.

Tong et al. (1998) reported an overview of all of the cognitive data and Pb measures with the inclusion of WISC-R data collected at age 7 years and again at 11-13 years (n = 375). The central aim of this analysis was to explore the reversibility of detrimental effects of Pb exposure and specifically to determine whether declines in PbB level documented beyond 2 years of age could be linked to a recovery of cognitive function (an improvement in scores). They graphed the differences in performance in cognitive measures (BSID, MSCA or WISC-R) by three exposure groups for average lifetime PbB concentration at age 2 years in simple plots (See Figure 5).

Figure 5 illustrates that children with differential exposure patterns at age 2 years followed distinct trajectories into adolescence; those with highest PbB exposure levels at age 2 years continued to perform below their cohort counterparts in future follow-ups. With adjustment for a range of covariates (gender, birth weight, birth rank, feeding style during infancy, duration of breastfeeding, maternal IQ, maternal age at child's birth, SES, HOME scores, parental smoking habits, parents living together), Pb exposure was inversely associated with cognitive measures at 2, 4, 7 and 11 - 13 years.

NOTE:
This figure is included on page 79
of the print copy of the thesis held in
the University of Adelaide Library.

Figure 5

Adjusted developmental scores at various ages by tertile of lifetime average PbB concentration at age 2 years (Tong et al., 1998, p. 1817).

Note. Adjustments made for potential confounders including child gender, birth weight, birth rank, feeding style during infancy and duration of breast feeding, maternal IQ, maternal age at birth, SES, HOME scores, parental smoking and marital status. Cognitive development measured at 2 years using the BSID, the McCarthy GCI at 4 years and the WISC-R at 7 and 11 - 13 years (Tong et al., 1998).

Sydney

The Sydney Lead study was a five-year project with an initial cohort of 318 children residing in Sydney, Australia and born in 1982 and early 1983. The population sampled has been described by Cooney et al. (1989) as well-educated and middle-class. Venous PbB samples were taken from the mother prior to birth and from the umbilical cord at delivery. Blood samples were taken from the child every 6 months until the age of 4 years and then again at 5 years. Geometric mean child PbB levels increased from birth (cord PbB = 8.1 µg/dL) to 18 months (mean PbB = 16.4 µg/dL) and then steadily declined over the 6-month intervals to 10.1 µg/dL at 48 months (see Table 9). To assess neurocognitive functioning, the BSID was administered at 6, 12 and 24 months and the MSCA was administered at 3 and 4 years. The covariate variables and PbB concentration data are summarised in Table 9.

Table 9

Study design and sample characteristics for the Sydney prospective study.

Sydney (*N* = 318)[a] General population				
Age	PbB[b,c] (µg/dL)	Cognitive Measures	Key covariates	Notable findings
Maternal	9.1 (range 3 - 28)		*Mother* Age (years), verbal Intelligence – PPVT, educational level, smoking & alcohol consumption. *Father* Age (years), PPVT educational level & Occupation. *Child* Gestational age, birth weight, height, head circumference, obstetrical complications & post-natal factors. *Other* CBCL at 4 & 5 years, HOME (48 months), Bayley Infant Behaviour and the Toddler Temperament Questionnaire.	• <u>12 months:</u> With covariate adjustment there were no significant correlations between cord PbB and maternal PbB and 12 month BSID MDI. For cord PbB, effects on 12 month MDI were insignificant, for PDI positive but significant effects are identified ($F(1, 244) = 4.08$, $p = 0.04$). • <u>36 months:</u> in path analysis there were no significant direct paths from fetal exposures to MDI or PDI development at any age. The authors interpreted this as indicating that neither maternal PbB nor cord PbB significantly influence changes in neurocognitive outcomes over time.
Cord	8.1 (range 1 - 36)			
6 months	n.d	BSID: MDI =109.9, *SD* = 14.4; PDI =106.1, *SD* = 13.5.		
12 months	15.0	BSID: MDI = 112.9, *SD* = 15.0; PDI = 97.7, *SD* = 16.4.		
24 months	16.4	BSID: MDI = 117.4, *SD* = 18.8; PDI = 109.0, *SD* = 15.2		
3 years	n.d	MSCA: GCI =109.0, D = 16.4; Motor = 50.4, *SD* = 7.8[d]		
5 years	10.1	MSCA (mean/*SD* not reported).		

Note. 'n.d' is indicative of 'no data' and means that research papers did not collect data at this time point or did not report data that was collected. BSID: Bayley Scales of Infant Development; CBCL: Child Behaviour Check List; GCI: General Cognitive Index; HOME: Home Observation for Measurement of the Environment Inventory; MDI: Mental Development Index; MSCA: McCarthy Scales of Children's Abilities; *N*: Sample size; PbB: blood lead; PDI: Psychomotor Development Index; PPVT: Peabody picture vocabulary test; *SD*: standard deviation; µg/dL: microgram per deciliter.

[a] This figure represents the number of children enrolled at birth.

[b] Standard deviation not reported.

[c] Arithmetic mean PbB levels.

[d] This subscale of the McCarthy Test has been normed to a mean of 50 and standard deviation of 10.

Significant correlations were identified between cord PbB and maternal PbB levels and 12 month MDI and PDI, respectively. However, these correlations were positive. With covariate inclusion the combined effects of cord and maternal PbB concentration were not statistically significant for MDI and PDI. The effect of cord PbB concentration was examined separately, given the earlier correlations with BSID scores. For cord PbB, effects on MDI were not significant and for PDI positive significant effects are identified.

Path analysis was conducted in order to explore the idea that the impact of Pb upon the developing infant is differential over time. The primary question for Cooney et al. (1987) at this time was to delineate how much (if any) neurocognitive change can be linked to pre-natal exposure up to 36 months as marked by maternal PbB and cord PbB concentration. The path analysis was based on correlations and background variables (mother's age, verbal ability and education; father's education and occupation; mother's history of smoking and alcohol consumption) and birth outcome variables were included in the analysis.

In the final path model there were no significant direct paths from fetal exposures to MDI or PDI development at any age. The authors interpreted this as indicating that neither maternal PbB nor cord PbB concentration significantly influenced changes in neurocognitive outcomes over time (Cooney et al., 1989). Other pathways identified were between gestational age and MDI and PDI, where there was a significant impact at 6 months but beyond this age any impacts on development were indirect. Maternal factors were found to impact significantly the nature of the care giving environment (total HOME score at 6 months) and via this pathway there was an impact on neurocognitive development. The direct pathway influence of HOME score was maintained till 12 months but it dissipated by 24 months for PDI.

At 4 years of age analyses showed that individual PbB concentrations and lifetime Pb exposure were not significantly associated with any MSCA measures. The Sydney cohort, the second Australian cohort, did not identify relationships (Bell, 1990) that paralleled those identified in Port Pirie.

Mexico City

The Mexico City Prospective Lead Study was initiated between 1987 and 1992 and participants were followed until 2002 (Schnaas et al., 2000; Schnaas, Rothenberg, Flores, Martínez, Hernández, Osorio et al., 2006). The sample was described as low to middle SES and generally exposed to Pb via atmospheric contamination. Women were recruited at 12 weeks pregnancy and venous PbB samples were measured every 8 weeks until delivery, at which point umbilical cord PbB level was collected. Accordingly, 321 children were included in the study at birth and by 5 years of age, sample attrition meant that 175 participants remained. Child cognitive development was measured using the GCI of the MSCA annually from 3 to 5 years and the WISC-R (Spanish version) at 6 years. The covariate variables and PbB concentration data are summarised in Table 10.

When CGI data across all ages were pooled, there was no significant association with 6 - 18 month PbB, effects for 24 - 36 month PbB approached significance and a significant association was identified for 42 - 54 month PbB data. Further, it was observed that increases in PbB concentration from 24 - 54 months were accompanied by decreases in GCI for all age data. This research suggested that previous PbB exposure at any age had the greatest detrimental influence on cognitive abilities at 48 - 54 months (Schnaas et al., 2000).

Exploring possible relationships between PbB levels and WISC data, Schnaas et al. (2006) ran fixed-effects panel regression analyses with unadjusted and adjusted pre-natal, perinatal and post-natal PbB concentration and FSIQ data. For the unadjusted data, all correlations showed a negative impact of increased PbB concentration on FSIQ but the only significant correlations were for FSIQ and third trimester pregnancy (28 - 36 weeks) PbB and concurrent PbB levels.

For adjusted data (maternal IQ, SES, gender, birth weight), negative correlations were not uniformly observed but significant associations were retained between FSIQ and third trimester pregnancy (28 - 36 weeks) PbB and concurrent PbB levels, as in the unadjusted model.

Table 10

Study design and sample characteristics for the Mexico City prospective study.

Mexico City (*N* = 502)[a] Low or middle SES				
Age	PbB[b] (range) (µg/dL)	Cognitive Measures [c, d]	Key covariates	Notable findings
Maternal 36 weeks	15.0 (5.5 - 42.0)		5 minute Apgar, birth weight, birth order, child's gender, SES, maternal IQ (WAIS-S), maternal education.	• <u>6 - 54 months:</u> Significant associations were identified between GCI and 6 - 18 month PbB levels and 24 - 36 month PbBs, respectively. When GCI data was age-collapsed a significant association with 42 - 54 month PbB was noted. • <u>WISC data:</u> For adjusted data significant associations were observed between FSIQ and third trimester pregnancy and concurrent PbB as in the unadjusted model. • Both VIQ and PIQ significantly, inversely related to 28-36 week maternal PbB. • Prenatal 28 week PbB significantly predicted lower FSIQ. Concluded that 28 weeks gestation was a critical window for development of the neonatal brain and a point of particular vulnerability to the toxicant Pb.
Maternal at birth	15.5 (6.0 - 33.5)			
Infant at birth	13.1 (3.0 - 33.5)			
6 months	mean PbB 12 months = 10.8 (4.0 – 22.0) mean PbB 6 -18 months = 10.1 (3.5 - 37.0)	MDI: 115.3 (89 – 144)		
12 months		MDI: 115.7 (93 – 134)		
18 months		MDI: 107.9 (88 – 128)		
24 months	12.8 (5.0 – 25.8)	MDI: 103.5 (79 – 132)		
36 months	11.3 (4.7 – 22.9)	MSCA: GCI: 100.8 (85 – 116)		
42 months	mean PbB 42-54 months = 8.4 (2.5 - 44.8) mean PbB 48 months = 10.3 (4.2 – 20.5)	GCI = 105.1 (86 – 121)		
48 months		GCI = 102.3 (81 – 122)		
54 months		GCI = 104.1 (89 – 119)		
60 months	9.3 (3.8 – 18.0)	GCI = 104.8 (88 – 119)		
6 years	7.9 (3.2 – 16.0)	WISC FSIQ = 105 (87 – 123)		
7 years	7.5 (3.0 – 13.8)	FSIQ = 109 (91 – 127)		
8 years	6.4 (2.8 – 12.8)	FSIQ = 108 (91 – 126)		
9 years	6.0 (2.8 – 11.8)	FSIQ = 109 (91 – 128)		
10 years	5.6 (2.5 – 11.2)	FSIQ = 109 (87 – 130)		

Note. BSID: Bayley Scales of Infant Development; FSIQ: Full Scale IQ; GCI: General Cognitive Index; MDI: Mental Development Index; MSCA: McCarthy Scales of Children's Abilities; *N*: Sample size; PbB: blood lead levels; PIQ: Performance IQ; SES: Socioeconomic status; *SD*: standard deviation; WAIS-S: Wechsler Adult Intelligence Scale – Spanish; VIQ: Verbal IQ; WISC: Wechsler Intelligence Scale for Children; µg/dL: microgram per deciliter.

[a] This figure represents the number of children enrolled at birth.

[b] Geometric mean PbB levels.

[c] Group with complete data.

[d] Mean (range) of cognitive ability measures are included where reported by research group.

Having identified negative correlations between FSIQ and PbB measures, Schnaas et al. (2006) sought to explore whether 28 - 36 week PbB levels differentially impacted VIQ and PIQ. Schnaas et al. (2006) used linear modelling to explore the data further, using VIQ and/or PIQ as the dependent variable and including maternal IQ and first FSIQ measurement as covariates. With VIQ entered as the dependent variable, the linear model showed that 28 - 36 week PbB levels were inversely associated with child FSIQ. When PIQ was entered into the linear model as the dependent variable, analyses showed that 28 – 36 week PbB levels were were inversely associated with child FSIQ. Hence, this work suggested that pre-natal Pb can impact a range of cognitive abilities and that performance losses may not stem from a signature deficit but rather a global impairment across verbal and abstract reasoning and problem solving domains.

A linear mixed model was conducted to investigate whether there is a pre-natal exposure point that may best relate to childhood cognitive outcomes using PbB data collected from the mother at weeks 12, 20, 28, or 36 of pregnancy. From the model it was found that pre-natal PbB at 28 weeks gestation significantly predicted lower FSIQ. Schnaas et al. (2006) concluded that 28 weeks gestation was a critical window for development of the neonatal brain and a time of particular vulnerability to Pb.

3.1.2 Other Prospective studies

New York City (1981)

Ernhart, Landa and Schell (1981) recruited New York City children ages 3 to 5.5 years (N = 359) with mean PbB levels of 16.7 µg/dL (geometric mean PbB = 15.64 µg/dL), to be assessed using the MSCA and a reading test and to be subsequently followed up at 8 - 10.5 years of age.

Exploring the relationships between early life Pb exposure markers (maternal PbB, cord PbB, venous samples (taken at 6 months, 2 years and 3 years) and later developmental function (concurrent and subsequent BSID MDI Scale at 6 months, 1 year, 2 years and

Stanford-Binet at 3 years), Ernhart, Morrow-Tlucak, Marler and Wolf, (1987) noted that relationships were attenuated with statistical control for covariates was applied (age, sex, race, birth weight, birth order, maternal intelligence, and several indicators of the quality of the care taking environment, gestational exposure to alcohol and other toxic substances; Ernhart et al., 1988). At ages 1, 2, and 3 years, the Sequenced Inventory of Communication Development (SICD) was also administered to gauge language development. Multivariate analyses with covariate control found no statistically significant associations between Pb exposure measures and the subscales of the SICD (Ernhart, & Greene, 1990).

With covariate control (parent IQ and child gender), significant correlations were identified between school aged PbB concentration and the GCI of the MSCA and subscales of verbal and motor ability. For Ernhart et al. (1981), these correlations pointed to the conclusion that "[t]here was no evidence that subclinical levels of lead detected during the preschool period were related to intellectual development or behaviour during school years" (p. 917) given that there were no significant relationships identified between preschool PbB or lifetime accumulated PbB concentration and 5 - 7 year IQ. Indeed only concurrent PbB concentration showed significant relationships with 5 - 7 years measures of cognitive functioning at both the global and subscale level. The absence of an identifiable accumulative effect of early life Pb exposure lead Ernhart et al. (1981) to suggest that early life effects maybe reversible.

Given the failure to identify a relationship between early life Pb (mean PbB at 3 years = 16.7 µg/dL) exposure and subsequent developmental status, Ernhart et al. (1989) assessed the cohort at 4 years 10 months of age. Using the WPPSI, the authors noted significant associations but these were diminished with the application of covariate control (gender, race, birth order, birth weight, gestational age at birth, parental education, maternal IQ (PPVT-R), Authoritarian Family Ideology Scale, Michigan Alcoholism Screening Test score, alcohol per day in pregnancy, cigarettes per day, use of marijuana and other drugs in pregnancy). In lieu of statistical significance, it was also not possible to observe any directional consistency in the

associations between WPSSI scores and Pb exposure indices. The authors concluded that findings support "an inference that lead exposure in the range examined has little effect on child development" (Ernhart et al., 1989, p. 167).

Glasgow, Scotland

Moore, Goldberg, Pocock, Meredith, Stewart, McAnespie, Lees and Low (1982) investigated the relationship between PbB levels in children and exposure to Pb contaminated water from Pb plumbing, using a sample of 151 participants, drawn from a larger initial sample of the general population in Glasgow, Scotland. Key covariates or potential covariates were birth weight, HOME, social class and incidence of pica.

Using maternal PbB data, the sample was categorised into high (≥ 30 µg/dL), medium (15 - 25 µg/dL) and low (< 10 µg/dL) exposure groups. The BSID was administered at 1 and 2 years of age, and performance tended to decrease in accordance with rising maternal PbB levels. Using stepwise linear regression it was noted that home environment, social class and birth weight accounted for a greater proportion of variance in Bayley performance than measures of PbB concentration (namely maternal PbB concentration, pica and water Pb levels; Tong, 1995). This research was limited by relatively small sample size, which may not have had sufficient statistical power to detect a small impact of Pb levels upon BSID performance. Additionally, PbB levels of the child were not directly measured but rather inferred from maternal PbB concentration, pica and water Pb.

New Zealand

The Christchurch Health and Development Study commenced with a birth cohort of 1265 infants and collected data at birth and 4 months and then annually until age 13 years (Fergusson & Horwood, 1993). Ninety percent of the participants provided PbD samples between 6 and 8 years of age (mean PbD = 6.2 µg/g). For analytic purposes, the sample was divided into three groups on the basis of PbD levels at 8 years; 0 - 3 µg/g, 4 - 7 µg/g and ≥ 8

µg/g. From 8 to 12 years the children were administered the New Zealand revision of the Burt Word Reading Test (BWRT) once a year. In addition, a range of covariates were captured including maternal education level, SES, family living standards, family size, HOME, duration of residence in weatherboard houses, gender, birth weight avoidance of punishment and maternal emotional responsiveness).

Fergusson & Horwood (1993) conducted an analysis of variance identifying a significant association between PbD levels and mean BWRT scores and a significant association between age and mean test scores.

Exploration of the data showed that unadjusted associations between PbD levels and emergence of word recognitions skills aligned with a 'constant decrement model' (Fergusson & Horwood, 1993). In terms of the relationship between PbD levels and BWRT performance, this decrement model translated into a 5 point decrease in mean Word Recognition for children with PbD levels beyond 8 µg/g, compared to children with PbD levels in the range 0 - 3 µg/g. Upon covariate control (maternal education, SES, family living standards, family size, avoidance of punishment and maternal emotional responsiveness), a statistically significant difference between the high and low groups reduced to approximately a 3 point difference favouring the lower group. The researchers concluded that their findings reflected the view that "early exposure to lead results in very small, statistically detectable but apparently enduring deficits in cognitive abilities" (Fergusson & Horwood, 1993, p.891).

Fergusson, Horwood and Lynskey (1997) conducted follow-up with the original cohort in order to ascertain associations between childhood PbD levels (at 6-to-8 years of age) and educational success at 18 years of age. The sample was assessed using measures of word recognition (New Zealand revision of the BWRT) and educational attainment (number of years of secondary school education, mean number of School Certificate passes and leaving school without formal qualifications). Fergusson et al. (1997) found that with covariate adjustment (gender, maternal age, maternal education, SES, standard of living, duration of breastfeeding, birth order, parental conflict, maternal punitiveness, class level, years lived

near busy roads) there were small but significant relationships between PbD levels measured at age 8 years and educational outcomes at age 18 years, for reading test scores, having a reading ability of less than 12 years, failing to complete 3 years of high school, leaving school without educational qualifications and the mean number of School Certificate subjects passed. Hence, this research provided some evidence that early life exposure to Pb can be associated with educational trajectory and the life course of an individual.

Denmark

Damm, Grandjean, Lyngbye, Trillingsgaardi and Hansen (1993) conducted a follow up with a group of first grade children with low-level Pb exposure in the municipality of Aarhus, Denmark. The sample was taken from first grade children (N = 162).

Using PbD samples participants were classified as either 'high Pb' (n = 78, PbD > 18.7µg/g) or 'low Pb' (n = 83, PbD < 5µg/g). The geometric mean PbB concentration at age 9 years was 5.7 µg/dL for the 'high Pb' group and 3.7 µg/dL in for the 'low Pb' group. At approximately 8-to-9 years of age, children were administered a cognitive assessment battery designed to include measures which had shown a quantifiable 'Pb effect' in previous research and a sensitivity to cognitive dysfunction. The assessment battery was comprised of the Bender Visual Motor Gestalt Test (a test for recognition of spatial attributes and reproduction), WISC (mean IQ 'low Pb' = 114.2, mean IQ 'high Pb' = 108.3), Seashore Rhythm Test (taken from the Seashore Test of Musical Talent; the test is designed to measure engagement of nonverbal auditory stimuli, sustained attention and the ability to perceive and compare different rhythmic sequences; Hansen, Trillingsgaard, Beese, Lynbye & Grandjean, 1989), Visual Sequential Memory (from the Illinois Test of Psycholinguistic Abilities; participant are exposed to an auditory sequence and are required to recall the sequence), Trail Making Test (Part A & B; requiring instantaneous identification of the symbolic relevance of numbers and letters and efficient scanning abilities), Sentence Repetition Test (repetition of

sentence of increasing syntactic complexity), CPT and a behavioural rating scale (derived from the Continuous Performance Test).

Hansen et al. (1989) found that the 'low Pb' group had significantly higher FSIQ, VIQ (including significantly higher Information, Comprehension, Similarities and Vocabulary scores) and significantly lower Bender Errors, than the 'high Pb' group. The 'low Pb' and 'high Pb' groups did not differ significantly on measures of PIQ, sentence repetition, Seashore Rhythm Test, Trail Making Tests or the Continuous Performance Task.

With control for confounding variables (pregnancy complications, extended period of hospital stay, left handedness, jaundice, phototherapy, SES, number of siblings, age of the mother adjusted for parity, maternal educational status, child gender and previous pica behaviour), Hansen et al. (1989) calculated the correlation coefficients of covariates for the main outcome measures as follows:

- The Bender test: final model accounted for 4% of the observed variance with a highly significant relationship between PbD level and Bender errors.
- VIQ: final model accounted for 26% of the variance observed and PbD level explained a significant portion of the variance.
- FSIQ: Final model accounted for 20% of the observed variance and PbD level explained a significant portion of the variance. Pb level variance explained only 2.8% of the total variance in FSIQ – most variance was accounted for by number of siblings and mother's age adjusted for parity.

The Danish cohort was revisited at 15 years of age (n = 141; Damm et al., 1993), at which time the WISC ('low Pb': VIQ = 111.0, PIQ = 115.8; 'high Pb': VIQ = 104.0, PIQ = 115.1) was readministered and supplemented by the Bender Visual Motor Gestalt Test, the Trail Making Test and the Visual Gestalt Test (testing the ability to reproduce and engage visuospatial information). For 15 year old data, bivariate analyses of age-adjusted data did not reveal any statistically significant differences between the low and high Pb groups on each of the WISC subtests, the subscales and FSIQ (Damm et al., 1993).

Multicentre USA: Baltimore, Cincinnati, Newark & Philadelphia.

In the Treatment of Lead-exposed Children study, Chen et al. (2005) conducted a multicentre (Baltimore, Maryland; Cincinnati, Ohio; Newark, New Jersey; and Philadelphia, Pennsylvania), randomised, placebo-controlled clinical trial of 780 children assessed at 12 – 33 months of age using the BSID (mean MDI = 82.2 , *SD* = 13.7) and followed up at 5 and 7 years of age with the WPPSI (mean IQ = 80.6, *SD* = 13.3) and the WISC-III (mean IQ = 86.7, *SD* = 13.3), respectively. The Treatment of Lead-exposed Children study investigated the impacts of succimer treatment (an oral chelating agent; Chen et al., 2007) on the IQ performance of children with high PbB levels at age 2 years (mean PbB = 26.2 μg/dL, *SD* = 5.1, range = 20 – 44 μg/dL).

Analyses showed that cross-sectional associations between Pb and IQ increased in strength as the children grew older, but that the association between 2 year PbB concentration and subsequent IQ diminished. In other words, concurrent PbB concentration tended to have the strongest association with IQ and with increases in age the strength of this relationship increased. The peak PbB concentration from baseline to 7 years of age was not associated significantly with 7 year IQ. The average PbB concentration from 2 years of age to 5 - 7 years of age inversely associated with IQ at 5 - 7 years of age. It was concluded from these analyses that peak PbB concentration did not satisfactorily account for associations between low PbB levels and IQ in older children (5 - 7 years in this case). Possible effects due to concurrent PbB concentration were documented in this research and therefore there may need to be a theoretical adjustment in the relative importance of concurrent PbB levels to the relationships between PbB and children's cognitive abilities.

New York City (2003)

Canfield et al. (2003) investigated the association between low-level Pb exposure (below 10 μg/dL) and intelligence. Venous PbB samples were collected at 6 months, 12 months, 18 months, 2 years, 3 years and 4 years and analysed in terms of lifetime mean PbB

(at 3 years of age: 7.7 µg/dL; at 5 years of age: 7.4 µg/dL), peak PbB (mean = 11.1 µg/dL, *SD* = 7.1), concurrent PbB (mean = 5.8 µg/dL, *SD* = 4.1), and mean PbB concentration in infancy (6 – 24 months mean PbB = 7.0 µg/dL, *SD* = 3.8). Lowest PbB levels were observed at 6 months (mean PbB = 3 - 4 µg/dL), peaking at 2 years (mean PbB = 9.6 µg/dL) and then declining at 5 years (mean PbB = 6 µg/dL). The mean PbB level tended to fluctuate around 10 µg/dL for most participants; specifically, at 3 years of age 57% of participant's peak levels were below 10 µg/dL and this declined slightly to 55.8 % by 5 years of age.

The Stanford–Binet Intelligence Scale (SBIS) were administered at 3 and 5 years of age (mean IQ = 89.8, *SD* = 11.4). A range of sample characteristics were collected such as child sex, birth weight, iron status, maternal IQ (abbreviated SBIS), maternal education, race, tobacco use during pregnancy, yearly household income and HOME.

Two important findings regarding the impact of Pb upon children with PbB levels below 10 µg/dL emerged from the analyses conducted by Canfield et al. (2003):

1. IQ at ages 3 and 5 years was significantly inversely correlated with PbB levels even when the child's peak lifetime PbB level was below10 µg/dL. Prior to application of covariate adjustment, mean lifetime PbB, concurrent PbB, peak infancy PbB and mean infancy PbB concentration, each significantly and inversely associated with IQ scores taken at 3 and 5 years. Using lifetime average PbB level, an increase of 1 µg/dL PbB was associated with a 0.87 decrement in IQ points.

   Following adjustment for covariates, inverse significant associations were maintained between IQ and all PbB levels: mean lifetime PbB, concurrent PbB, peak PbB in infancy and mean PbB in infancy. Increases in lifetime PbB exposure by 1 µg/dL were associated with a decrease of 0.46 IQ points. Hence the finding of inverse significant association between low-level PbB and IQ finding was maintained in different calculations of PbB concentration and with or without adjustment for covariates.

Furthermore, a subgroup of children (*n* = 105) were identified, whose PbB levels never exceeded 10 µg/dL and linear models were applied to their data for each PbB outcomes variable. Prior to application of covariate adjustment, mean lifetime PbB, concurrent PbB, peak PbB in infancy and mean PbB in infancy, were each significantly and inversely associated with IQ scores taken at 3 and 5 years. Following adjustment for covariates, inverse significant associations were maintained between IQ and all PbB levels: mean lifetime PbB, concurrent PbB and peak PbB in infancy. A significant association was not identified between IQ at 3 and 5 years and mean PbB in infancy. An increase in lifetime exposure by 1 µg/dL was associated with a decrease in 1.37 IQ points (95% CI = 0.17, 2.56). Thus, for children whose peak PbB levels never exceeded 10 µg/dL, the estimated IQ loss was 13.7 points for each increase in PbB concentration of 10 µg/dL. This loss was much greater than the estimated increase of 4.6 points per increase in 10 µg/dL for the remainder of the sample.

2. Canfield et al. (2003) identified a nonlinear relationship between PbB concentration and IQ when nonlinear models were applied to all PbB measures and IQ data. The model is summarised in Figure 6, where the line of 'best fit' characterises the relationship between IQ and mean lifetime PbB levels, estimated by the covariate-adjusted penalised-spline mixed model. Individual data points visible on the graph represent the unadjusted mean lifetime PbB levels and IQ values. From these semi-parametric analyses, a loss of 7.4 IQ points with mean lifetime PbB levels up to 10µg/dL was estimated and in the range 10 µg/dL to 30 µg/dL, a decrease of 2.5 IQ points was estimated (Canfield et al., 2003).

   Polynomial models were also applied in order to confirm the departure from linearity that was observed at the semi-parametric level. As Canfield et al. (2003) report, the polynomial model quadratic term was significant in the model for mean lifetime PbB levels. An increase in PbB concentration from 1 to 10 µg/dL was

followed by an 8.0 point decrement in IQ (95 % CI = – 12.9, – 3.2). For peak PbB and concurrent PbB concentration, significant nonlinearity was also identified between PbB level and IQ.

These findings implied that Pb related deficits observed in children with PbB levels exceeding 10 µg/dL may be due to early losses in the 10 µg/dL or less, range and that the influence of Pb upon cognition in ranges beyond 10 µg/dL may be overestimated. Canfield et al. (2003) acknowledged the "counterintuitive" (p.1523) nature of these findings.

Hence, the work of Canfield et al. (2003) was the culmination of international prospective efforts to identify the abilities and age of maximal susceptibility to toxic Pb exposure.

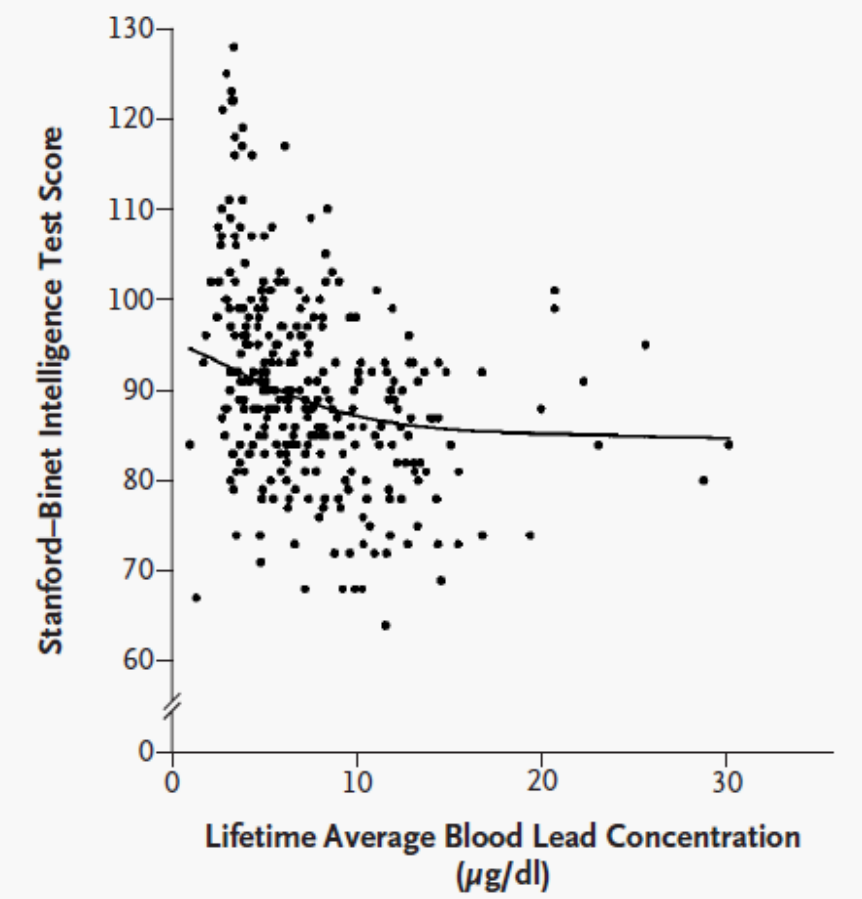

Figure 6

IQ (SBIS score) as a function of Lifetime Average Blood Lead concentration (Canfield et al., 2003, p.1525).

3.1.3 Summary of Prospective studies

The work of Canfield et al. (2003) shifted the public health research agenda regarding Pb exposure; following Canfield et al. (2003), the most significant question became the "counterintuitive" (Canfield et al., 2003, p.1523) suggestion that low-level Pb exposure (≤ 10 µg/dL) could, in fact, be more detrimental to the developing brain and human cognitive abilities, than higher levels of exposure. This new agenda reflected the ever-declining levels of Pb in the general population of developed countries (due to eradication of Pb based petrol and paint and successful remediation programs).

3.2 A non-linear relationship between lead and cognitive abilities?

While the prospective studies, initiated in the 1980's and continuing into the 21st century, sought to identify the period of maximal effects of PbB concentration on the developing brain and the most vulnerable abilities, as population level PbB declined, questions about the relationship between increasingly low-level PbB concentrations and childhood cognitive abilities came to the fore. Curiosity and concern about the possible non-linear relationship between Pb and childhood cognitive abilities were spearheaded by the "counterintuitive" findings of Canfield et al. (2003, p.1523) and low-level Pb exposure populations were sought upon which to conduct investigations. The research methodology shifted back to cross-sectional designs because data was quickly sought to address the new research question and also to the use of meta-analytic and pooled analyses which capitalised upon the extensive exposure data that had already been collected.

Kordas, Lopez, Rosado, Vargas, Rico, Ronquillo et al. (2004) investigated the association between low-level venous PbB (mean = 11.5 µg/dL, *SD* = 6.1) samples and cognitive performance in 602, 6 to 8 year olds in Torreón, Mexico. Not only did this study target a low-level Pb exposure population but it sought to examine the Pb – cognitive abilities relationship in careful detail by considering the Wechsler scales in terms of their global, subscale and subtest components. A 14 test battery was used to assess cognitive ability,

comprised of the Cognitive Abilities Test, and WISC-RM Coding, Digit Retention and Arithmetic, Number and Letter sequencing, Sternberg Memory Test, Prueba de Habilidades (a computer-based cognitive test), curriculum based Maths Achievement Test, a test of Visual-Spatial abilities and the Peabody Picture Vocabulary Test (Spanish Version; PPVT-S). Unadjusted PPVT, WISC-RM Coding, Number Sequencing, and Letter Sequencing, were statistically significantly negatively associated with PbB levels so that as PbB levels increased, participants were less likely to perform well. An almost linear relationship was observed between PPVT-S performance and PbB levels – for each 10 µg/dL increase in PbB concentration, an associated 3.7 point decrease in PPVT-S performance was noted. The authors concluded that the importance of their study lies in "the negative association between lead exposure and verbal recognition" (p. 368). Hence, while Ernhart and Greene (1990) failed to identify Pb related disruption to verbal skill acquisition in children under 3 years of age, Kordas et al. (2004) found evidence for a verbal deficit in their early school years age group.

Kordas, Canfield, Lopez, Rosado & Garcia (2006) expanded upon their previous analyses (Kordas et al., 2004), using the same dataset to investigate the apparent nonlinear Pb – cognitive abilities relationship by applying and comparing both linear and spline/segmented regression models.[15] In the adjusted analyses, Mathematics, PPVT-S and the Sternberg Memory Test were all significantly negatively correlated with PbB concentration. When linear models were applied, the slopes of the plots suggested that the linear model may not appropriately explain the variability in the entire PbB range represented in the sample. This interpretation tended to support the notion that the "true model" (Kordas et al., 2006, p. 377) for the Pb - cognitive abilities relationship was nonlinear. Given this observation, the segmented regressions were applied to explore differences in the slope of the graph below and above certain selected PbB levels (these levels were 8, 10, 12, 14 µg/dL) and for most of the outcomes the estimation of the Pb - cognitive abilities relationship significantly differed

[15] Spine regression can be used to investigate the specific PbB levels that accompany changes in the Pb-cognitive abilities slope (Kordas et al., 2006).

below and above the PbB concentration cut off point. The pattern of differences between cognitive outcome coefficients showed that the relationship between Pb and cognitive abilities were stronger and more negative at lower PbB levels as compared to higher PbBs. This observation was maintained when adjustments for covariates were applied but the difference between coefficients was only statistically significant for Figure Design and approached significance for PPVT-S for the 12 μg/dL cut-off.

The authors went further and applied segmented regressions, stratifying the data based on covariates like SES, maternal education and 'forgetting to do homework.' When stratified, high and low PbB levels were compared and the pattern of steeper slope estimation at low PbBs (compared to high PbB levels) was maintained. Kordas et al. (2006) noted highly statistically significant interactions and concluded that the nonlinear relationship was more pronounced for the "children who already tend to be at risk for poorer performance (fewer family resources, lower maternal education, low parental involvement in school work)" (Kordas et al., 2006, p.378).

Surkan, Zhang, Trachtenberg, Daniel, McKinlay and Bellinger (2007) used data for 534 children aged 6 - 10 years (mean age = 8.0 years, *SD* = 1.4 years) originally enrolled in the New England Children's Amalgam study in Boston and Maine, Massachusetts. FSIQ from the WISC-III (mean FSIQ = 95.7, *SD* = 13.5) was used as the primary outcome measure and this was supplemented with data from the Wechsler Individual Achievement Test (WIAT). The KBIT was used to measure parental IQ and the Parenting Stress Index was used to measure parent stress levels. Data for 512 children was analysed and their mean PbB level was 2.3 μg/dL (*SD* = 1.6). A dose-response model for WISC-III FSIQ and PbB concentration (data were grouped into categories: 1 - 2 μg/dL, 3 - 4 μg/dL and 5 - 10 μg/dL) was constructed and adjusted for parental IQ, SES, race and birth weight. A significant difference was identified between the IQ scores for the 5 - 10 μg/dL versus 1 - 2 μg/dL. Overall the authors noted that children in the 5 - 10 μg/dL group presented significantly lower IQ, achievement, attention and working memory compared to the 1 - 2 μg/dL group. Indeed the

authors concluded that given these findings it would seem “inappropriate to regard 10 μg/dL as a ‘lowest observed adverse effect level’” (p.1176).

Some level of co-ordination in the prospective studies has allowed meta-analyses (Pocock et al., 1994) and pooled-data analyses (Lanphear et al., 2005) of the data accumulated around the Pb – cognitive abilities relationship. However, it should be noted that aggregate studies, like cross-sectional and prospective research possess a range of methodological limitations that qualify findings. These issues include unknown individual exposure and body - Pb burdens, differences between and within studies in exposure level due to variation in location, unassessed covariates, changes in chemical toxicity and mixtures of chemicals, as well as weak statistical power and the latency of impact (Brown, 1995). Another widely acknowledged limitation of systematic reviews and meta-analysis is the ‘filing-cabinet’ phenomenon whereby only research that reports significant effects is published or pursued to be published. Hence, this publication bias means that research that includes negative or non-significant findings fails to enter the public domain. For example, regarding their systematic review, Pocock et al. (1994) conceded knowledge of a prospective study in Leeds that reported ‘negative’ findings about the association between Pb and cognitive abilities but remains unpublished and therefore casts doubt about the exhaustiveness of the Pocock et al. (1994) review.

Pocock et al. (1994) conducted a systematic review of studies investigating the relationship between FSIQ and body Pb burden in 5 year old children. Their review (N = 26 studies) included prospective studies with repeated measures of PbB concentration (Boston, Cincinnati, Cleveland, Port Pirie and Sydney) and cross-sectional FSIQ and PbB concentration (n = 14) or PbD level (n = 7) and IQ studies. The combined prospective studies tended to dispel the hypothesis that pre-natal Pb exposure may be especially influential on later outcomes because Pocock et al. (1994) noted that peak Pb levels at 2 years of age, the period of peak lifetime exposure, showed a larger inverse IQ and Pb association than pre-natal levels.

Cross-sectional studies indicated a significant inverse association between PbB concentration and IQ, but these findings were hampered by interpretative difficulties due to the considerable heterogeneity of studies. Cross-sectional studies of the relationship between PbD concentration and cognitive abilities were somewhat more definitive, indicating a consistent inverse association between PbD studies and IQ; there was a 1 IQ point increase from 5 µg/g to 10 µg/g.

In combination, the 26 studies, with varying methodologies, led Pocock et al. (1994) to conclude that the weight of evidence pointed to an inverse association between body Pb burden and child IQ. The authors specifically indicated that with an increase of body Pb burden (from 10 to 20 µg/dL PbB concentration or 5 to 10 µg/g PbD level) there is an average IQ deficit in the range of 1 to 2 IQ points. A number of explanations are offered for the observation of Pocock et al. (1994) from the accumulated data (adapted from Pocock et al., 1994):

1. The associations are due to chance; this does not seem plausible because an accumulated body of work provides evidence of an association between Pb and cognitive abilities.
2. Low level Pb exposure produces IQ deficits.
3. Published studies are not representative.
4. Even the most thorough approach to the measurement of covariates will not adequately capture their widespread and pervasive influence upon child outcomes and potentially IQ.
5. Available markers of body - Pb burden provide imperfect estimates.
6. A range of selection biases exist (e.g., attrition rates).
7. An issue of reverse causality exists, whereby a child's behaviour patterns enhance Pb exposure and uptake.

In the same year as the publication of Pocock et al. (1994), Schwartz (1994) published a meta-analysis of cross-sectional and prospective studies (N = 8) which measured FSIQ and PbB concentration and (the majority of which) included measures of parental IQ and the home environment. The PbB level of the included studies ranged from 6.5µg/dL (Bellinger et al., 1992) to 23 µg/dL (Hatzakis et al., 1987).

In Schwartz' (1994) baseline analyses (excluding one study), the estimated decrease in IQ associated with an increase in PbB concentration from 10 to 20 µg/dL was 2.57 IQ points. Schwartz et al. (1994) also analysed the data based solely on studies that reported PbB levels less than or equal to 15 µg/dL (Fulton et al., 1987; Yule, Lansdown, Millar & Urbanowicz, 1981; Bellinger at al., 1992; Dietrich et al., 1993). Schwartz (1994) reported the effect size of these studies as 3.23 IQ points compared to 2.32 IQ points in studies with PbB levels 20µg/dL and over (Baghurst et al., 1992; Hatzakis et al., 1987; Hawk, Schroeder, Robinson, Otto, Mushak, Kleinbaum & Dawson, 1986). Based on his analyses of the IQ loss associated with an increase of 10µg/dL PbB, versus the mean PbB concentration for each study, Schwartz (1994) observed "a trend toward a higher slope at lower blood lead concentration" (p. 50).

Schwartz' (1994) meta-analysis provided the first evidence of a possible non-linear relationships between low-level PbB and IQ and indeed a possible logarithmic dose-response relationship (later shown by Canfield et al. (2003) and Kordas et al. (2004, 2006)). Schwartz (1994) strongly concluded that there is no threshold level free from the deleterious impacts of Pb as supported by reanalysis of the Boston cohort where effects are seen below 7µg/dL and the Schwartz (1993) reanalysis of Needleman et al. (1979) where no threshold level was observed even at concentrations of 1ppm PbD level.

Lanphear et al.'s (2005) pooled analysis of data collected from key prospective studies is of particular interest. Sites contributing their data to the analysis were Boston, Cincinnati, Cleveland, Kosovo, Port Pirie, Mexico City and New York City (Canfield et al., 2003). The Sydney Prospective Study was not included due to an inability to contact the researchers (Cooney et al., 1989).

The pooled analysis used the Wechsler scales' FSIQ (taken from the WISC, WISC-R, WISC-RM, WISC-III or WPPSI) administered between 4 years 10 months and 7 years (except in Boston where the WISC-R was administered at 10 years of age) as the primary outcome measure. Covariate data were available for nine variables across all studies (child's gender, birth order, birth weight, maternal education, maternal age, marital status, pre-natal alcohol exposure, pre-natal tobacco exposure and the HOME) for 83% (n = 1,308) of the eligible children (N = 1,581). PbB measures were uniformly sampled at 6, 12 (or 15), 36, 48 and 60 months and these data were used to calculate a number of PbB summary measures:

- Concurrent PbB concentration: PbB measured closest to administration of the target IQ test.
- Maximum PbB concentration: peak PbB measure at any point in the child's life.
- Average lifetime PbB concentration: mean PbB from 6 months to concurrent PbB measures.
- Early childhood PbB concentration: mean PbB from 6 to 24 months.

In the pooled analyses, child FSIQ significantly related to maternal IQ, HOME score, maternal education, marital status, birth weight, maternal age, birth order, race and pre-natal tobacco use, but not gender and pre-natal alcohol consumption (Lanphear et al., 2005). In an exploration of the four PbB measures and FSIQ, concurrent PbB concentration was identified as the variable with the strongest correlation with FSIQ, although all four measures were highly correlated (r = 0.74 - 0.96). It was decided therefore that in all subsequent analyses, concurrent PbB concentration would be used as the primary measure of PbB exposure.

Modelling revealed that the shape of the exposure-response relationship between concurrent PbB concentration and FSIQ was non-linear and the log-linear model provided a good fit, such that the log of concurrent PbB concentration was used in all subsequent analyses. The preferred model included six terms (log of concurrent PbB, site, maternal IQ, HOME, birth weight, and maternal education) and from Figures 1 and 7, it can be seen, given

the slope of the line, that the most extreme drops in IQ occurred at ≤ 10 μg/dL. From this model Lanphear et al. (2005) estimated that a jump in concurrent PbB concentration from 2.4 – 30 μg/dL (the 95% CI for log concurrent PbB concentration of the pooled dataset), would be accompanied by a decrement of 6.9 IQ points (95% CI = 4.2, 9.4).

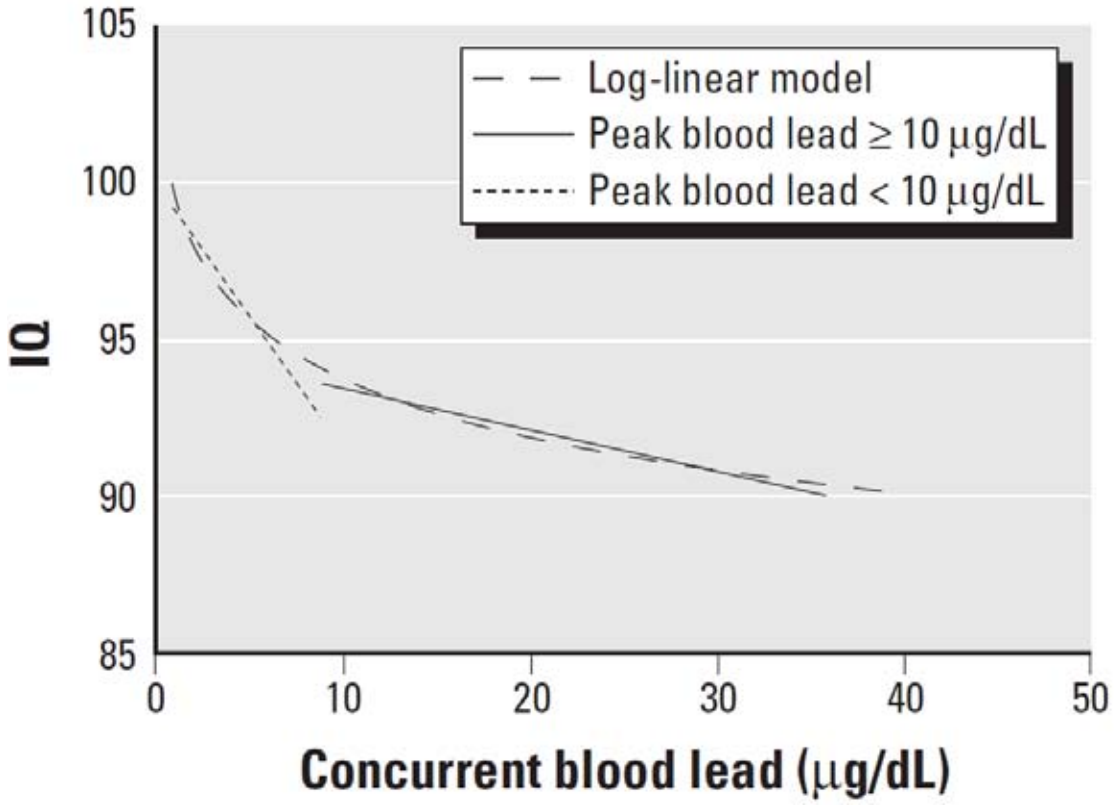

Figure 7

Log-linear model for concurrent blood lead concentration along with linear models for concurrent blood lead levels among children with peak blood lead levels above and below 10 μg/dL (Lanphear et al., 2005, p.898; Reproduced with permission from Environmental Health Perspectives).

When the 2.4 - 30 μg/dL PbB exposure range was carefully explored according to changes associated with 10 μg/dL increases in PbB levels, it was noted that the decrement in IQ points was even more marked. For example, the decrements were:

An increase from 2.4 → 10 μg/dL: a **3.9** IQ point loss (95% CI = 2.4, 5.3).

An increase from 10 → 20 μg/dL: a **1.9** IQ point loss (95% CI = 1.2, 2.6).

An increase from 20→ 30 μg/dL: a **1.1** IQ point loss (95% CI = 0.7, 1.5).

The data were divided and analysed according to maximum PbB levels above and below 10 μg/dL and maximum PbB levels above and below 7.5 μg/dL, to allow further investigation of decrements observed at low-level PbB exposure. With these divisions in place, linear models were fitted to each dataset so that the PbB coefficients could be compared and Lanphear et al. observed that the intellectual decrement observed below 7.5 μg/dL significantly exceeded intellectual decrement noted above 7.5 μg/dL:

- *For the 7.5 μg/dL cut-off*, the coefficient for the 103 children with PbB levels < 7.5 μg/dL (linear β = - 2.94, 95% CI = - 5.16, - 0.71) was significantly (p = 0.02) greater than the coefficient estimated for the 1,230 children with PbB levels measured as > 7.5 μg/dL (linear β = - 0.16, 95% CI = - 2.4, - 0.08).
- *For the 10 μg/dL cut-off*, the coefficient for the 244 children with PbB levels < 10 μg/dL (linear β = - 0.80, 95% CI = - 1.74, - 0.14) did not differ significantly (p = 0.10) from the coefficient for the 1,089 children with < 10 μg/dL (linear β = - 0.13, 95% CI = - 2.3, - 0.03).

Cognitive ability was further explored by investigating the relationship between PbB levels and the VIQ and PIQ subscales of the Wechsler scales. The difference between the coefficients for VIQ and PIQ were not found to be statistically significant.

Rothenberg and Rothenberg (2005) reanalysed Lanphear et al.'s (2005) pooled analysis of data from the seven prospective studies with the aim of comparing the multiple regression models with linear PbB terms and natural-log-transformed Pb terms, respectively. The log-linear Pb - FSIQ relationship identified was a significantly better fit than the linear Pb - FSIQ relationship.

Lanphear et al. (2005) confirmed the inverse association between PbB levels and IQ noted by Pocock et al. (1994) and Schwartz (1994) in their meta-analyses. However, in a breakdown of PbB levels below 30 µg/dL, Lanphear et al. (2005) noted that the intellectual decrements observed below 7.5 µg/dL significantly exceeded observed declines beyond 7.5 µg/dL. The US co-authors concluded the paper with the comment that, collectively, these data provided sufficient evidence to mount an aggressive campaign to eliminate childhood Pb exposure (Lanphear et al, 2005). This was further supported by Schwartz (1994) who acknowledged the "substantial public policy implications" (p.53) of such a finding.

3.3 Potential mechanisms underpinning lead-induced cognitive deficits

As outlined in Chapter 2, animal studies have provided insights about the potential physiological impacts of Pb exposure and in particular have noted Pb-induced disruptions to the hippocampus (Altmann et al., 1998), DNA binding in the cerebellum and the hippocampus (Basha et al., 2003), and expression of NMDA and peripheral nervous system nicotinic cholinergic receptors (Hubbs-Tait et al., 2005; Zhou & Suszkiw, 2004). While a number of authors have proposed physiological mechanisms that may underpin Pb-induced deficits in children's cognitive functioning (Canfield et al., 2003; Schwartz et al., 1994), recent understanding of the mechanisms underpinning Pb-linked cognitive deficits has been forwarded by epigenetic advances (Pilsner, Hu, Ettinger, Sánchez, Wright, Cantonwine et al., 2009; Zawia, Lahir & Cardozo-Pelaez, 2009). As a caveat, Mudge (1996) recognised that it is unlikely that one sole mechanism can account for the range of functional deficits that have been attributed to Pb exposure; nevertheless several propositions will be discussed.

In response to their "counterintuitive" (Canfield et al., 2003, p.1523) finding, Canfield et al. (2003) hypothesised that high levels of heavy metal exposure may serve as a protective factor in the human organism by initiating cellular defense mechanisms to optimise the organisms' biological protection defenses (Canfield et al., 2003). These protective mechanisms may not be initiated at lower levels of Pb exposure, allowing lower level Pb to

poison the brain. Canfield et al. (2003) proposed that there may be a threshold level at which these protective mechanisms are launched and that at low-level exposure, the protective mechanisms may remain inactive, leaving the brain vulnerable to Pb's toxicity. Schwartz (1994) explained that "[t]here are toxicological effects that show saturation phenomena, and there are complex feedback control mechanisms in the human body, often with a series of feedbacks that cut in as homeostasis becomes more disturbed. This makes such a finding plausible." (p. 53).

Epigenetic investigations of Pb exposure have provided evidence that early life Pb-exposure may insult cellular development (Pilsner et al., 2009) and can be imprinted on and reflected in an individual's genetics (WHO, 2010). In particular the impacts of Pb on DNA methylation have been investigated.

Zawia et al. (2009) described DNA methylation as a "major epigenetic event" (p.5) occurring in the early stages of *in utero* development, with the propensity to impact gene expression and imprinting and the development of heritable methylation patterns; evidence exists that these vital, delicate and complex processes can be altered by the fetal environment with lifelong implications to functional abilities and disease susceptibility (Zawia et al., 2009). Zawia et al. (2009) specified that environmental toxin exposure may impact DNA methylation by disturbing enzymes that play key roles in methylation processes and reactions.

Recognising that the influence of *in utero* environmental Pb exposure on DNA methylation levels in humans represented a substantial research gap, Pilsner et al. (2009) sought to explore the associations between measure's of pre-natal maternal Pb levels (K-X-ray measures of maternal tibia and patella bone Pb) and the DNA methylation identified in cord blood samples (N = 103 samples). Pilsner et al. (2009) noted inverse associations between genomic DNA methylation in cord blood and pre-natal Pb exposure; this suggested to the authors that "the epigenome of the developing fetus can be influenced by maternal cumulative lead burden, which may influence long-term epigenetic programming and disease susceptibility throughout the life course" (p.1466).

Adding weight to the possibility that Pb may impact genome development, Zawia et al. (2009) have used animal studies to elicit evidence that early Pb exposure may play a role in the development of neurodegenerative disorders such as Alzheimer's Disease. While their work departs from the focus of this thesis, for Zawia et al. (2009), the links they have drawn between early life Pb exposure and late-onset disease pathology, supports the possibility that Pb exposure can insult the genome of distinct and continually dividing cells, which can uniquely go undetected by DNA repair enzymes which seek to restore genetic damage and deviations.

3.4 What are the public health implications of an apparent 1 to 3 point IQ loss associated with lead exposure?

With IQ used as a proxy for 'intelligence' and 'cognitive abilities,' it is valid to question the individual and population-level implications of 1-to-3 point IQ detriments associated with Pb exposure below 30 µg/dL (the most consistent findings from meta-and pooled analyses of data on the relationship between Pb and cognitive abilities; Lanphear et al., 2005; Pocock et al., 1994; Schwartz, 1994).

The criteria for 'intellectual disability' vary but generally it is agreed that an individual's functioning is assessed in terms of their:

- Performance on a standardised IQ measure;
- Adaptive behaviour (conceptual, social and practical skills); and
- Age; generally the diagnosis of 'intellectual disability' needs to be formally made prior to 18 years of age (American Association on Intellectual and Developmental Disabilities; AAIDD, n.d).

The AAIDD currently indicate that an IQ score between 70 and 75 is indicative of limitations in intellectual functioning. In Australia, formal assessment of an IQ of 70 or less enables people to access services that may provide specialist care, additional education, respite for carers, and skill based training (Australian Psychological Society; APS, 2010).

Fewtrell et al. (2003) MMR as less than or equal to 70 IQ points, but above 50 IQ points. Further, Fewtrell et al. (2003) defined Mental Retardation (MR) as below 50 IQ points.

The APS maintain that the current theoretical conceptualisation of 'intellectual disability' is a departure from the medical model that has previously dominated. The APS currently view 'intellectual disability' as an educational and/or developmental problem. This shift recognises that people with intellectual disabilities can learn skills with appropriate, flexible support and that there is scope for inter-individual variability in terms of ability-based strengths and weaknesses. It is also recognised that children with intellectual disabilities become adults with intellectual disabilities and that their supportive needs evolve with age (APS, 2010).

For the majority of people in this well below average range, classification of 'Intellectual disability,' MMR and/or MR, indicates that their low level cognitive functioning impedes their ability to learn, their educational attainment, interpersonal relationships, independent functioning, decision making prowess and employment opportunities. Even seemingly small detriments linked to Pb exposure, such as 1 to 3 IQ points (Pocock et al., 1994; Schwartz, 1994; Lanphear et al., 2005), therefore can have severe and distinct functional implications for an individual's daily life and their life trajectory.

Viewing the impact of a 1-to-3 IQ point detriments from a population level offers a macro view of the possible pervasiveness of the Pb – cognitive abilities relationship outlined and investigated in this thesis. This task has been undertaken by Fewtrell et al. (2003) who sought to calculate the disease burden linked to a Pb-related loss of IQ points. In doing so, Fewtrell et al. (2003) calculated the number of people in a given population whose IQ score places them on the cusp of the 'intellectual disability' threshold and who would enter the MMR range through loss of IQ points due to Pb exposure (See Figure 8).

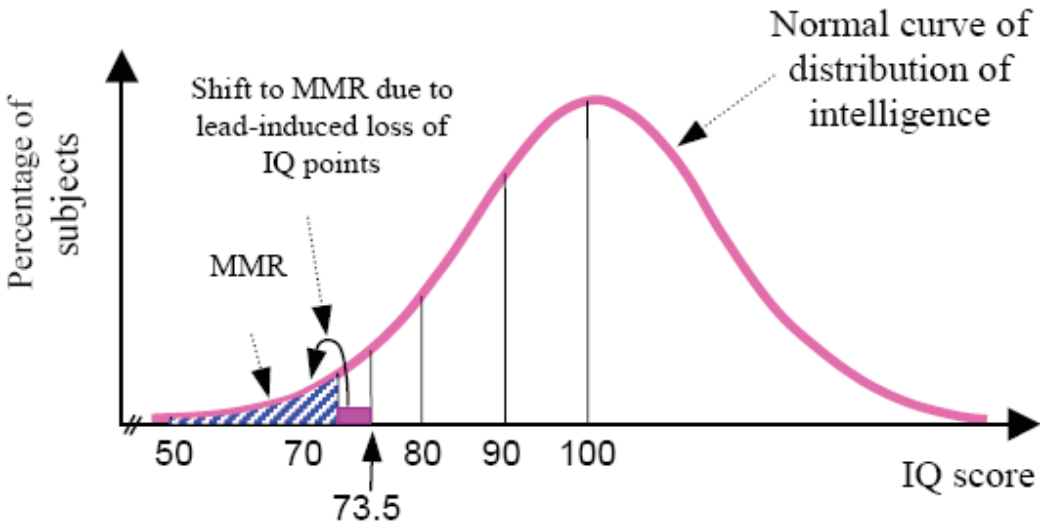

Figure 8

Shift to Mild Mental Retardation as a result of Pb-induced IQ loss (Fewtrell et al.,2003, p.11).

Specifically, Fewtrell et al. (2003) calculated the percent of school-aged children that could be deemed 'intellectually disabled' via the neurotoxic effect of Pb exposure. Using Schwartz' (1994) meta-analytic data, Fewtrell et al. (2003) applied a step-wise approach, assuming a linear dose-response relationship and a 1.3 IQ points loss per 5 µg/dL increase in PbB concentration between 5 – 20 µg/dL. Using this approach, the average IQ loss per 5 µg/dL increase interval was assigned to the following values:

- 7.5 µg/dL is assigned a 0.65 IQ point decrement;
- 12.5 µg/dL is assigned a 1.95 IQ point decrement;
- 17.5 µg/dL is assigned a 3.25 IQ point decrement; and
- ≥ 20 µg/dL is assigned a 3.5 IQ point decrement.

Fewtrell et al. (2003) were thus able to estimate the percentage of a school-aged population with IQs estimated as between 70 and 73.5 IQ points that would subsequently shift

to the range for diagnosis of 'intellectual disability' based purely upon their IQ scores (as noted, in a clinical setting IQ is supplemented with information about adaptive functioning in order to make the formal diagnosis of 'intellectual disability'). This information is summarised in Table 11.

Table 11

Distribution of a normal population within specified IQ intervals (Fewtrell et al., 2003) and application of estimates to population of children in Australia.

IQ interval	Population in IQ interval (%)	Estimated number of Australian children[a] in IQ intervals[b]
70 – 70.65	0.24	10,056
70 – 71.95	0.80	33,520
70 – 73.25	1.45	60,755
70 – 73.50	1.59	66,621

[a] The ABS defines 'children' as aged less than 15 years (0-to-14 years of age;ABS, 2007b).
[b] As of June 30, 2009, the ABS estimated the residental population of Australia as 21,960,000. people and that the total number of children under 15 years of age was 4,190,000 (ABS, 2007b).

According to Fewtrell et al.'s (2003) estimates, depending upon the 'true' effect of Pb on IQ (a decrement between 1 ≤ and ≤ 3 IQ points is based on empirical evidence) the number of children shifting to an IQ range of possible 'intellectual disability' is between 0.24 and 1.59 % of the population. Based on the 2006 Australian census, the ABS estimated that

there were 4,190,000 children in Australia (ABS, 2007b) and hence when these estimates are applied to the Australian population of children already functioning in the 'well below average range,' it was estimated that approximately 10,056 to 66,621 children would shift into the 'intellectual disability' range on account of Pb exposure.

Because the majority of children in Australia would have PbB levels in the lower end of exposure range, this estimate needs to be further refined to represent the number of children in the vulnerable IQ range *and* with corresponding PbB levels. In Table 12, ABS (2007b) population data were coupled with data taken from Donovan and Anderson (1996), which approximates the number of Australian children with PbB levels in each exposure range. From this calculation it is estimated that depending upon the individual and the 'true' effects of Pb on IQ, approximately 4,400 Australian children would shift to IQ ranges below 70 points for exposure ranges from 5 µg/dL to greater than or equal to 20 µg/dL. Having outlined the trajectory of children functioning at this low level, the individual, community and policy implications of even the most conservative (or crude) of these estimates, is sizable.

Some cautionary comments are necessary to qualify these estimates based on the work of Fewtrell et al. (2003), coupled with the early data of Schwartz (2004) and Donovan and Anderson (1996).

Firstly, it is noted that in Australia primary Pb exposure pathways are likely to have changed since the collection of Donovan and Anderson's (1996) data due to the eradication of leaded petrol. Regrettably no national evaluation of Pb exposure in Australia was conducted before or subsequent to Donovan and Anderson's (1996) work. In the absence of updated data, estimates of numbers of population affected by Pb exposure are crude.

Secondly, Fewtrell et al. (2003) noted that the normal distribution for human IQ performance may not be represented in all countries and regions – where available country distribution information can be used or a corrective factor can be applied.

Table 12

Estimated total number of Australian children that would shift to IQ ranges below 70 points for exposure ranges from 5 µg/dL to greater than or equal to 20 µg/dL based on data available from Donovan and Anderson (1996) and the ABS (2007b).

Pb exposure range (µg/dL)	% of Australian children in PbB exposure range[a]	Estimated number of Australian children[b] in corresponding IQ intervals[c]	Approximate number of children with given PbB exposure and in IQ interval
5 - 10	0.24	10,056	1,400
10 – 20	0.80	33,520	1,000
≥ 20	1.45	60,755	2,000
Estimated total number of Australian children that would shift to IQ ranges below 70 points for exposure ranges from 5 µg/dL to greater than or equal to 20 µg/dL			Approximately 4,400 children

[a] According to Donovan and Anderson (1996).
[b] The ABS defines 'children' as aged less than 15 years (0-to-14 years of age;ABS, 2007b).
[c] As of June 30, 2009, the ABS estimated the residential population of Australia as 21,960,000 people and that the total number of children under 15 years of age was 4,190,000 (ABS, 2007b).

Thirdly, there are a number of diseases that can influence IQ in childhood (anaemia, meningitis, pertussis, Japanese encephalitis, ascariasis, trichuriasis, hookworm infection, cretinoidism and cretinism due to iodine deficiencies; WHO, 2001) and hence Fewtrell et al. (2003) calculated regional adjustment ratios for MR rates caused by disease or iodine deficiency. In terms of the Global Burden of Disease methodology utilised by the WHO for their estimations, Australia is grouped in the Western Pacific Region A (with Brunei Darussalam, Japan, New Zealand and Singapore) and the corrective factor to account for childhood illness contributions is 1.00 for this region.

Fourthly, Fewtrell et al.'s (2003) analyses were conducted prior to the publication of Lanphear et al. (2005) and were based on the earlier work of Schwartz (1994) and assumed a linear relationship between Pb and IQ. Hence, these estimates do not represent the more recent findings of Lanphear et al. (2005), that lower level Pb exposure may be associated with greater IQ decrements than higher exposure levels; that is a nonlinear relationship between Pb and IQ. If this approach was applied to the data of Lanphear et al. (2005) and the log-linear model presented in Figure 1, then the greatest level of IQ decrement (3.5 IQ point) could be associated with the lowest level of exposure (7.5 µg/dL) and potentially, even more Australian children could shift into the threshold level for 'intellectual disability.'

Fifthly, coupled with this, Fewtrell et al.'s (2003) estimates of the detriment of Pb on IQ assumed that there is no effect below < 5 µg/dL; however, some research groups (Chiodo et al, 2004; Schwartz, 1993, 1994) have suggested that there is no threshold level free from the effects of Pb on cognitive abilities, hence the calculations above may underestimate the burden of Pb on cognitive abilities and hence MMR.

Chapter 4: Study objectives, hypotheses and theoretical underpinnings

Chapter summary

Chapter 4 outlines the Cattell-Horn-Caroll model of intelligence, a psychometric model of intelligence that will provide a framework for this study's investigations into the associations between children's cognitive abilities and Pb exposure.

In addition Chapter 4 outlines unresolved issues in the field and the aim, objectives and hypotheses of the current study.

4.1 Psychometric theories of intelligence

Given that exploration of the relationship between Pb and cognitive abilities is the primary research interest of the current study it is timely to establish the theoretical orientation of this research in approaching the measurement of cognitive abilities.

As noted, the primary outcome measure in previous studies on the effect of elevated PbB level on human intelligence has been the Wechsler Intelligence Scales (e.g., WISC-R, WISC-III, WISC-IV, etc) and to allow comparability to previous research, the WISC-IV will be the primary outcome measure in the current study. The Wechsler family of tests have proven to be the most widely used individual IQ tests since the publication of the Wechsler-Bellevue Scale in 1939 (Mackintosh, 1998). Using the Wechsler test, a single examiner administers a series of individual tasks to a participant to assess intellectual functioning. The Wechsler set of tests have also provided innovation in the measurement of intelligence by constructing tests that are suitable for broad age ranges, as evident in the WISC-III for 5-to-16 year olds and the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) for 17 years and beyond.

Although, the Wechsler scales have received widespread support as clinically useful tools (Zhu & Weiss, 2005), they lack a strong theoretical underpinning and produce a general factor "biased towards verbal components" (Deary, 2000, p.193). Rather than discounting the scale as atheoretical, Zhu and Weiss (2005) highlighted that David Wechsler, the battery's primary developer, did not work in isolation but rather he was influenced by dominant theoretical perspectives of the time such as those of Edward L. Thorndike and Charles Spearman.

Understandings of 'intelligence' have progressed considerably in the last few decades, with the advent of sophisticated statistical techniques to 'flesh out' the structure of cognitive abilities. The Cattell-Horn-Carroll model of intelligence (CHC) represents one contemporary theoretical and empirical orientation in the study of intelligence. The field of individual differences and intelligence has a rich history of theoretical models and CHC represents the synthesis of Cattell-Horn Fluid-Crystalised ability (Gf-Gc) theory and Carroll's three-stratum theory of cognitive abilities (Floyd, Evans & McGrew, 2003). CHC theory provides a hierarchical model of human cognitive abilities, consisting of general intelligence (*g* factor: stratum III), the common variance among abilities, broad cognitive abilities (stratum II) and narrow cognitive abilities (Stratum I; Floyd, Evans & McGrew, 2003).

The broad abilities derived from the CHC that will be measured in this study are summarised in Table 13. While earlier studies have not directly measured the CHC factors, studies summarised in Chapters 2 and 3 have measured a broad range of cognitive abilities, many of which are comparable to the CHC factors and that have been detrimentally impacted by Pb exposure; relevant previous research is summarised in Table 13.

It is recognised that the CHC model of intelligence does not include a neuro or psychomotor factor; an ability which has been shown to be negatively impacted by Pb exposure in the research of Després et al. (2005) and in the CLS cohort by Ris et al. (2004) and Dietrich and colleagues. However, it is argued that psychomotor function is captured within specific timed tasks (e.g., WISC-IV Block Design, Digit Symbol, Symbol Search; Gs

Invaders) within the assessment battery administered to children in this study and hence this cognitive ability is not overlooked.

In accordance with Floyd et al.'s (2003) view that the CHC model, with supporting validity evidence, is an established point from which to investigate deviations in intellectual functioning, we propose to supplement children's scores from the WISC-IV with measures that are located within this model of intelligence. The proposed assessment battery for the current study is summarised in Figure 9 and individual components will be explained in greater detail in Chapter 5.

Table 13

CHC broad abilities and associated previous research.

CHC broad ability **Symbol**: name	Description	Comparability to previous research findings (first author, date)
***g* factor**: General ability	The *g* factor represents general ability and in a theoretical sense it is comparable to summary measures such as FSIQ from the Wechsler scales.	Significant inverse associations have previously been identified between Pb exposure indices and general ability indices such as: • FSIQ from Wechsler scales (Canfield, 2003; Chen, 2005; Chiodo, 2004; Hansen, 1989; Kim, 2009; Schnaas, 2006; Stiles, 1993; Surkan, 2007) • MPC (from the K-ABC; Dietrich, 1991), MDI (from the BSID; Chen, 2005; Hu, 2006; Wasserman, 1992) • GCI (from the MSCA; Ernhart, 1981; McMichael, 1992; Schnaas, 2000) • KBIT composite score (Davis, 2004) • BAS composite score (Fulton, 1987).

Note. BAS: British Ability Scales; BSID: Bayley's Scale of Infant Development; CHC: Cattell-Horn-Carroll model of intelligence; FSIQ: Full Scale IQ; GCI: General Cognitive Index; K-ABC: Kaufman Assessment Battery for Children; KBIT: Kaufman Brief Intelligence Test; MDI: Mental development Index; MPC: Mental Processing Composite standard score; Pb: lead.

Table 13

Continued.

CHC broad ability **Symbol**: name	Description	Comparability to previous research findings (first author, date)
Gv: Visuo-spatial ability	The perception and processing of visual form and spatial relationships	Researchers noted that Pb exposure detrimentally impacted performance on the: • Bender-Gestalt (De la Burdé, 1975; Hansen, 1989) • Visual motor integration task (Winneke,1983) • Beery Visual-Motor Integration & Matching familiar figures task (Chiodo, 2004) • Rey-Osterrieth Complex Figure (Stiles & Bellinger, 1993) • Visuoconstruction (factor comprised of Block Design from the WISC-III & Rey-Osterrieth Complex Figure; Ris, 2004)
Gc: Crystallised ability	Breadth of knowledge, experience, learning and acculturation	Previous research identified significant inverse associations between Pb exposure and: • VCI from the Wechsler scales (Chiodo, 2004; Hansen, 1989; Kim, 2009; Kordas, 2004; Schnaas, 2006; Stiles, 1993; Wasserman, 1992) • Verbal subscales from MSCA (Ernhart, 1981) • ACHIV (from the K-ABC; Dietrich, 1991) • BWRT (Fergusson & Horwood, 1993) • Measures of educational attainment (Fergusson, 1997; Fulton, 1987; Stiles & Bellinger, 1993; Wang, 2002). • Verbal Learning subtest of the Wide Range Assessment of Memory and Learning (Chiodo, 2004)

Note. ACHIV: Achievement standard score; BWRT: Burt Word Reading Test; CHC: Cattell-Horn-Carroll model of intelligence; MSCA: McCarthy Scales of Children's Abilities; Pb: lead; VCI: Verbal Comprehension Index; WISC-III: Wechsler Intelligence Scale for Children – Third Edition.

Table 13

Continued.

CHC broad ability **Symbol**: name	Description	Comparability to previous research findings (first author, date)
Glr: Long-term storage and retrieval	The fluency and breadth of retrieval of stored information	Previous research suggests that Pb has a detrimental impact upon short term and long term memory abilities as illustrated through poor performance on the: • K-ABC (especially the SIM score; Dietrich, 1991) • Freedom from distractability subscale of the WISC-III (Wasserman, 1992) • Sternberg Memory Test (Kordas, 2006). • Story Memory subtest of the Wide Range Assessment of Memory and Learning (Chiodo, 2004) • Benton Visual Retention Test (Sovcikova, 1997).
Gsm: Short-term memory	Aspects of working memory, information processing, apprehension and retention.	In terms of Gsm, Lanphear (2000) and Caldéron (2001) identified significant inverse associations between PbB level and Digit Span and Arithmetic, Digit Span and Coding, respectively. Evidence has been delineated regarding a detrimental effect of Pb on: • Attentional and cognitive control abilities (Cho, 2010; Davis, 2004; Nigg, 2008), • Executive functions (Minder, 1994) • Measures of working memory (Chiodo, 2004).

Note. CHC: Cattell-Horn-Carroll model of intelligence; K-ABC: Kaufman Assessment Battery for Children; Pb: lead; SIM; Simultaneous processing standard score; WISC-III: Wechsler Intelligence Scale for Children – Third Edition.

Table 13

Continued.

CHC broad ability **Symbol**: name	Description	Comparability to previous research findings (first author, date)
Gf: Fluid ability	The basic processes of reasoning.	Ravens progressive matrices have traditionally been considered measures of Gf and shown to be significantly inversely associated with PbB level (Rabinowitz, 1991; Rahman, 2002; Sovcikova, 1997). In addition inverse assicitaions have been noted between PbB level and: • An order problem solving from the K-ABC (Dietrich, 1991). • PIQ from Wechsler scales (Schnaas, 2006; Wasserman, 1992) and the factor score Perceptual Organization (Wasserman, 1992).
Gs: Speed of information processing	Cognitive processing speed	• A significant positive relationship between RT and indicides of Pb exposure has been established (Chiodo, 2004; Després, 2005; Hunter, 1985; Lanphear, 2000; Minder, 1994; Needleman, 1979, 1990; Winnecke, 1983). • Significant correlations were also identified between Trail Making Task (viewed as measure of Gs) and Pb exposure (Minder, 1994).
Ga: Auditory ability	Perception or discrimination of auditory patterns of sound or speech	Auditory processing has not been extensively studied in previous research: • In the Cinncinati cohort (Dietrich et al., 1987) significant inverse associations were identified between Pb exposure and performance on the Filtered Word Subtest. • De la Burde & Choate (1975) noted significant that performance on the auditory-vocal association subtest of the Illinois Test of Psycholinguistics significantly declined with increasing Pb levels.

Note. CHC: Cattell-Horn-Carroll model of intelligence; K-ABC: Kaufman Assessment Battery for Children; PbB: blood lead; PIQ: Performance IQ; RT: Reaction Time; VCI: Verbal Comprehension Index; WISC-III: Wechsler Intelligence Scale for Children – Third Edition.

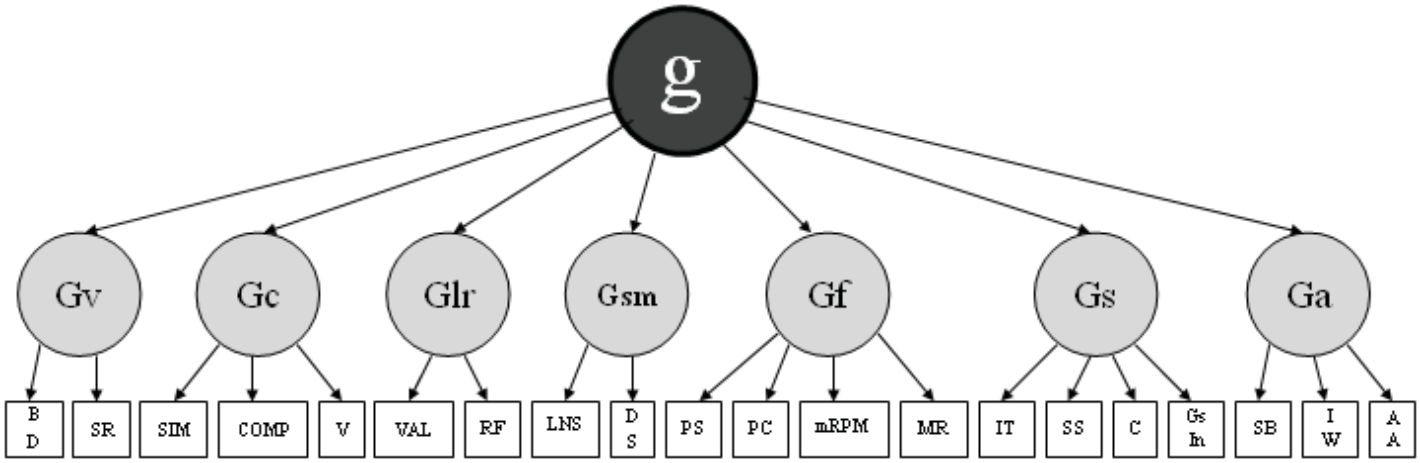

Figure 9

Hypothesised CHC theoretical factor structure of tests administered to assess child cognition.

Note. AA: Auditory Attention from the WJ-III; BD: Block Design from the WISC-IV; C: Coding from the WISC-IV; COMP: Comprehension from the WISC-IV; DS: Digit Symbol from the WISC-IV; IT: Inspection Time; IW: Incomplete Words from the WJ-III; LNS: Letter-number Sequencing from the WISC-IV; MR: Matrix Reasoning from the WISC-IV; mRPM: modified Raven's Progressive Matrices; *g*: general intelligence; Ga: Auditory ability factor; Gc: Crystallised ability factor; Gf: Fluid ability factor; Glr: Long-term storage and retrieval factor; Gs: Speed of information processing factor; Gs In: Gs Invaders; Gsm: Short-term memory factor; Gv: Visuo-spatial ability factor; SR: SIM: Similarities from the WISC-IV; V: Vocabulary from the WISC-IV; VAL: Verbal-Auditory Learning from the WJ-III; RF: Retrieval Fluency from the WJ-III; PC: Picture Concepts from the WISC-IV; PS: Picture Swaps; SS: Symbol Search from the WISC-IV; SB: Sound Blending from the WJ-III.

4.2 The current research

The introductory chapters have placed the current research within its historical setting. What now follows is a review of the study aims, objectives and hypotheses.

4.2.1 Aim

The aim of this study is to examine the relationship between putative low level Pb exposure (i.e., around 10µg/dL) and cognitive abilities in children living in Port Pirie and Broken Hill.

There are at least three important reasons for conducting the proposed study:

1. Successful Pb abatement programs mean that in non-industrial areas nearly all children now have PbB concentrations below 10 µg/dL. Children living in proximity to mining and smelting plants represent a group whose average PbB levels approach the highest PbB concentration whilst remaining below the WHO safety threshold and they are a population of particular interest. The research of Canfield et al. (2005) and Pocock et al. (2005) each produced counterintuitive findings suggesting that, whilst a significant inverse association exists between Pb exposure and intelligence outcomes, the range below 10 µg/dL may represent the most detrimental level of exposure for intelligence. This hypothesis requires thorough investigation.
2. With the value of hindsight, the current study addresses some of the methodological limitations of previous research. Key covariates such as heritable and socio-cultural determinants of IQ will be addressed. More thorough treatment of covariates like paternal IQ will aid in dispelling the possibility of residual confounding (Bellinger & Needleman, 2003).
3. The theoretical concept of ‘intelligence’ has evolved during the last 20 years. A primary outcome measure in previous studies on the effect of PbB levels on human intelligence has been a version of the Wechsler Intelligence Scales for Children (e.g., WISC-R, or WISC-III, etc). Contemporary theories of intelligence will drive inclusion

of a range of additional measures of intelligence to supplement the Wechsler Scales and to better explore the relationship between IQ and Pb exposure. Of particular note is the inclusion of measures of auditory abilities, which may be differentially susceptible (De la Burdé & Choate, 1975; Dietrich et al., 1987) and has not been studied extensively in previous research.

4.2.2 Objectives

1. To determine whether there is an inverse association between children's neurocognitive development and Pb exposure at levels previously thought to be safe, that is, approximately 10 µg/dL or less;
2. To characterise any such association and describe any confounding effects of socio-demographic, familial, environmental, pre- and post-natal factors that influence the development of children's cognitive abilities;
3. To explore the associations between Pb exposure and children's cognitive abilities as measured by both Wechsler IQ scales and by tests not included in the Wechsler Scales but described in the comprehensive CHC account of the structure of intelligence.

4.2.3 Hypotheses

1. Across the Pb exposure range of Port Pirie and Broken Hill children, there will be an unadjusted inverse association between:
    - FSIQ and PbB concentration, and
    - The *g* factor of intelligence and PbB concentration.
2. Associations between all cognitive ability measures and Pb exposure will be attenuated by measures of demographic, familial, psycho-social and environmental, pre- and post-natal factors.

METHODOLOGY

Chapter 5: Study Design and Methods

Chapter summary

This chapter describes the design of the current study. The study location, design and population will be described, including approaches to recruitment and data collection. This will be followed by an overview of the measurement of PbB concentration, children's cognitive functioning and potential covariates to the association between PbB concentration and children's cognitive abilities.

Finally, a brief outline of the approaches to data management, ethical issues and data analysis will be provided.

This chapter also acknowledges some limitations relating to the final dataset: for some children there was a time-lag between their cognitive assessment and subsequent PbB sampling due to operational changes occurring at the primary PbB analysis lab in South Australia. It was also the case that PbB samples were not available for all of the children recruited over the course of the study; however, it is shown that the cognitive functioning of children who did not provide PbB samples did not significantly differ from the cognitive functioning of the children included in the final dataset.

5.1 Study locations

This study recruited families living in the Australian communities of Port Pirie and Broken Hill (see Figure 2), two communities with present-day and historical links with the Pb smelting and mining industries, respectively. Characteristics of these communities are summarised in section Chapter 1.

In summary, Port Pirie and Broken Hill have been identified as the most appropriate locations for the study for the following reasons:

1. In each community there is an awareness of the public health implications of Pb, and families are accustomed to on-going monitoring programs to ensure the safety of their children.
2. The exposures experienced by the children in these communities currently result in a high percentage of children (approximately 70%; Population Health Division, New South Wales Government, 2008; Department of Health, South Australia, 2011) having PbB levels in the range of interest (≤ 1 to 10 µg/dL), whereas in non-industrially exposed cities mean PbB concentrations have declined; in the only nationwide survey of the PbB concentrations of Australian children, conducted in 1995 (nine years after leaded petrol was banned in Australia; NHMRC, 2009a), the mean PbB levels of children aged 1 to 4 years was 5.1 µg/dL (Donovan & Anderson, 1996), more recently the mean PbB concentration of children in Sydney (aged 6-to-31 months of age; *N* = 113) in Sydney, Australia, was 3.1 µg/dL (Gulson, Mizon, Taylor, Korsch, Stauber, Davis et al., 2006).
3. Despite remediation, monitoring, and education programs, residents of Port Pirie and Broken Hill are vulnerable not only to present day contamination of the region's environment but historically persistent contamination (White et al., 1998). In addition to the exposure pathways to which the general population of Australia are exposed, for children living in Port Pirie and Broken Hill additional contamination can occur through the following pathways:
    - Inhalation of airborne Pb, a product of industrial activities in the area.
    - Ingestion of Pb contaminated rainwater.
    - Ingestion of Pb material entering the home via Pb industry workers.

5.2 Study design

The design is cross-sectional and will enable treatment of potential covariates to the relationship between children's cognitive abilities and Pb exposure. Children living in Port

Pirie or Broken Hill and their parents were invited to enrol in the study from October 2006 to September 2010.

The study design sought information from each member of the Mother, Father and Child triple (MFC). Initially, the study eligibility criteria mandated that for a family to be enrolled in the study, both biological parents needed to be available in Port Pirie or Broken Hill, surrounding towns, or in Adelaide. This criterion reflected the desire to collect comprehensive measures of covariates like parental IQ. As the study recruitment progressed, it became apparent that a) the recruitment process was slow and that b) many children in each centre lived in single care-giver families (this will be discussed further in 3.1). Hence, children were recruited on the basis of the availability of at least one biological parent.

Eligibility criteria employed were:

Entry criteria

1. The index child must be 7 or 8 years old.
2. At least one biological parent must be accessible in Port Pirie or Broken Hill, surrounding towns, or in Adelaide.
3. Each member of the MFC must have had a sufficient grasp of spoken English to understand the tasks required for testing.

Exclusion criteria

The family were not eligible to participate if any of the MFC:

1. Were formally diagnosed with an intellectual disability[16] or,
2. Had suffered from brain trauma (injury and/or encephalitis) or,
3. Suffered from a disability that hindered their motor ability.

Since a formal medical assessment was beyond the scope and resources of the current study, mothers were asked to answer a range of questions seeking to capture their child's incidence of health difficulties as well as their concerns and perception of their child's health.

[16] In Australia, formal diagnosis of 'intellectual disability is based upon assessment of an IQ of 70 or less before the age of 18 years and diminished adaptive functioning capabilities (APS, 2010).

The questions posed to mothers are summarised below and both ‘yes/no’ answers and written responses were facilitated by the questionnaire design:

- Would you describe your child as ‘healthy’?
- Does your child have any on-going medical conditions requiring special medication or equipment?
- How many days has your child been absent from school in last month due to ill health or any other unplanned reasons?
- Have you ever had any concerns about the growth or development of your child?

Responses are summarised in Table 14 and it is evident that the majority of mothers reported that their child had no chronic medical conditions and only a small amount of school time (mean of less than one whole day off school) had been lost to illness or unplanned reasons over the last month. Likewise, the majority of mothers considered their child ‘healthy’ and had no concerns about their child’s growth and development.

Of the mothers that did report ongoing medical problems these included two cases each of ADHD, dyslexia and eczema. Given that this report relied on maternal reports in the cases of ADHD and dyslexia it is not known whether these maternal reports represent professionally diagnosed cases, although one mother reported the prescription of medication to manage ADHD which suggested formal medical diagnosis. Other medical problems included single cases of asthma, constipation, incontinence, Type I Diabetes, severe peanut allergy, and multifactorial allergy.

Approximately 19% of mothers reported concerns about the growth and development of their child. A number of mothers reported concerns about their child’s intellectual functioning (6.1%) and speech development (5.1%). Linked to developmental capacity were specific concerns about concentration (one case), homework compliance (one case), and vision (one case). One mother reported concerns that her child’s skills were too advanced compared to classmates. Other concerns related back to medical difficulties in the domains of gastrointestinal functioning (one case) and nutrition and growth (two cases).

Table 14

Mothers' responses to child health questions (n = 96).

Child health questions		Maternal reports
Describe child as 'healthy' (%)	Yes	97.9
	No	2.1
On-going medical conditions requiring special medication or equipment (%)	With conditions	20.8
	Without conditions	79.2
Reported medical conditions (%):	ADHD[a]	2.1
	Dyslexia	2.1
	Eczema	2.1
	Asthma	1.0
	Constipation	1.0
	Incontinence	1.0
	Type I Diabetes	1.0
	Severe peanut allergy	1.0
	Multifactorial allergy	1.0
Days absent from school in last month due to ill health or unplanned reason[b]	Mean days absent (*SD*)	0.77 (2.11)
	Range	0 – 17 days absent
Concerns about the growth or development of child [c] (%)	Yes	19.1
	No	80.9
Domain of concern (%):	Intellectual development	6.2
	Speech development	5.1
	Bowel movements	2.1
	Nutrition/growth[d]	2.1
	Concentration	1.0
	Vision	1.0
	Advanced skills	1.0
	Compliance (refusal to do homework)	1.0

Note. ADHD: Attention deficit hyperactivity disorder; *n*: subsample size; *SD*: Standard deviation;
[a] One case reported that medication had been prescribed for the management of ADHD.
[b] *n* = 92; 5 responses missing.
[c] *n* = 94.
[d] One child described as 'underweight' and one child described as 'overweight.'

Of the children recruited, none was subsequently excluded from the formal analyses based on maternal reports of exclusion factors such as formal diagnosis of an intellectual disability, brain trauma (injury and/or encephalitis), or disability hindering motor ability. These data relating to maternal reports of health and concerns were collected as a screen of the sample and were not included in subsequent analyses. Reports of conditions which may be reflected in or linked to cognitive ability performance (Dyslexia and ADHD) were noted.

5.3 Study Sample

Study participants were 151 families with 7 or 8 year-old children attending primary schools in Port Pirie and Broken Hill. Where available, information was sought from each member of the MFC.

In Port Pirie the total number of families recruited was 93 and in Broken Hill total recruitments were 58 families.

Despite the total number of recruitments, PbB samples were not subsequently available for all 151 children[17] and the total number of families included in subsequent statistical analyses was 106. The sample size will be further discussed in Chapter 5 and possible reasons for recruitment difficulties will be discussed in Chapter 11.

5.4 Recruitment

Recruitment was initiated through primary schools in both Broken Hill and Port Pirie.

In Port Pirie the children already participated in a PbB monitoring program run by the Environmental Health Centre. The schools in the region have a long-standing history of supporting health initiatives relating to Pb. In Broken Hill, families are also familiar with monitoring programs, although these have previously been concentrated on the pre-school

[17] Changes to the Institute of Medical and Veterinary Science procedure for blood collection and analysis meant that the decision was made to delay the collection of PbB samples in Port Pirie and Broken Hill and the lag time between cognitive assessment and PbB sampling varied in the sample. This unavoidable time lag meant that some children were no longer available for blood sampling.

years rather than middle-childhood. Communication with the schools in each region commenced with telephone conversations and in-person meetings with the school principals and members of the research team. This enabled explanation of the reasons for the study program and negotiation of school involvement.

In general, participants were recruited via information letters sent home from the school, these introduced the study and invited participation (see Appendix C). These letters targeted children from participating schools in, or approaching, the age range 7 to 8 years. Letters invited the child, biological mother and father to undertake separate interviews with a trained researcher and to undertake cognitive testing (irrespective of whether the parents still lived together). Families were able to claim up to $AU100 per family to cover costs and inconvenience.

5.5 Data Collection

Cognitive assessments of 151 children were carried out by a trained researcher, during school hours in an appropriately quiet and illuminated room at the respective schools. Children were assessed individually during two separate sessions, with each session lasting up to approximately one hour. These assessments comprised both paper-and-pencil testing and a computerised battery. Assessment scheduling was negotiated with teachers so as to minimise disruptions to other school activities.

In a home visit with the mother, the research assistant administered the WAIS-III and the computerised Inspection Time (IT) task (see below). The first home visit was also used to begin an observational assessment of the home environment using the HOME Inventory. The family was given two questionnaires to be completed by available caregivers (mother and/or father; see Appendix D) and a time was negotiated for the researcher to pick up a sealed envelope containing the completed forms. These envelopes were forwarded directly to the Adelaide research team to maintain participant confidentiality. Questionnaires gathered information including basic demographics (age, educational status, family living

arrangements, household income bracket, years lived in Port Pirie or Broken Hill, etc.), information about the target child (e.g., pre- and post-natal information) and information on the experiences and psychological profile of the child's parents.

In the second home interview, the father was administered the IT task and Standard Progressive Matrices – Classic Version (SPM: Raven, 1989; see below). This short paternal assessment sought to maximise the likelihood of obtaining the fathers' participation in cognitive testing; the research team considered the computerised IT task to be less threatening than the one-on-one testing required with the full cognitive abilities battery. Nonetheless, the cognitive tasks administered to fathers allowed estimation of functioning and specifically, the collection of IT data allowed comparison of the scores calculated for children and mothers. This approach enabled statistical analyses to proceed while obviating the possibility that fathers might refuse to co-operate in more intensive cognitive testing. This second visit was also used to complete the assessment via the HOME Inventory.

Capillary PbB testing on each index child was conducted in conjunction with the Environmental Health Centre in Port Pirie, and with the Far Western Area Health Service in Broken Hill. The Environmental Health Centre's current testing schedule ceases at age 7 – but the Environmental Health Centre, extended the schedule to include 8 year-olds (Year 3 children) in order to integrate the current research with their activities. Ideally, capillary PbB sampling would have been conducted in parallel to cognitive texting but due to changes in the Institute of Medical and Veterinary Science testing protocol there was a time lag between collection of children's cognitive data and PbB sampling. This will be discussed further in Chapter 5.

At all times during data collection the researchers were blind to the Child's PbB concentration to protect data collection from investigator bias.

All of the measures administered to the MFC triple are summarised in Table 15 and will be discussed in turn.

Table 15

Summary of the exposure, outcome and covariate measures administered.

Construct		Measures & questionnaire targets	
EXPOSURE MEASURE			
Lead exposure		Capillary Blood samples taken from child	
OUTCOME MEASURES			
Child cognitive abilities		• Wechsler Intelligence Scale for Children-Fourth Edition, Australian Standardised Edition • Chronometric test – Inspection Time • Psychometric tests - Picture Swaps, Modified version of the Raven's Progressive Matrices, selected subtests from the Woodcock Johnson-III Tests of Cognitive Abilities (Visual-auditory Learning, Retrieval Fluency, Sound Blending, Incomplete Words, Auditory attention, Spatial Relations) & Gs Invaders.	
MEASUREMENT OF POSSIBLE COVARIATES			
Demographics		Gender of the child	
Familial variables	Parental cognitive abilities	*Maternal* • Wechsler Adult Intelligence Scale – Third Edition • Chronometric test – Inspection Time	*Paternal* • Standard Progressive Matrices – Classic Version • Chronometric test – Inspection Time
		Highest level of parental education	
Psycho-social & environmental factors	Markers of Socioeconomic Status	• Combined annual family income • Number of children in family	
	Care-giving environment	Middle Child Home Observation for Measurement of the Environment Inventory	
	Parent's depressive symptomology	Beck Depression Inventory – II	
	Stressful Life events	Recent Life Events Questionnaire	
	Quality of Dyadic Relationship	Dyadic Adjustment Scale	
	Current tobacco exposure	Parent's current smoking behaviour	
	Parental exposure to Pb	Parent's period of residence in centre	

Table 15

Continued.

Construct		Measures & questionnaire targets
MEASUREMENT OF POSSIBLE COVARIATES continued.		
Biomedical, Prenatal & post-natal factors	Maternal factors	Maternal age at child's birth Gravidity of mother Pre-natal exposure to teratogenic agents
	Delivery factors	Mode of delivery Neonatal Intensive Care Unit admission (of more than a few hours)
	Neonatal factors	Birth order Gestational age Birth weight
	Nutritional factor	Incidence and duration of breast-feeding

5.6 Measures

5.6.1 Blood sampling and analysis

Capillary blood samples were collected by staff at the Environmental Health Centres in Port Pirie and Broken Hill following a strict standardised skin-cleaning protocol which is essential for avoiding surface contamination.

The Environmental Health Centres in Port Pirie and Broken Hill sent the blood samples to the Institute of Medical and Veterinary Science, which is a public research body located in Adelaide, for analysis.

Institute of Medical and Veterinary Science analysed samples using a Perkin Elmer Sciex, Elan II DRC (MDS Sciex, Concord, Ontario Canada) Inductively Coupled Plasma Mass Spectrometer (ICP-MS) linked to an AS-10 auto sampler (Perkin Elmer Pty. Ltd. Singapore).

The instrument was calibrated with five calibrators covering the range 0 – 4.83 micrograms per mol (µmol) Pb per litre. Iridium was used as the internal standard for Pb because it has an ionisation potential similar to Pb (which was measured in the Inductively ICP-MS plasma) and because they are rare earth elements, they are unlikely to be contained in any of the samples. The calibration solutions were prepared from stock reference solutions obtained from Chem Service Inc, West Chester USA, Lead 10.00 g/L. The internal standards solutions were purchased from Australian Chemical Reagents, Moorooka, Queensland, Australia (Iridium standard solution 978 micrograms per litre (µg/L) ± 5 at 20°C). All calibration solutions are National Institute of Standards and Technology traceable.

Samples and calibration solutions were mixed and then 100 micro litre (µL) was diluted with 4.0mL of diluting solution containing 0.4% Ammonium Hydroxide, 0.05% EDTA and 0.2% Triton X-100. 50µL of each of the internal standards solutions was added per litre of diluting solution. Diluted samples were then mixed and centrifuged for analysis. All sample and calibration solution dilutions were performed immediately before analysis. Pb was measured at masses 205.97, 206.98, 207.98; reported Pb results are the mean of the concentrations measured at these masses. Corrections were made on recovery of the internal standard.

All analyses performed on the ICP-MS used internal standards to correct any variation in ionisation and recovery during analysis. Accuracy and precision were monitored using a commercially available tri level whole blood quality control material that satisfies acceptable performance limits, and the Institute of Medical and Veterinary Science laboratory participates in two external quality assurance programs for Pb - one run out of Birmingham in the United Kingdom and the other run by the Royal College of Pathologists in Australia.

5.6.2 Assessment of children's cognitive abilities

The following measures were used to assess children's cognitive abilities. As illustrated in Figure 9, the cognitive battery administered to children was informed by the CHC model of the structure of intelligence. In addition to the WISC-IV, tests were included based on theoretical and empirical evidence that they measured individual CHC factors.

Wechsler Intelligence Scale for Children-Fourth Edition, Australian Standardised Edition (WISC-IV; Wechsler, 2005)

The WISC-IV (mean of 100 and a *SD* of 15) is an individually administered instrument for assessing the cognitive ability of children, aged from 6 years 0 months to 16 years 11 months.

The WISC-IV consists of 15 subtests, including 10 core subtests and 5 supplementary tests. This study used the 10 core subtests (See Appendix E for a full description of each WISC-IV subtest), which took approximately 65 - 80 minutes to administer (see Table 16 for a list of the subtests).

The core tests yielded a number of scale and subscale scores and each subtest contributes to one or all of these summary scores; these are summarised in Table 16).

FSIQ represented overall cognitive functioning and is comprised of four composite scores which capture performance ability in more distinct areas of cognitive functioning; Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI) and Processing Speed Index (PSI).

The subtests of the WISC-IV were administered according the Australian manual (see Table 16) and scoring followed the protocol outlined in the manual. See Appendix F for a summary of psychometric information pertaining to the WISC-IV.

Table 16

Subtest and related composite scores on the WISC-IV

WISC-IV subtests	FSIQ	VCI	PRI	WMI	PSI
Vocabulary	√	√			
Similarities	√	√			
Comprehension	√	√			
Block Design	√		√		
Matrix Reasoning	√		√		
Picture Concepts	√		√		
Letter-number Sequencing	√			√	
Digit Span	√			√	
Coding	√				√
Symbol Search	√				√

Note. √ indicates that a subtest contributes to the calculation of a given summary score. FSIQ: Full Scale IQ; PRI: Perceptual Reasoning Index; PSI: Processing Speed Index; VCI: Verbal Comprehension Index; WISC-IV: Wechsler Intelligence Scale for Children-Fourth Edition, Australian Standardised Edition; WMI: Working Memory Index.

Chronometric Tests

Additional tasks were administered to estimate Gs:

Inspection Time (IT)

Visual IT is the capacity to detect change in a briefly viewed visual array. The task measuring IT requires a simple judgement about which of two vertical lines joined at the top is shorter than the other. With unlimited exposure, errorless decision making will occur. Observation is limited by the introduction of a 'backward masking pattern,' preventing further processing of the stimulus. Decision making accuracy is explored via variation in mask onset time (Vickers, Nettelbeck & Wilson, 1972). IT is not a direct index of performance speed, rather speed is inferred from the exposure duration required to resolve a simple judgement with a given accuracy.

When IT was administered, the participant was seated in front of a laptop computer at a viewing distance of approximately 0.7 metres. The IT task consisted of a target figure comprised of two vertical lines, one subtending a visual angle of 2.1 degrees and the other 2.5 degrees and joined at the top by a horizontal line at an angle of 1.2 degrees (see Figure 10). One of the vertical lines was markedly longer than the other and appeared on the left or right equiprobably. Following exposure of the target stimulus for the relevant stimulus onset asynchrony (SOA), it was immediately replaced by a "flash" masking stimuli of approximately 320 milliseconds (m/sec) and comprised of two vertical lines subtending at a visual angel of 3.3 degrees and shaped as lightening bolts (see Figure 10; Evans & Nettelbeck, 1993). The participant's task was to indicate whether the shorter line in the target stimuli had appeared on the left or the right of the screen by pressing the corresponding button on the computer mouse.

(a) (b)

Figure 10

Stimuli presented in the inspection time (IT) task. (a) stimulus to be discriminated (left leg shorter form); (b) masking stimulus (Preiss & Burns, n.d)

Task instructions emphasised accuracy over speed of responding. Task requirements were primarily explained via diagrams and the unmasked target stimuli was viewed on the monitor. A series of practice trials were included using unmasked stimuli to ensure that the participant understood task requirements. These practice trials required 100% correct responding for 10 trials with a SOA of approximately 835 m/sec and 10 correct trials out of 10 for a SOA of approximately 420 m/sec; all participants met this criterion to proceed onto formal testing.

The testing trial began with a SOA of approximately 250 m/sec and proceeded via an adaptive staircase algorithm (Burns & Nettelbeck, 2005). The algorithm required three correct responses for a given SOA to initiate a SOA reduction of approximately 17 m/sec for subsequent trials. When an incorrect response as registered, the SOA was increased by approximately 17 m/sec. An average SOA was calculated over eight reversals of direction on the staircase, producing an estimate of the SOA with an associated probability of 79% for making a correct response (Burns & Nettelbeck, 2005). The IT task took approximately 10 minutes to administer.

Gs Invaders

Gs Invaders (McPherson & Burns, 2007) is a computerised adaptation of the WAIS-III subtest, Digit Symbol. Digit Symbol is considered a measure of Gs (McPherson & Burns, 2007) and requires participants to fill in blank cells according to a key provided on each test sheet. Gs Invaders has the same task requirements as Digit Symbol, but it has been adapted using various computer game-like features that appeal to participants. The screen layout of Gs Invaders represents a spaceship cockpit with a numerical grid central to the screen. To enhance the ease of use of the number grid, the numbers change from being white to blue as the cursor runs over them. The cursor is limited so that it cannot leave the boundaries of the grid.

The stimuli consist of 5 x 5 centimetre coloured space ships that are viewed through the window of the cockpit. At the bottom of the cockpit there are nine different space ships presented, each is paired with a single digit (from 1 - 9), which is presented directly above each spaceship. On-screen instructions explain that spaceships can be destroyed by firing the number that corresponds with each given spaceship. Upon a correct response the spaceship explodes and an audible laser sound is heard. Incorrect responses elicit a flash on the screen and a ‘banging’ noise. Seven practice items are completed pre-testing. Instructions encourage participants to perform with accuracy and speed. Participants have 2 minutes to destroy as many spaceships as possible. According to McPherson and Burns (2007), the “sequence of responses required is the same as for [WISC-IV] Digit Symbol” (p. 879).

Psychometric Tests

Picture Swaps

In the Picture Swaps test (Crawford, 1988; Stankov & Crawford, 1993), participants are required to mentally swap the order of three numbered pictures presented on a computer monitor and then to indicate the final order of the pictures. A number of possible final sequences are given on the next screen and participants decide which sequence (1, 2, 3 or 4)

represents the final swapped order of the pictures. During the introduction and practice for the task, the response keys were explained and both speed and accuracy were highlighted as important factors in performance.

There are four levels, which differ in the number of Picture Swaps required (1, 2, 3, or 4 swaps). For example a two swap instruction would be 'Swap 1 and 2, then 3 and 1.' This test yields number correct and correct decision speed measures for each level and an overall measure of performance; and assesses Gf (Stankov, 2000; Stankov & Crawford, 1993).

Modified version of the Raven's Progressive Matrices (mRPM)

A modified version of the Raven's Progressive Matrices (mRPM; Raven, 1956) was administered to the children. Participants work through a series of 36 visual analogical problems. Each item consists of a geometric design with a section missing. The participant's task is to determine which of six options would best complete the given design. According to Zajac and Burns (2007) the items included are chosen in order to maximise discriminability.

The mRPM stimuli were viewed on a computer monitor. Each item was presented and below each item there were numbered alternative solutions and these corresponded with a numeric response pad that remained visible at all times. Participants respond by clicking (with the mouse) the number that corresponds with their response. A timed version of the test was used allowing 20 minutes for administration. Utilising a computer for presentation of the items allows speed scores to be recorded for each item. mRPM measures reasoning ability which is generally identified as Gf (Carroll, 1993; Jensen, 1998; McGrew & Flanagan, 1998). There is currently no normative data available for the mRPM task.

Woodcock Johnson-III Tests of Cognitive Abilities (WJ-III; Woodcock, McGrew & Mather, 2001)

The Woodcock Johnson-III Tests of Cognitive Abilities (WJ-III) comprises 20 tests. Each of the tests can be conceived as a single measure capturing a specific cognitive ability

(Schrank, 2005). Six subtests have been chosen to supplement the WISC-IV and computerised battery in this study. The rationale for the inclusion of these subtests from the WJ-III battery was that they are designed to measure the CHC factors of Ga, Glr and Gv. The WJ-III subtests administered were:

Visual-auditory Learning

The Visual-auditory Learning task requires participants to learn a "pictographic language" (McPherson & Burns, 2007, p. 879). The participant learns that visual stimuli represent common words and the participant is asked to read aloud, sentences constructed from visual stimuli. As the test progresses the number of associations required to read the sentence increases. This task draws upon learning, storage and retrieval processes (Mather & Woodcock, 2001). Visual-auditory Learning has a median reliability of 0.86 for 5 to 19 years olds (Mather & Woodcock, 2001). This test measures of Glr.

Retrieval Fluency

Retrieval Fluency requires the participant to name as many items as possible from one category in one minute. The three categories used were: (1) things to eat or drink; (2) first names of people; and (3) animals. Retrieval Fluency has a median reliability of 0.83 for 5 to 19 years olds (Mather & Woodcock, 2001). This test is regarded as a measure of Glr.

Sound Blending

In Sound Blending the participant listens to an audio recording from a laptop using headphones. The stimulus is a series of syllables that make up a distinct word. The participant's task is to report what word is formed when the syllables are blended. According to Mather and Woodcock (2001), Sound Blending has a median reliability of 0.77 for 5 to 19-years-olds and 0.90 in the adult range. This test measures of Ga.

Incomplete Words

In Incomplete Words the participant listens to an audio recording played from a laptop using headphones. The recording has important phonemic components missing from the words and the participant is asked to identify the word. According to Mather and Woodcock (2001), Incomplete Words has a median reliability of 0.77 for 5 to 19 years olds and 0.90 in the adult range. This test measures Ga.

Auditory attention

In the Auditory Attention task participants listened to a word while looking at four pictures and they are asked to point to the picture that corresponds with the word they have heard. The task difficulty increases by including pictures in the visual array that have similar sounding names and by increasing the intensity of background noise. As Mather and Woodcock (2001) report, the Auditory Attention task measures Ga and it tests a participant's selective attention ability by exploring aptitude in discriminating between forms of oral language, which may be masked or distorted. According to Mather and Woodcock (2001) Auditory Attention has a median reliability of 0.87 for 5 to 19 years olds.

Spatial Relations

Spatial Relations requires participants to choose components from an array that would successfully join to form a target shape. The difficulty of Spatial Relations increases as the drawings of the components are flipped or rotated and become more difficult to distinguish. Spatial Relations has a median reliability of 0.81 for 5 to 19 years olds (Mather & Woodcock, 2001). Spatial Relations is a measure of Gv.

5.6.3 Collection of descriptive variables

Data pertaining to the ages of the MFC triple and information about parent occupation were gathered in order to describe the characteristics of the sample.

In particular, parent occupation data were not investigated as potential covariates in multiple regressions due to the interpretative challenges of this categorical variable. Instead parent occupation was used for descriptive purposes as an indicator of social status (Tong, 1995). Despite the decision to use parent occupation data solely for descriptive purposes, it is worth acknowledging that, theoretically, parent occupation is a variable that can have impacts upon childhood development because parental IQ scores are predictive of occupational status (more intelligent individuals may be more suitable for complex roles; Neisser, Boodoo, Bouchard Jr., Boykin, Brody, Ceci et al., 1996) and it is possible that certain work environments may enhance what Kohn and Schooler (1973, cited in Neisser et al., 1996) deem ‘intellectual flexibility.’ Specifically, occupation of parent has previously been associated with child PbB levels (Baghurst et al., 1992), because Port Pirie smelter workers brought Pb accumulated on clothes, hair or skin into the home. Freidman, Lukyanova, Kundiev, Shkiryak-Nizhnyk, Chislovska, Mucha et al. (2005) also identified a strong association between the PbB levels of (mean PbB = 4.65 µg/dL) Ukrainian 3 year olds and paternal occupation in Pb associated manual labor. Since approximately 1984 workers at the Port Pirie smelter have been provided with shower facilities and uniforms that remain onsite (Tong, 1995), aiming to minimise this exposure pathway.

Parents were asked to supply details of their current field of work and position title via questionnaire format. The Australian and New Zealand Standard Classification of Occupations (ANZSCO), First Edition (Trewin & Pink, 2006) was used to categorise the occupations reported. Occupations with similar attributes were then grouped. The ANZSCO is a measure of occupational skill rather than occupational prestige and hence occupations are not ranked but rather categorised on the basis of skill requirements.

The ANZSCO has five hierarchical levels of description and specificity for capturing occupations - major group, sub-major group, minor group, unit group and occupation. For the purpose of this study, occupations reported by parents were classified according to major groups and these major groups are summarised in Table 17. When it was difficult to categorise a given occupation based on ANZSCO major groups it was possible to delve deeper into the hierarchy where more specific information about the occupations comprising each major group is available.

In addition to the eight major groups classified by the ANZSCO, two additional categories were identified as relevant based on the occupations listed; ‘Home Duties’ and ‘Student.’ The ANZSCO does not include a category for ‘Home Duties’ because it only captures formal employment category linked to the Australian and New Zealand labour market. Hence, data about the qualifications and skill base associated with ‘Home Duties’ are not provided, but this is not problematic given the categorical nature of the use of these data in the current study.

Table 17

Major groups used to classify parent occupations, their skill description and the associated subgroups (adapted from Trewin & Pink, 2006).

Occupational characteristic	Managers	Professionals	Technicians & Trade workers	Community & personal service workers	Clerical & administrative workers	Sales workers	Machinery operators & drivers	Labourers
Description	Plan, organise, direct, control, coordinate & review the operations of organizations and industry.	Perform analytical, conceptual & creative tasks through the application of theoretical knowledge & experience.	Perform skilled tasks, applying broad or in-depth technical, trade or industry specific knowledge.	Assist Health Professionals with patient care, provide information & support on social welfare matters.	Provide organizational support to Managers, Professionals & organisations.	Sell goods, services & property, & provide sales support.	Operate machines, plant, vehicles & other equipment in agriculture, manufacturing & construction	Routine and repetitive physical tasks using their hands, tools, and machines as an individual or as part of a team.
Occupational subgroups	Chief executives, general managers, legislators. managers in hospitality, retail, service & agriculture.	Legal, Welfare, Information & communication technologies, Health, Education, Design, Engineering, Science, Transport, Business, Human Resource, Marketing, Arts & Media Professionals.	Engineering, Information & communication technologies, Science Technicians, Automotive, Construction, Electrotechnology, Telecommunications, Food, Skilled Animal and Horticultural technicians and trades Workers.	Sports, personal protective, hospitality carers, health & welfare (support) workers.	Clerical, office Support Workers, numerical clerks, receptionists, assistants, office managers.	Sales assistants, Salespersons, & agents.	Store persons, road & rail drivers, machine & stationary, plant operators.	Workers in food preparation, laundries, farm, forestry, factory processes, construction, mining. Labourers, cleaners.
Bachelor degree[a]	X	X						
Other qualifications[a b]			X	X	X	X	X	X
≥ 5 years experience [c]	X	X						
< 5 years experience			X	X	X	X		X

Note. X indicates that a qualification or level of experience is assumed to be relevant to a given occupation.
[a] Relevant experience and/or on-the-job training may be required in addition to the formal qualification, or no formal qualification or on-the-job training may be required
[b] Australian Qualifications Framework (AQF) Associate Degree, Advanced Diploma or Diploma (or certificates I, II, III).
[c] May substitute formal qualification.

5.6.4 Covariate measurement

An important methodological consideration for both cross-sectional and longitudinal studies of human teratology is that causal inferences cannot be made due to the possibility of spurious correlations. As Jacobson and Jacobson (2005) indicated, wherever a correlation is noted between an outcome and exposure measure it must be considered that a range of confounding variables may explain the association. Jacobson and Jacobson define a covariate as "[providing] an alternative causal explanation for an observed relation between a teratogenic exposure and a developmental outcome" (p. 397). The comprehensive evaluation of covariates in epidemiological research exploring the influence of Pb has been criticised for producing studies considered to be "over controlled" (Banks, Ferretti & Schucard, 1997, cited in Chiodo et al., 2004) but researchers maintain that the approach remains an important method of statistical adjustment (Chiodo et al., 2004).

Previous research has taken two distinct approaches to measuring and controlling covariates in studies of Pb exposure and children's cognitive abilities, with focuses on:

1. Potential covariates that are understood to potentially impact children's cognitive abilities (for example, Després et al., (2005), Dietrich et al. (1987), Hu et al. (2006) & Surkan et al., (2007)); and
2. Potential covariates that are understood to potentially impact children's cognitive abilities *and* Pb levels (for example, Bellinger et al. (1992) & Chiodo et al. (2004)).

This study will favour the first approach by focusing upon variables that impact children's cognitive development and the primary outcome of WISC-IV performance; 20 variable groups were identified as potentially impacting children's cognitive development. This approach was chosen in order to place a limit upon the plethora of potential covariates to the associations between Pb exposure and children's cognitive abilities that could be considered and also recognising that there is overlap between the variables that may impact children's cognitive development and Pb exposure levels; a wide range of demographic,

familial, psycho-social and environmental and pre- and post-natal variables are considered. In particular potential covariates were selected based upon:

- A review of previous literature. A full summary of the variables collected as potential covariates is presented in Appendix G. It was beyond the scope of this study and its resources to collect data on all of these potential covariates and a selection of categories were chosen.
- Jacobson and Jacobson's (2005) review indicated that the majority of studies exploring developmental exposure to neurotoxic agents assessed demographic variables, pre-natal and post-natal medical risks, exposure to other teratogenic agents and a range of socio-environmental influences as potential covariates. This was supported by review of previous covariates which tended to fall into the categories of demographic, familial, psycho-social and environmental, and pre-and post-natal factors.

The known or suspected impact of these variables on the Pb – cognitive abilities relationship will now be addressed. These variables were as follows:

Demographic Variables

1. *Gender of the child* – Historically, gender has been measured as a potential covariate in numerous cross-sectional (Chiodo et al., 2004; Cho et al., 2010; De la Burde et al., 1975; Kim et al., 2009; Lanphear et al., 2000; Pocock et al., 1987; Sovcikova et al., 1997) and prospective studies (Bellinger et al., 1991; Canfield et al., 2003; Dietrich et al., 1987; Ernhart et al., 1987; Ernhart et al., 1988; Fergusson & Horwoood, 1993; Hansen et al., 1989; Schnaas et al., 2006; Tong et al., 1998; Wasserman et al., 1992) investigating the associations between Pb exposure and cognitive abilities. Some researchers have identified gender as a possible covariate to the association between Pb exposure level and cognitive abilities. For example, Pocock et al. (1987) reported a significant correlation between PbD level and the child's gender such that the correlation between PbD level and cognitive abilities was statistically significant for

boys but not girls. Other groups have identified gender as an important moderator, for example in the CLS, Dietrich et al. (1987), found that for a significant inverse association existed between 6 month MDI and the 'maternal PbB and child gender' interaction variable. Reference to the data showed that for maternal PbB dose-related deficits were most notable for males in the cohort at 6 months such that each µg/dL increase in maternal PbB concentration was accompanied by a 0.84 decrement in MDI points ($p \leq 0.01$). McMichael et al. (1992) also identified gender as an effect moderator in correlations between PbB concentration and cognitive performance measures at 2 and 4 years, respectively; the association between Pb exposure and neurocognitive measures were more pronounced and significant for girls for the GCI and for Memory measures. The target child's gender was coded in the study dataset and gender information was collected via routine components of the WISC-IV.

Familial variables

Neisser et al. (1996) indicated that "a sizeable part of the variation on intelligence test scores is associated with genetic differences among individuals" (p.85). These genetic differences have a heritable component that can be explored with measures of maternal and paternal cognitive abilities (or IQ). Neisser et al. (1996) indicated that the contribution of heritability (h^2) to offspring's intelligence approximates 0.50 and that between-family (c^2) variance is in the order of 0.25. Interestingly, it is noted that heritability of traits follow a developmental shift which increases with age from 0.45 in childhood to 0.75 by late adolescence (Neisser et al., 1996), so that the influence of genetics upon the development of cognitive abilities increases with age.

Not only is there a heritable and genetic influence upon cognitive abilities worth mentioning but the cognitive abilities of a parent can also influence parental provision of care which can also impact a child's development. Some of the ways that this may occur are through (adapted from Llewellyn, McConnell, & Bye, 1995):

- Child care: knowledge of developmental milestones, intellectual stimulation (especially verbal stimulation; HealthyStart, 2011), discipline, hygiene and decisions relating to medical emergencies and home safety.
- Domestic provisions: nutritional choices, food shopping and preparation, home cleanliness and management of finances.
- Social and community interactions: assertiveness, marital relations, vocational skills/training, use of community resources, friendships and involvement in leisure activities.

Some of these care, domestic and social and community factors linked to parental cognitive abilities will be also measured with assessment tools characterising the socioenvironmental environment.

Recognising the importance of the heritable component of cognitive abilities, this study has collected data about maternal and paternal cognitive abilities. Maternal cognitive abilities have been assessed as a potential covariate in both cross- sectional (Chiodo et al., 2004; Després et al., 2005; Fulton et al., 1987; Hu et al., 2006; Kordas et al., 2006; Pocock et al., 1987; Surkan et al., 2007) and prospective (Bellinger et al., 1991; Bellinger, Leviton et al., 1994; Canfield et al., 2003; Cooney et al., 1989; Ernhart et al., 1987; Ernhart et al., 1988; McMichael et al., 1992; Schnaas et al., 2006; Wasserman et al., 1992) research. Paternal cognitive abilities have been considered less frequently and the only report of measurement of paternal cognitive abilities was in the prospective research of Cooney et al. (1989) where the PPVT was used to assess paternal verbal ability.

As a secondary measure of cognitive abilities, highest level of parental education was also considered; some measure of parental education has been a variable collected widely in previous research (parental education: Baghurst et al., 1992; Calderón et al., 2001; Cho et al., 20101; Cooney et al., 1989; Ernhart et al., 1987; Ernhart et al., 1988; Després et al. 2005; Kim et al., 2009; Lanphear et al., 2000; Pocock et al., 1987; Rabinowitz et al.., 1991, Schnaas et al., 2006; Wang et al. 2002; Maternal education: Bellinger et al., 1991; Canfield et al., 2003;

Chiodo et al., 2004; Fergusson & Horwood, 1993; Hansen et al. 1989; Sovcikova et al. 1997; Wasserman et al. 1992).

2. *Maternal cognitive abilities*: Maternal cognitive abilities were assessed using two cognitive ability measures; the WAIS-III (Wechsler, 2003) and IT (as described in 2.4.2).

   The WAIS-III is an individually administered instrument for assessing cognitive ability in adults in the age range 16 years to 89 years.

   The WAIS-III consists of 14 subtests, including 13 core subtests and 1 supplementary test, Object Assembly. In the interests of time management the 13 core subtests were used in this study and took about 65 - 95 minutes to administer (See Table 18 for a list of WAIS-III subtests). The WAIS-III yields an overall cognitive functioning score, FSIQ and two composite scores, VIQ and PIQ, which capture functioning in more distinct areas of cognitive functioning and each subtest's contribution to FSIQ. In addition four Index Scores are also available; Verbal Comprehension (VC), Perceptual Organisation (PO), Working Memory (WM) and Processing Speed (PS). The subtests were administered according the WAIS-III manual including a specific administration order (see Table 18).

3. *Paternal cognitive abilities*: Paternal cognitive abilities were assessed using two cognitive ability measures; SPM and IT (as described in 2.4.2).

   In the SPM participants have 25 minutes to work through a booklet of 60 visual analogical reasoning problems. Like in the mRPM administered to the children, each item consists of a geometric design with a section missing and it is the participant's task to determine which of six options would best complete the given design, recording their answer on a numeric response sheet. SPM was administered to fathers as a measure of the *g* factor or Gf (Carroll, 1993; Jensen, 1998; McGrew & Flanagan, 1998).

Table 18

Subtest and related composite scores on the WAIS-III (adapted from the Wechsler, 1997).

NOTE:
This table is included on page 148 of the print copy of the thesis held in the University of Adelaide Library.

4. *Highest level of parental education*. Research (Deary, Strand, Smith & Fernandes, 2007; Lynn & Mikk, 2007) has shown "broad agreement that there is a moderate to strong correlation" (Deary et al., 2007, p.13) between cognitive abilities (IQ) and educational attainment and hence data were collected regarding the educational levels of the parents of children in the sample as an additional measure or proxy for cognitive ability. Parents were asked to indicate whether their highest level of education was at the primary school level, some years of high school, completion of secondary school, attainment of technical, trade or Technical and Further Education (TAFE) certificates or a University degree.

Psycho-social and environmental variables

A combination of socioenvironmental factors and heritability impact child development (Neisser et al., 1996). Based on previous research and findings of the cross-sectional and prospective studies in the field, the current study measured a range of factors theorised to influence child development such as the home environment, parent's psychiatric status, recent stressful life events and dyadic dynamics. These factors and the relevant assessment approach will be discussed in turn:

5. *Markers of socioeconomic status (SES; combined annual family income, number of children in family):* According to Brown (1995), Pb exposure is the sole environmental pollutant with notable race and class associations. Hence, it is important to include a measure of SES in subsequent analyses. The association between increased vulnerability to Pb and SES are linked to widespread inconsistencies in public awareness and education about Pb toxicity, differences in sources and types of exposure, and inadequate access to resources like medical care. This is supported by WHO (2010) who report that children from disadvantaged backgrounds exhibit the greatest BoD linked to Pb due to increased likelihood that they reside in proximity to industry, polluted sites and heavy traffic and to live in deteriorated housing, in communities with limited political power.

   Brown (1995) poses the question: What came first, the toxic hazard or vulnerable populations? For Broken Hill and Port Pirie, geology and geographical location, respectively, can account for the proximity of these communities to sources of Pb. Hence, the populations in these areas tend to conform to Brown's (1995) 'drift' argument, whereby communities are built around resources due to work availability and the possibility of "low rent or home prices" (Brown, 1995, p. 27) due to remoteness. Brown (1995) indicates that in a 'drift' explanation of population movement, a degree of systematic inequality exists, so that "poor and minority groups are subject to multiple environmental, residential and other burdens" (p.27) in addition to Pb exposure.

Sociodemographic correlates of PbB levels have previously been identified. In phase one of NHANES III (1988 - 1991). Brody, Pirkle, Kramer, Flegal, Matte, Gunter and Paschal (1994) noted that in children aged one to five years, PbB levels were highest in the non-Hispanic, black children of low-income families residing in urban areas. The PbB level of this group was 9.7µg/dL compared to 3.7 µg/dL in the rest of the study population.

The measurement of SES is fraught with theoretical inconsistencies and limitations (Braveman, Cubbin, Egerter, Chideya, Marchi, Metsler et al., 2005; Jeynes, 2002; Oakes & Rossi, 2003) and a poor choice of markers for SES can contribute to the possibility of residual confounding (Tong, 1995). As Tong (1995) indicated, while markers of SES may not directly impact a child's cognitive development, SES may represent characteristics of care or the environment that may causally impact cognitive development (e.g. provision of medical care and educational stimulation; Tong, 1995). Raven (2000) observes that based on the work of colleagues and scholars, that "a simple index of fathers' occupational status is the best single measure of a general factor of family socioeconomic status" (p.36), when compared to mothers' occupational status, combined parental income and parents' levels of education. Indeed, previous research in the field has used parental (father and/or mother) occupation as the primary index of SES (Chiodo et al., 2004; Cooney et al, 1989; Dietrich et al., 1987; Fulton et al., 1987; McMichael et al., 1992; Rabonowitz et al., 1991; Wang et al., 2002; and the Boston cohort). Researchers in the field have also considered variables such as number of children in the family (Chiodo et al., 2004; Després et al., 2005; Dietrich et al., 1991; Fergusson & Horwood., 1993; Hansen et al., 1989, McMichael et al., 1992; Minder et al., 1994), possessions (e.g., ownership of car, computer, VCR, TV set, stove, refrigerator and radio; Kordas et al., 2006; Sovcikova et al., 1997), home ownership (Kordas et al., 2006), area of residence (Cho et al., 2010; Rabinowitz et al., 1991), type of home (Fergusson & Horwood., 1993; Wasserman et al., 1992), proximity to plant or

busy road (Fergusson & Horwood, 1993; Sovcikova et al., 1997), combined annual income (Canfield et al., 2003; Kim et al., 2009; Schnaas et al., 2006) as markers of SES. Others have also gauged SES using scales such as the the Bronffman index of SES (comprising crowding, housing conditions, potable water availability, drainage and fathers education; Calderón et al., 2001).

In sum, the author shares Raven's (2010) view that "it is not only impractical to base the classification of SES on more information than we would have been able to collect ... collection and composition of such information would not be expected [or likely] to yield a ''better'' overall index" (p.36). Hence, for this study it was decided that combined annual income per family would be used as a maker for SES. This decision followed from the challenges of coding and categorising parental occupation and the use of the ANZSCO which was designed for use with Australian populations based on the Australian and New Zealand labour markets in terms of their skill requirements and assumed formal qualifications. Since the ANZSCO measures occupational skill and assumed qualification, rather than prestige, the information obtained through variables capturing highest level of education and combined family income were more definitive and were used in this study in lieu of parental occupation.

Data regarding combined annual income were gathered via the questionnaire administered to the mother and father. Specifically, participants were asked to indicate the income bracket ('Less than $20 000/year or under $400/week'; 'Less than $50 000/year or under $1000/week'; 'Less than $80 000/year or under $1600/week'; 'More than $80 000/year or over $1600/week') corresponding with their combined annual or weekly income. Since all children in the sample lived with at least their mother (see section 6.1), data provided by the mother were used and cross-checked with reports provided from fathers (where available). This approach to the measurement of SES is indeed limited due to the sensitive nature of financial information – 7.2 % of participants did not answer the question relating to annual income and it is possible that

families may have incorrectly reported their income. Additionally, annual income is merely a simple proxy for SES and the other complex components of the social environment that may impact child development.

SES will also be gauged using family size (number of children in family). Numbers of siblings, or family size, are variables that have been linked to SES via theory that applies a 'quality-quantity' economic model to the rearing of children (Black, Devereux & Salvanes, 2007). In short, the model stipulates that as the number of children in a family increases, so too do the budgetary pressures placed upon the family (Black et al., 2007). Family size has also been linked to inverse associations with cognitive outcomes, but it is difficult to ascertain whether there is a causal link between family size and cognitive outcomes; or, if there is something characteristic about families which choose to have more children (Black et al., 2007). In their research study Black et al. (2007) used a large data set of information about Norwegian men and found no significant associations between family size and cognitive outcomes, but they did identify negative associations between the birth of twins on the functioning of their older siblings.

6. *Care-giving environment*. Sound neurocognitive development is reliant upon environments that are conducive to learning and safe exploration, whereas those characterised as "severely deprived, neglectful or abusive" (Neisser et al., 1996, p.88) may hinder optimal intellectual development. This may include environments that are limited in the encouragement of communication skills, speech development, independence, emotional expression, and where stimulating resources and activities are not made available, or where a high level of parental stress or marital discord is evident.

The nature of the care-giving environment was measured using the Middle Childhood Home Observation for Measurement of the Environment Inventory (MC HOME). The MC HOME captures components of social, emotional and cognitive support gained via the home environment (Bradley, Caldwell, Rock, Hamrick & Harris,

1988). Use of the MC HOME is mandated by the need to make this study comparable with previous prospective studies of Pb and child development which have used the HOME inventories (cross-sectional studies: Chiodo et al., 2004; Després et al., 2005; prospective studies: Bellinger et al., 1991; Canfield et al., 2003; Cooney et al., 1989; Dietrich et al., 1987; Fergusson & Horwood, 1993; McMichael et al., 1992, Moore et al., 1982; Wasserman et al., 1992).

The impetus for inclusion of the MC HOME in studies of this type follows the work of Bradley and colleagues, pointing to an association between an infant's environment and subsequent intellectual development. Bradley and Caldwell (1984) found that HOME scores at 2 years of age correlated with SBIQ at 3 and 4.5 years and the Science Research Associates Achievement battery at 7 years. In particular, the MC HOME is designed for use with children between 6 and 10 years and is an extension of two previously developed HOME inventories suitable for children from birth till three years and three to six years respectively. The inventory is administered within the home in the presence of the child and primary caregiver. Other family members are welcome to be present in order to reinforce the informality of the inventory and to capture the child's 'typical' behaviour. The MC HOME involves use of observation and interview techniques, such that the administrator is encouraged to utilise "open-ended probes" (Bradley et al., 1988, p.61) to gather information. It takes one hour to administer the MC HOME.

The scale was constructed from item and factor analyses of a 91- item version of the MC HOME. The reduction in total items to 59 enabled a decrease in administration time. The 59-item MC HOME has been reported as having high reliability. For the 59-item scale Cronbach's alpha was 0.90 (Bradley et al., 1988) and coefficients for each subscale ranged from 0.52-0.80 (Bradley et al., 1988). Bradley et al. (1988) also reported inter-observer agreement, with ratings from four research assistants for a subset

of 40 cases. The average inter-observer agreement was 93%, with a Kappa coefficient of 0.88.

The validity of the MC HOME has been shown via correlations in the range 0.2-to-0.5 with demographic variables such as mother and father's educational level, mother and father's occupation and family's SES (Bradley et al., 1988). The MC HOME has been shown to produce a low-to-moderate correlation with the SRA Achievement Battery and a low correlation with the Classroom Behaviour Inventory (Bradley et al., 1988). See Appendix H for a summary of items in the MC HOME.

7. *Parent's depressive symptomology*. Depressed parents have been described as "less involved with their children and showing increased friction, resentment, and helplessness, and decreased interaction and affection" (Orvaschel, Wallis-Allis & Ye, 1988, p.18). While it is unclear whether depression *per se* is responsible for these effects, or whether the depression is secondary to marital discord, significant life events or other adverse circumstances, it is highly desirable to ascertain parental mental status as part of a battery of predictors of 'intelligence.' Maternal mental health has been measured previously as a potential covariate in the cross-sectional research of Pocock et al. (1987) and Després et al. (2005) and Fulton et al. (1987) measured parental mental health.

The Beck Depression Inventory – Second Edition (BDI-II; Beck & Steer, 1993) is a self-report measure of experiences of depressive sympotomology captured via a group of graded statements. These statements are weighted from 0 to 3 in term of severity and a total score is determined by summing the weighting of the items, with a maximum score of 63. For example a four choice item is as follows: 0 - I don't have any thoughts of killing myself; 1: I have thoughts of killing myself, but I would not carry them out; 2: I would like to kill myself; 3: I would kill myself if I had the chance.

Although, no normative data are available, interpretation guidelines are available with clinical cut-offs (Spreen & Strauss, 1998); 0 – 9: normal range; 10 – 15: minimal

depression; 16 – 19: mild-moderate depression; 20 – 29: moderate-to-severe depression; 30 – 63: severe depression.

The 21 items of the BDI-II are derived from clinical perspectives and do not favour a specific theoretical account of depression. The BDI-II takes 5 to 10 minutes to administer. Statements refer to 21 different areas of experiences and these are summarised in Table 19 (adapted from Spreen & Strauss, 1998).

Test-retest reliability of the BDI-II has been reported as above 0.90 (Beck, 1970, cited in Spreen & Strauss, 1998) and internal consistency at 0.86 (Reynolds & Gould, 1981, cited in Spreen & Strauss, 1998). Advantages of the inventory are its high internal consistency, high content validity, validity in differentiating between depressed and non-depressed subjects, sensitivity to change, and international proliferation. Since the test construction in 1961, the test has been employed in more than 2000 empirical studies (Richter, Werner, Heerlein, Kraus & Sauer, 1998).

Table 19

Depressive experiences measured by the BDI-II.

Sadness	Guilt	Irritability
Pessimism/discouragement	Self-dislike	Social withdrawal
Sense of failure	Self-accusation	Indecisiveness
Dissatisfaction	Suicidal ideation	Unattractiveness
Crying	Loss of appetite	Work inhibition
Expectation of punishment	Weight loss	Fatigability
Somatic preoccupation	Loss of libido	Insomnia

Note. BDI-II: Beck Depression Inventory - Second Edition.

8. *Stressful Life events in family*. The experience of stressful life events in a family can be theorised to influence cognitive development in terms of disruption or changes to parenting, experience of emotional distress and exposure to parental anxiety, depression or substance abuse. Secondary to this, short term and chronic stress can impact and, in fact, change the functioning of the brain, with impacts to functional outcomes such as attention and academic attainment. Hippocampal (a facilitator of verbal memory) damage is one of the main impacts of stress and this occurs through increases in coritsol, which inhibit the hippocampus, (McEwen, 1998) and through damage to the dendrites of neurons in the hippocampus. Both damage linked to increased coritsol and atrophy of dendrites is reversible in the short-term but longer term stress can kill the hippocampus' neurons permanently. McEwen (1998) also reported animal studies in which rats' experiences of early life stress influence cognitive impairment because these experiences trigger hyper-sensitive responses in the Hypothalamic–pituitary–adrenal (HPA) axis and autonomic immune system. This view is supported by Perry, Pollard, Blakeley, Baker and Vigilante (1995), who argued that a child who experiences stress via abuse or neglect can have a brain that develops or 'hardwires' itself in such a way that a state of hyper-arousal as a result of threatening experiences can become the norm. Behaviourally, attentional difficulties may be an example of a maladaptive cognitive response that has its basis in the adaptive response to an original (and perhaps ongoing) stressful situation.

Previous researchers have sought to capture familial stress by using various measures. For example, in the Boston Cohort a range of family cohesion and stress experience scales were administered (the Family Stress Index, Family Adaptability and Cohesion Evaluation Scales, Social Readjustment Rating Scales, Parenting Stress Index, Children's Life Events Inventory, Social Support Network and Child Stress Index) and Després et al. (2005) measured intra family violence as an indicator of stress. In the current study, the focus has been on parental reports (in lieu of child

reports) because the assessment demands placed upon the child are already sizeable. Hence, the Recent Life Events Questionnaire (RLE: Cox & Bentovim, 2000) administered to parents to identify events (such as marital separation, death, or severe illness, or injury of a significant other) that have been experienced over the previous 12 months. The RLE is a 21-item questionnaire based on the work of Brugha, Bebington, Tenant and Hurry (1985) in which participants are cued to indicate (by ticking two adjacent boxes), which events have been experienced in that last year and which continue to emotionally affect them. Cox and Bentovim (2000) indicated that the primary aims of the use of the RLE are to:

- Compile a social history of a family, by building a thorough picture of the current context and situation for the family.
- Aid in understanding how recent life experiences may be impacting upon the carer and the remainder of the family.
- Gain additional information about the family unit in matters that may have previously been overlooked.

The RLE takes about 15 minutes to complete. Scoring takes place by initially tallying the life events that have happened using a binary system (1 = the life event has happened, 0 = the life event has not happened). The numbers of events that are still affecting the participant are then summed. Hence, the total RLE score is the sum of the events experienced and the events still affecting the participant (Cox & Bentovim, 2000). In pilot testing (Brugha et al., 1985) the average number of events experienced in the previous year was between 7 and 8 and, on average, half of these events continued to impinge on the participants. In interpretation, the questionnaire does not have inherent cut off points, but rather it is believed that “the more life events that adult has been through, the higher the score, and therefore the greater the likelihood that of some form of longer term impact on the adult, child and family” (Cox & Bentovim, 2000, p.38).

9. *Quality of the relationship between parents (or partners).* An extensive body of research and scholarship has documented consistent associations between dyadic (parents or partners) discord and conflict and "increased probability [of] children's disorders ... including effects on cognitive, social, academic, and even psychobiological functioning" (Cummings & Davies, 2002, p.31) of children. There are several pathways believed to explain these associations including detriments to parenting style and capacity and exposure of children to physical, verbal and psychological aggression, alcoholism and depression (Cummings & Davies, 2002). While previous research has collected demographic data gauging marital status (Bellinger et al., 1991; Lanphear et al. 2000) and family living arrangements (Tong et al., 1998), the quality of the relationship between parents (or partners in the MFC) has seldom been considered with the exception of Després et al. (2005; intra family violence), Fergusson and Horwood (1993; who collected information about parental conflict: (a) whether the parents had engaged in prolonged arguments during the last 12 months; (b) whether the child's mother had reported being assaulted by her spouse in the last 12 months; and (c) whether the child's mother had reported experiencing sexual difficulties in the last 12 months) and Pocock et al. (1987) who assessed the quality of the dyadic relationship based on interview data and observations.

Hence, the Dyadic Adjustment Scale (DAS: Spanier, 1976) was administered to parents of children in the cohort as a measure of the degree to which partners in a committed dyadic relationship (married or cohabiting) regulate themselves and their partner. Respondents answer to 32 items, indicating their extent of agreement with their partner on some instances and quantifying how frequently the dyad engages in certain activities (Budd & Heliman, 1992). The DAS is appealing to both clinical and research settings because it is brief, worded pragmatically, has an administration time of about 10 minutes and findings can be interpreted in isolation from or in conjunction with the dyadic partner's results (Budd & Heilman, 1992).

The content of the DAS is not grounded in any theoretical approach to relationships; rather, it is drawn from a review of all inventories in the field dating back to 1933, which yielded 300 pooled items. Elimination of duplicate items and those diverging from content validity produced a sample of 200 items. Factor analysis was then conducted upon the responses of 109 married couples and 94 divorced couples to delineate the final 32-items. These groups were non-representative, characterised as white and lower-middle-class. Arbitrary assignment of a score of 100 as representing healthy adjustment is documented; however, clinical research supporting such a position is lacking in the investigations of the DAS (Budd & Heliman, 1992; Stuart, 1992). Despite these limitations the DAS remains the most widely used measure of dyadic interaction.

Four components of the DAS have been delineated via factor analysis: Dyadic consensus (13 items), Affectional Expression (4 items), Dyadic Satisfaction (10 items) and Dyadic Cohesion (5 items) (Stuart, 1992). Hence, scores can be expressed in a total DAS score, or as scores for each subscale.

Stuart (1992) reported reliabilities for the DAS in the vicinity of 0.90 have consistently been noted; additionally, agreement between partners has been reported in the moderate range (0.44 to 0.58). The test-retest reliability of the DAS is 0.96 over an 11 week interval (Stuart, 1992). Slightly lower reliabilities have been documented for the Affectional Expression and Dyadic Cohesion subscales as a consequence of the limited number of items comprising the subscales (Budd & Heliman, 1992).

The DAS has been shown to have convergent validity through its correlation with other measures of marital interaction such as the Locke-Wallace Marital Adjustment Scale (Stuart, 1992), owing largely to its development from the content of similar tools (Budd & Heliman, 1992). Predictive validity has also been established, with low DAS scores indicative of a greater chance of experiencing incidences of

domestic violence, depression, dysfunctional families and communications (Stuart, 1992) and social anxiety (Budd & Heliman, 1992).

In the interests of retaining participant co-operation, it was decided that items pertaining to ratings of how often one is 'Too tired for sex' and incidents of 'Not showing love' would be eliminated due to their sensitive content.

10. *Current exposure to parental smoking*. Exposure to cigarette smoke has been shown to be detrimental to both children's neurocognitive status and development (Neisser et al., 1996). In the current study both parents were asked to indicate whether or not they were smokers at the time of assessment (yes/no). This is a variable that has been considered as a potential covariate by McMichael et al. (1992), Minder et al. (1994) and Sovcikova et al. (1997).
11. *Parent's period of residence in Port Pirie or Broken Hill:* Parents of children in the sample were asked to estimate the number of years that they had been living in each centre. Years of residence gives some indication of the parent's level of Pb exposure and is a possible covariate to both parental and child cognitive functioning due to the heredity component of cognitive abilities and the accumulation of Pb in the maternal system (some Pb is mobilised in pregnancy and transferred to the fetus). In a more qualitative, informal sense, period of residence in Port Pirie or Broken Hill gives some information about an individual's ties to the community and integration into these industrial communities.

Pre- and post-natal variables

A number of variables were measured in order to determine the contribution of early life experiences that may influence neurocognitive development (Neisser et al., 1996). The variables of interest are discussed in terms of maternal, delivery, neonatal, and nutritional factors:

Maternal factors

12. *Maternal age at child's birth*: Views about the effects of maternal age at birth on child outcomes are equivocal. Ketterlinus, Henderson and Lamb (1991) reported consensus that the development of children with adolescent parents (10 to 19 years old) is poorer than that of children with adult parents (20 to 34 years old), although their own research program failed to identify effects of maternal age on school performance after covariate control. Perinatal outcomes are believed to be less optimal with very young parents due to factors such as late onset of pre-natal care and missed appointments, use of abortive procedures at the onset of gestation, low educational attainment, lack of partners, low birth weight, preeclampsia, prematurity and lower incidence of cephalo-pelvic disproportion and preeclampsia[18] (Santos, Martins, Sousa & Batalha, 2009). At the other end of the spectrum, a large research base has established that the risk of miscarriage increases with maternal age (Roman, Doyle. Beralz, Alberman & Pharoah, 1978; Santow & Bracher, 1989), particularly beyond 35 years of age (Santos et al., 2009), as does the incidence of pregnancy complications like diabetes, pre-eclampsia, premature membrane rupture, rates of caesarean section and lower Apgar scores (Santos et al., 2009), and chromosomal abnormalities (Rom, 2007). Maternal age at child's birth has been collected as a potential covariate in the research of Bellinger et al. (1993), Cooney et al. (1989), Dietrich et al. (1987), Ernhart et al. (1988), Hansen et al. (1989), Kim et al. (2009), Tong et al. (1998) and Wasserman et al. (1998).
13. *Maternal Gravidity (how many times the mother has previously been pregnant):* Casterfine (1989) maintained that, the "probability of loss varies substantially over the reproductive career" (p.186) such that the likelihood of fetal death and development and pregnancy complications increases with the number of births per woman. Some researchers (Roman et al., 1989; Santow & Bracher, 1989) have argued that biomedical

[18] Preeclampsia is a maternal hypertensive syndrome (von Dadelszen, Magee & Roberts, 2003) that can negatively impact both maternal and child outcomes (Duley, Henderson-Smart, Walker& Chou, 2010).

variables such as ‘gravidity’ and ‘maternal age at birth’ show trends that are artefacts; it is possible that women with heightened risk (and incidence) of fetal loss have more pregnancies to obtain the same number of live births, leading to a grouping of high risk women with higher gravidity and older age. Nevertheless gravidity and parity have been considered by a number of researchers in the field as potential covariates to the association between Pb exposure and cognitive abilities (Chiodo et al., 2004; Després et al., 2005; Dietrich et al., 1991; Ernhart et al., 1988).

Despite some disagreement about what gravidity measures, mothers were asked to indicate the number of times they had been pregnant before becoming pregnant with the target child. A measure of ‘parity’ (how many live births the mother has experienced) was included in the questionnaire but excluded from data analysis because parity data were larger than gravidity figures, suggesting some confusion and unreliability in maternal reporting for that variable.

14. *Pre-natal exposure to teratogenic agents:* Prenatal alcohol exposure can result in Fetal Alcohol Syndrome (FAS), characterised by birth defects and cognitive damage (Mattson & Reily, 1998). Even when the extremes of FAS are not diagnosed, pre-natal exposure to alcohol can influence neurological development and intelligence (Neisser et al., 1996). Striessguth, Barr, Sampson, Darby and Martin (1989, cited in Neisser et al., 1996) showed that the children of mothers who reported 1.5 ounces or more of alcohol consumed per day whilst pregnant scored up to 5 IQ points lower than controls. Indeed pre-natal exposure to teratogenic agents (such as alcohol, tobacco and illicit drugs) has been measured as potential covariate in the research of Baghurst et al. (1992), Canfield et al. (2003), Chiodo et al. (2004), Cooney et al., (1989), Després et al. (2005), Dietrich et al. (1991) Ernhart et al. (1987), Ernhart et al. (1988) and Kim et al. (2009).

In this study mothers were asked to indicate whether they had consumed alcohol and smoked cigarettes around the time of their child’s conception and whether they had consumed alcohol or smoked during the pregnancy. Information about

smoking and alcohol consumption around the time of conception were used in a descriptive sense while smoking and drinking during pregnancy were specifically considered for inclusion in multiple regressions.

Delivery factors

15. *Mode of delivery:* There is some evidence that mode of delivery can significantly impact the rate of neonatal intracranial injuries (Towner, Castro, Eby-Wilkens & Gilbert, 1999) with possible long-term impacts upon neurocognitive functioning. In their extensive study (*N* = 340 live-born singleton infants born to nulliparous women), Towner et al. (1999) explored the associations between mode of delivery and neonatal outcomes, in particular injuries to the infant's skull. Their investigations found when neonatal outcomes were compared for children born through spontaneous labour versus those born through caesarean delivery, caesarean delivery was associated with significantly higher rates of subdural or cerebral haemorrhage, intraventricular haemorrhage, convulsions, central nervous system depression, feeding difficulty, and mechanical ventilation but a lower rate of brachial plexus injury (nerve injuries in the upper limbs; Towner, 1999). On the whole, the rate of intracranial haemorrhage in children born through caesarean section was 2.1 times (95 % CI = 1.6, 2.7) the rate associated with spontaneous delivery. Since there are variations in interventions occurring during vaginal delivery, Towner et al. (1999) found that the rate of intracranial haemorrhage associated with caesarean section did not differ from the rate associated with vaginal delivery interventions such as vacuum extraction (odds ratio (OR), 0.9; 95% CI = 0.7, 1.3), or forceps delivery (OR, 0.7; 95 % CI = 0.4, 1.1).

Mothers were asked to report whether their child was born through caesarean section or vaginal delivery and to describe any complications with the birth of the target child. Similarly, Rabinowitz et al. (1991) collected information about mode of deleivery as a potential covariate to the association between Pb exposure and cognitive abilities.

16. *Neonatal Intensive Care Unit (NICU) admission (of more than a few hours):* In line with the research of Pocock et al. (1987) and Hansen et al (1989), mothers were asked to record whether their child was admitted to NICU for more than a few hours (yes/no) as a proxy for incidence of birth and post-natal complications which can impact subsequent neurological development. Mothers were also asked to record any neonatal or birth complications and these were summarised for descriptive purposes.

Neonatal factors

17. *Birth order*: In plain terms, Dumitrashku (1997) has reported that "[a]s the number of children goes up, the level of their intellectual development goes down" (p.55) an effect that is consistent despite variation in ages of children, assessment measure, nationality and urban or rural living. This phenomenon has been explained in the literature by 'Confluence theory' (Scott-Jones, 1984), which suggests a child's cognitive capacity is influenced by a family's average cognitive functioning (Simpson, 1980) and that older children benefit from the experience of teaching their younger siblings skills and knowledge. Birth order was collected as a potential covariate to the association between Pb exposure and cognitive abilities in the work of Bellinger et al. (1991), Dietrich et al. (1991), Ernhart et al. (1987), Ernhart et al. (1988), Minder et al. (1994), Pocock et al. (1987), Tong et al. (1998) and in the Mexico City cohort.

Parents of the target child were asked to list the ages of any other children who lived in their house, from which birth order could be determined. This question was worded in this fashion to avoid errors due to misinterpretation of the question and to allow information about number of siblings to be cross-checked. Data for three sets of twins and seven singletons (n = 13) did not have birth order data entered because because the birth order of the twins could not be verified and the theoretical benefits and disadvantages of birth order cannot be applied to the subsample of 'only children.'

18. *Gestational age:* Following previous research in the field that considered gestational age as a potential covariate (Cooney et al., 1989; Dietrich et al., 1987; Pocock et al., 1987), mothers were asked to estimate their child's gestational age as a measure for the incidence of preterm birth. Preterm birth has been established as an important risk factor for neurosensory disability and in particular, cerebral palsy (Crowther, Doyle, Haslam, Hiller, Harding & Robinson, 2007).

19. *Birth weight:* Low birth weight can be indicative of premature birth or suboptimal development of the fetus. Established positive associations between birth weight and subsequent cognitive abilities have been noted across the range of birth weights (from very low birth weight children (< 1500 g; Mu, Tsou, Hsu, Fang, Jeng, Chang et al., 2008) to children in the normal range) and this association has not been accounted for by effect modifying social factors (Jefferis, Power & Hertzman, 2002). Specifically, Neisser et al. (1996) highlighted a small positive correlation between birth weight and later cognitive abilities in the range 0.05 to 0.13 (Broman, Nichols, Kennedy, 1975, cited in Neisser et al., 1996). Mu et al. (2008) reported that very low birth weight children in Taiwan had significantly lower school-aged performance on FSIQ and all subscales of the WISC-III than children with birth weight in the normal range. There is also extensive longitudinal data investigating the associations between birth weight and cognitive outcomes. Jefferis et al. (2002) reported on the 1958 British Birth Cohort study (N = 10,845), which sampled seven measures of cognitive and educational outcomes at 7, 11, 16, and 33 years of age. Overall cognitive and educational performance improved significantly as birth weight increased. In particular mathematical ability was measured at 7 years of age and Jefferis et al. (2002) found that, for each kilogram increase in birth weight, mathematics *z* scores increased by 0.17 (adjusted estimate = 0.15, 95% CI = 0.10, 0.21) for males and 0.21 (adjusted estimate = 0.20, 95% CI = 0.14, 0.25) for females. Birth weight has been collected extensively as a potential covariate in studies exploring the association between Pb exposure and

cognitive abilities (Bellinger et al., 1991; Canfield et al., 2003; Cho et al., 2010; Cooney et al., 1989; Dietrich et al., 1991; Ernhart et al. 1987; Ernhart et al., 1988; Fergusson & Horwood, 1993; McMichael et al., 1992; Moore et al. 1982; Pocock et al., 1987; Schnaas et al., 2006; Surkan et al., 2007; Wasserman et al., 1992), hence, mothers were asked to record the birth weight of their child and were given the option of recording either the weight in grams or pounds and ounces. For the purposes of analyses, all birth weights were converted to grams.

Nutritional factors

20. *Incidence and duration of breast-feeding*: As mentioned, consumption of breast milk is the most efficient form of nutrient delivery for infants even despite the possibility of neonatal and infant Pb intake (Ettinger et al., 2004) and WHO has recommended that mothers exclusively breastfeed infants for the first 6 months of life (WHO, 2011). Despite this recommendation, some variation exists in the incidence and duration of breastfeeding for infants due to factors such as negative attitudes toward breastfeeding, conflicting responsibilities or schedules, convenience, negative breastfeeding experiences, health or medical reasons (Dix, 1991), and maternal preference. Previous research has investigated the long-term impacts of breastfeeding on child development and in particular cognitive abilities. Anderson, Johnstone and Remley's (1999) meta-analysis of studies comparing breast and formula fed infants found that in controlled analyses, breastfed children performed significantly better in tests of cognitive function from ages 6 to 23 months and beyond. These differences amounted to an approximate 3.16 (95% CI = 2.35, 3.98) point discrepancy between the groups on cognitive measures. Additional findings were that children born prematurely gained more benefits from breastfeeding than term infants and that the benefits linked to breastfeeding increased with duration of breastfeeding (Anderson et al., 1999).

Mothers of the target child were asked to estimate the number of months for which their child was breastfed and from this whether a child was breast or formula fed could be deduced. These data were combined into a categorical variable comprising "No breastfeeding," "Breastfeeding for ≤ 6 months" and "Breastfeeding for ≥ 7 months." Duration and incident of breastfeeding was considered by Fergusson and Horwood (1993) and McMichael et al. (1992) as a potential covariate in their investigations of association between Pb levels and children's cognitive abilities.

5.7 Data Processing and Management

Cognitive abilities data

Data collected by research assistants in Port Pirie and Broken Hill were scored on location and duplicate copies of forms were mailed to the Public Health Research Unit based at the University of Adelaide, in Adelaide, South Australia. At the Public Health Research Unit, Ms Rachel Earl verified the scoring of all verbal (research assistants recorded participants' responses verbatim) and non verbal questions for the WISC-IV, WJ-III, WAIS-III and SPM. All sums were verified as was the calculation of scaled scores. Data were then entered into an Excel spreadsheet and later exported into SPSS 17.0 for analysis.

Electronic data were copied from research laptops in Port Pirie and Broken Hill, onto Compact Discs and mailed to Adelaide, where it was retrieved and entered into an Excel spreadsheet.

Questionnaires

Questionnaires (see Appendix D) were distributed to parents with reply-paid envelopes addressed to the Public Health Research Unit at the University of Adelaide. Once questionnaires were completed, parents mailed them directly to Adelaide for data entry. This procedure sought to maximise and maintain participant confidentiality.

Questionnaires administered to parents were designed so that they could be electronically scanned using the program Readsoft's Eyes & Hands Forms Version 5. This required questionnaires to be deigned using a template where each page is marked with positional coordinates so that the computer program can read the data. Once the data are scanned these were compiled into data spreadsheets. Not only is this approach time efficient, it reduces the possibility of data entry errors because all ambiguous responses are verified by hand.

5.8 Ethical considerations

The University of Sydney Human Research Ethics Committee approved the research on the 25 July 2006. The research was also approved by the New South Wales Department of Education and the University of Adelaide Human Research Ethics Committee. This research was also approved by the Human Research Ethics Committee of the Women's and Children's Hospital, Children Youth and Women's Health Service, in Adelaide.

Families invited to participate in the study were provided with an information package (see Appendix C), which outlined the study and methodology. Questions were invited and it was reinforced that the family was free to withdraw participation at any point. Subsequent to this, parents provided written consent (see Appendix C). Children were free to refuse participation at the time of psychological assessment, despite their parents' consent; this occurred in Port Pirie on one occasion.

In designing the study and its operational procedures, maintenance of a participant's confidentiality was paramount. Each participant's data were coded in terms of their family study ID. Likewise, questionnaires were only identified by family ID (which specified mother or father).

At the request of the families, performance feedback was available and as a whole, the cohort was also contacted with details regarding the progress of the study (see Appendix I for an example of a newsletter sent to participating families) and the eventual results of analyses.

5.9 Dataset

While there were challenges encountered in recruiting participants, secondary challenges were faced once participants were recruited and data collection commenced.

As previously noted, changes to the Institute of Medical and Veterinary Science procedure for blood collection and analysis meant that the decision was made to delay the collection of PbB samples in Port Pirie and Broken Hill. Methodologically, this means that the time between cognitive assessment and PbB sampling varied in the sample.

Of the children who provided PbB samples (N = 106), the mean time elapsed between cognitive assessment and PbB sampling was 21.4 months (SD = 12.0) or 1.8 years. In Figure 11 it can be seen that elapsed time ranged from PbB sampling approximately 5 months prior to cognitive assessment, to a PbB sample taken 48 months post cognitive assessment.

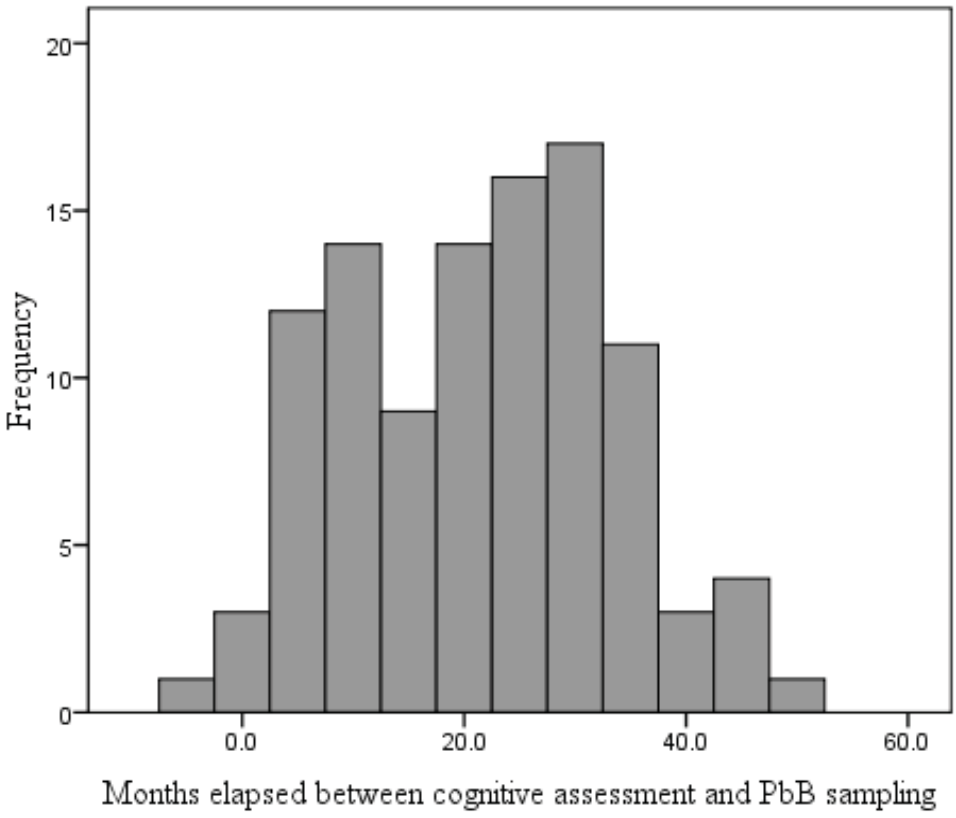

Figure 11

The frequency of months elapsed between cognitive assessment and PbB sampling.

This unavoidable time lag meant that some children were no longer available for blood sampling because their families had moved from Port Pirie or Broken Hill. Upon follow-up for PbB sampling, a portion of families were not contactable or did not attend their appointments (despite reminders and subsequent bookings). Given the somewhat intrusive nature of 'finger prick' tests for PbB estimation, some children refused to undergo the procedure. This information is summarised in Table 20.

Availability of a PbB sample was viewed as the limiting factor for the use of a child's data since the focus of this study is the association between Pb levels and cognitive abilities. Table 21 presents the WISC-IV, main cluster scores for the cognitive battery and an independent assessment, Raven's computerised battery and summarises the performance of the full sample, those children with PbB measures and those children without PbB measures.

On the whole, children with PbB measures performed slightly better (higher mean scores) than those without PbB measures. An exception was WMI, where children without PbB samples (mean = 96.4, *SD* =13.59) performed higher than those with PbB samples (mean = 94.5, *SD* = 15.31), however this difference was not statistically significant and had a small effect size (d = - 0.13, $p > 0.05$).[19]

Given that the WISC-IV and main cluster scores did not differ significantly based on PbB sample availability, it is reasonable to conduct the remainder of the analyses using data taken from only children who provided a PbB sample (N = 106).

[19] Negative Cohen's d indicates that PbB unavailable children had higher mean scores than PbB available children.

Table 20

Summary of data obtained and missing data from Port Pirie and Broken Hill.

PbB measures	Port Pirie	Broken Hill	Total
Total with PbB levels measured	**78**	**8**	**106**
Did not attend appointments	2	n/a	2
Could not be contacted	9	24	33
Moved from centre	n/a	5	5
Family declined further involvement	1	n/a	1
Child Refused PbB sampling	2	1	3
Insufficient PbB sample taken	1	n/a	1
Total participants recruited	93	58	151

Note. n/a: not applicable. PbB: Blood lead.

Table 21

WISC-IV, main cluster scores for the cognitive battery and an independent assessment, Raven's computerised battery, for the full sample, those children with PbB measures and those children without PbB measures.

Cognitive measure	Full sample			PbB sample available			PbB sample unavailable			Difference between PbB sample available and PbB sample unavailable children	
	N	Mean (*SD*)	Range	*n*	Mean (*SD*)	Range	*n*	Mean (*SD*)	Range	Mean difference	Cohen's *d*[a]
FSIQ	147	99.7 (14.07)	69 – 141	106	100.2 (14.59)	69 - 134	41	98.4 (12.70)	73 - 141	1.80	0.13
VCI	147	100.44 (13.84)	71 – 144	106	100.8 (13.95)	71 - 144	41	99.6 (13.67)	71 - 130	1.22	0.09
PRI	147	101.3 (14.42)	69 – 135	106	102.2 (14.97)	69 - 133	41	99.0 (12.75)	75 - 135	3.16	0.22
WMI	147	95.0 (14.83)	50 – 141	106	94.5 (15.31)	50 - 129	41	96.4 (13.59)	68 - 141	- 1.86	- 0.13
PSI	147	100.1 (13.15)	65 – 141	106	100.5 (13.65)	65 - 141	41	99.0 (11.86)	80 - 131	1.56	0.11
Glr	142	103.3 (14.70)	63 – 158	104	103.5 (14.53)	63 - 158	38	102.6 (14.27)	76 - 144	0.98	0.07
Ga	142	108.7 (14.56)	79 – 150	105	108.8 (14.53)	79 - 140	36	108.3 (14.85)	87 - 144	0.55	0
Ravens	142	6.7 (4.1)	0 – 18	103	7.0 (4.08)	1 - 16	39	6.08 (4.15)	0 - 18	- 0.88	0.21

Note. FSIQ: Full Scale IQ; Ga: Auditory Processing; Glr: Long-term storage and retrieval; *N*: sample size; *n*: subsample size; PbB: blood lead; PRI: Perceptual Reasoning Index; PSI: Processing Speed Index; Ravens: modified Raven's Progressive Matrices; *SD*: standard deviation; VCI: Verbal Comprehension Index; WISC-IV: Wechsler Intelligence Scale for Children-Fourth Edition**;** WMI: Working Memory Index.

[a] negative Cohen's *d* indicates that 'PbB sample unavailable children' had higher mean scores than 'PbB sample available children.'

5.10 Data analytic approach

As outlined, this study sought to measure children's cognitive abilities comprehensively (see Figure 9). The WISC-IV was administered and supplemented with a selection of measures to tap CHC factors not measured by WISC-IV. Statistical analyses were performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Statistical inferences were based on the level of significance $p < 0.05$.

When this research program was designed, based on communications with the Environmental Health Centre in Port Pirie and the Department of Health in Broken Hill, it was anticipated that more than 150 families could be enrolled in each centre. *A priori* power analyses indicated that a study recruiting 300 families would have facilitated (after adjustment for potential covariates) the detection of a Spearman correlation between cognitive abilities and PbB concentration ± 0.19 explaining as little as 3.5% of the variance in IQ with 80% power. This figure (3.5%) compares very favourably with the variation explained in earlier studies – and since Lanphear et al. (2005) have proposed that there are much greater effects over the range 1 – 10 µg/dL than over the higher ranges previously studied, the study should have been amply powered. As described earlier, the eventual size of the sample (with PbB concentration data) was 106 families, a figure well below the projected figures.

To be consistent with the cohort study analyses, multiple regression analyses will be conducted with cognitive ability scores as dependent variables and relevant covariates as (such as maternal WAIS-III FSIQ scores, MC HOME score, parental smoking behaviours, pre- and post-natal variables) as predictors.

Based on an alpha level of 0.05, anticipated effect size of Cohen's $d = 0.15$, and a desired statistical power level of 0.80, the minimum sample size to accommodate three predictor variables (not including the regression constant) is $N = 76$ families.

It should be noted that no attempt is made here to adjust for the number of comparisons made in subsequent analyses and the associated possibility of Type II errors. This approach follows the recommendation of Rothman (1986) that "the best course for the

epidemiologist to take when making multiple comparisons is to ignore advice to make … adjustments in reported results. Each finding should be reported as if it alone were the sole focus of a study" (p.150). In addition, it is noted that exploration of effect modification[20], is beyond the scope of this dataset because there is "insufficient statistical power to characterize effect modification with adequate precision" (Bellinger, 2000, p. 133).

This thesis will explore the effects of Pb upon children's cognitive abilities in two ways using multiple regression modelling:

1. ANALYSIS 1: Given the widespread use of the Wechsler Scales in the Pb - cognitive abilities literature, analyses will commence by exploring the relationship between PbB concentration and the WISC-IV and its subscales (VCI, PSI, WMI and PRI). The relationship between WISC-IV FSIQ and subscale scores and possible covariates will be explored to inform adjusted multiple regression analyses.
2. ANALYSIS 2: The second approach presented here will be to combine the WISC-IV scores with supplementary measures of cognitive ability in Factor Analysis (FA). FA will seek to generate CHC clusters and a general ability factor (*g*; factor scores for seven broad cognitive abilities: *g*, Ga, Gf, Gc, Gv, Gs, Gsm and Glr) factor based on the sample data. These analyses require specification of an appropriate measurement model and can be implemented in mPlus. These factor scores will then in turn serve as dependent variables in multiple regression models as described above. These supplemental analyses will seek to evaluate the effect of PbB concentration on cognitive abilities in more depth than allowed by the use of traditional Wechsler IQ scores, as described earlier. The associations between PbB concentration and cluster scores will be explored to investigate whether one component of the taxonomy of

[20] Bellinger (2000) discusses effect modification in the context of epidemiologic studies of low-level neurotoxicant exposures and health outcomes and explains that effect modification occurs when "the magnitude of the association between an exposure and an outcome varies across strata of some other factor" (p.133); this is explored statistically through the inclusion of an interaction term in multiple regression analyses (e.g., effect modifier X exposure of interest).

human cognitive abilities is the particularly susceptible to the deleterious impact of Pb exposure.

Structure of the remaining Chapters

Chapters 6, 7, 8, 9, 10 and 11 of this thesis present:

- Chapter 6: The dataset and the demographic characteristics of the sample (including distribution of children's PbB levels and cognitive ability measures);
- Chapter 7: A summary of the distributions of possible covariate measures and their relationship with PbB concentration and cognitive measures;
- Chapter 8: The adjusted and unadjusted relationship between PbB concentration and WISC-IV performance;
- Chapter 9: A description of the FA methodology and the adjusted and unadjusted associations between PbB levels and cognitive ability cluster scores and the *g* factor;
- Chapter 10: Additional analyses which explored the associations between PbB concentration and contemporary computerised measures of cognitive abilities as well as the relationships between PbB levels and potential covariates; and
- Chapter 11: An overview and discussion of the research findings, limitations to the study, implications and directions for future research in this field.

DATA ANALYTIC CHAPTERS

Chapter 6: Characteristics of the Study Population

Chapter Summary

This chapter summarises the demographic characteristics of the sample, comparing families recruited in Port Pirie with those from Broken Hill.

This chapter goes on to present the descriptive statistics for children's PbB levels and cognitive performance measures.

In general the sample can be described as a group of 7 - 8 year olds (*N* = 106; mean age = 7.96 years, *SD* = 0.59 years) with mean arithmetic PbB concentration of 4.97 µg/dL (*SD* = 3.52) and average FSIQ. The majority of children in the sample lived in two parent families with at least one sibling. The families living in Broken Hill tended to have a higher annual income than those in Port Pirie and Broken Hill parents had higher levels of educational attainment than parents in Port Pirie. The majority of parents in the sample did not currently smoke cigarettes.

6.1 Sample demographics

Reports concerning family composition, family income and number of parents smoking in the family, were taken from maternal reports and cross-checked with paternal data, where available.

Another characteristic of the sample is that, in some instances, siblings were recruited from the same family (*n* = 6 families; including three pairs of twins). When calculating descriptive statistics for the sample, data specific to the parent (e.g., cognitive measures and BDI-II) were only summarised once per family.

Age and gender of the target child

The study recruited children aged 7 and 8 years (*N* = 106). The mean age of the sample at assessment was 95.6 months (*SD* = 7.15 months) or 7.96 years (*SD* = 0.59 years). In Port Pirie the mean age of participants was 7.95 years (*SD* = 0.63 years) and 8.02 years (*SD* = 0.51 years) in Broken Hill (see Table 22).

There were 52 males in the sample (49.1%) and 54 females (50.9%). When the gender distribution was considered in terms of city of recruitment, this relatively even divide between males and females was consistent across centres (see Table 22).

Family composition and number of children per family

As shown in Table 22, 79.2% of children sampled from Port Pirie and 72.0% from Broken Hill, lived in two parent families. Single parent families were reported for 12.5% of Port Pirie children and 8% of Broken Hill children, equating to a sample total of 11.3% of children living in a single parent family. In all cases, children in single-parent families lived the greater part of their time with their biological mother. Of the families that reported the 'Other' category to describe their living arrangements, only one written explanation was provided and that family indicated that an adult boarder lived with the two parent family.

Across both centres, over 50% of families comprised two or more children (including the target child). The mean number of children per family was 2.8 (*SD* = 1.09).

Table 22

Demographic characteristics of the Port Pirie, Broken Hill and Total sample.

Demographics		Port Pirie (*n* = 78)	Broken Hill (*n* = 28)	Total sample (*N* = 106)
Age of child	Mean months (*SD*)	95.4 (7.5)	96.2 (6.1)	95.6 (7.15)
	Mean years (*SD*)	7.95 (0.63)	8.02 (0.51)	7.96 (0.59)
Gender of child	% Males	48.7	50.0	49.1
	% Females	51.3	50.0	50.9
Family composition[a] (%)	Two biological parents	79.2	72.0	78.0
	Single parent	12.5	8.0	9.9
	Live with partner who is not child's biological parent	4.2	4.0	4.4
	Other	1.4	8.0	3.3
	Not reported	2.8	8.0	4.4
Number of children per family[a] (%)	One	3.8	14.3	6.5
	Two	35.9	28.6	33.6
	Three	32.1	28.6	30.8
	≥ four	19.1	14.3	17.7
	Not reported	9.0	14.3	11.2
Mean number of children per family (*SD*)		2.9 (1.11)	2.5 (0.98)	2.8 (1.09)
Self-report combined family annual income[a] (%)	Less than $20,000	6.9	16.0	9.3
	$21,000 to $ 50,000	20.8	20.0	20.6
	$51,000 to $80,000	36.1	16.0	30.9
	More than $81,000	26.4	48.0	32.0
Parent's educational attainment[b] (highest level of education) (%)	Completed only Primary school	0	0	0
	Some years of high school	24.8	8.0	20.6
	Ceased at Year 12 matriculation (or equivalent)	20.3	0	18.6
	Technical, Trade or TAFE certificate	33.8	52.0	34.0
	A University degree	15.8	40.0	21.6
	Not reported	5.3	0	5.3

Note. N: sample size; *n*: subsample size; *SD*: standard deviation; TAFE: Technical and Further Education.
[a] based on answers provided by mother.
[b] categories are mutually exclusive.

Family income, educational attainment and occupation of parents (variables considered markers of SES)

According to the 2006 Australian Census (ABS, 2007b), the median family income for Australian families was $1,171 per week or $60,892 per year. As summarised in Table 22, the majority (36.1%) of families in Port Pirie reported a combined annual income in the range $51,000 to $80,000, which aligns with the Australian median and is slightly higher than the Port Pirie median reported in the 2006 Australian Census ($819 per week or $42,588 per annum; ABS, 2007).

In Broken Hill the largest number of families (48%) reported their annual income at $81,000 or above, which is higher than the Australian and Broken Hill ($814 per week or $42,328) median family incomes as reported in the 2006 census (ABS, 2007a).

This disparity in combined annual income is also reflected in educational attainment where the majority of both samples reported their highest level of educational attainment as the completion of Technical, Trade or TAFE certificate; however this was to a greater extent in Broken Hill (52.0%) than in Port Pirie (33.8%). Likewise, more Broken Hill parents reported University education (40.8%) than did Port Pirie parents (15.8%; see Table 22).

In terms of maternal occupation (see Table 23), 28.3% of mothers reported employment as a ‘professional,’ followed by 26.4% who reported undertaking home duties. In a comparison between the centres, 34.6% of women in Port Pirie reported undertaking home duties versus just 3.6% in Broken Hill. The dominant occupations of fathers in the total sample was as labourers (23.6% - this includes working at the mines or smelter), followed by occupations in the category of ‘professionals.’

When occupational data for the sample were compared to estimates gathered about each centre in the 2006 Australian Census, it became apparent that our sample was relatively representative of the population in both centres in that the most common responses for occupations for employment for persons 15 years and over in Port Pirie were as Technicians and Trade workers (16.0%), Labourers (14.4%) and Professionals (12.4%) and the most

common industries for employment were Basic Non-Ferrous Metal Manufacturing (9.7%), school education (6.0%) and Hospitals (5.4%). In Broken Hill the most common occupations were as Technicians and Trade workers (15.7%), Professionals (14.5%) and Community and Personal service (12.5%) working in Metal Ore Mining (7.7%), School Education (5.5%) and Hospitals (5.2%).

Age of parents and years of residence in Port Pirie and Broken Hill

The mean age of mothers in the sample was 36.6 years (*SD* = 5.08) and the mean age of fathers was 40.5 years (*SD* = 6.31; see Table 23).

For mothers, the mean years of residence in each centre was 18.7 years (*SD* = 13.23). The mean years of residence for fathers was 23.0 years (*SD* = 13.79; see Table 23). Nineteen mothers (21.8%) and nineteen fathers (24.4%) reported having been born in either Port Pirie or Broken Hill and having lived in the communities for their entire lives.

Parental smoking behaviour

At the time of assessment, parents were asked to indicate whether they were current smokers. Mothers tended to report more current smoking (22.0%) than fathers (14.8%; see Table 23). When overall percentage of smoking prevalence was considered per family, according to maternal reports, no parents currently smoke in 69.2 % of families, with 6.6 % of families including two smoking parents and in 18.7% of families one parent was a current smoker.

Table 23

Parent's mean age, occupation, smoking behaviours and years of residence in each centre.

Characteristic		Port Pirie		Broken Hill		Total	
		Mother	Father	Mother	Father	Mother	Father
Parent's mean age (*SD*)		36.4 (4.67)	41.11 (6.38)	36.9 (6.14)	39.2 (6.05)	36.6 (5.08)	40.5 (6.31)
Parent's mean years of residence in Port Pirie or Broken Hill (*SD*)		19.7 (13.39)	23.7 (13.90)	16.2 (12.72)	22.1 (13.79)	18.7 (13.23)	23.0 (13.79)
Parent's occupation (major group; %)							
Managers		0	10.3	3.6	7.1	0.9	9.4
Professionals		26.9	15.4	32.1	17.9	28.3	16.0
Technicians & trade workers		2.6	7.7	0	7.1	1.9	7.5
Community & personal service workers		10.3	5.1	21.4	10.7	13.2	6.6
Clerical & administrative workers		16.7	9.0	3.6	3.6	13.2	7.5
Sales workers		5.1	1.3	14.3	0	7.5	0.9
Labourers		1.3	26.9	0	14.3	0.9	23.6
Home duties		34.6	2.6	3.6	0	26.4	1.9
Student		1.3	3.8	0	0	0.9	2.8
Not reported		1.2	17.9	21.4	39.3	6.8	23.8
% of Parents currently smoking		22.1	15.5	21.7	13.0	22.0	14.8
Smokers per family [a] (%)	Both parents	3.4		4.5		6.6	
	One parent	19.0		9.1		18.7	
	No smokers	65.5		86.4		69.2	

Note. SD: standard deviation.
[a] based on answers provided by child's mother.

6.2 Blood lead concentration

Mean arithmetic and geometric PbB levels for children in each centre and the total sample are presented in Table 24. The mean arithmetic PbB concentration for the total sample was 4.97 µg/dL (*SD* = 3.52) and the geometric mean was 4.02 µg/dL.

Mean arithmetic PbB concentrations were 5.78 (*SD* = 3.70) and 2.70 µg/dL (*SD* = 1.32) in Port Pirie and Broken Hill, respectively. Independent samples t-tests revealed children in Port Pirie had significantly higher PbB levels than children in Broken Hill (mean difference = 3.08 µg/dL, $t_{(1, 104)} = 4.30$, $p = 0.001$, $d = 1.40$). This difference may be accounted for by the greater extent to which particulate material is released through Pb smelting in Port Pirie versus mining activities in Broken Hill.

Table 24

Mean Pb concentration (µg/dL) in blood samples collected at 7 and 8 years.

Location	*N*	Arithmetic Mean (*SD* factor)	95% Confidence Interval	Range	Geometric mean
Port Pirie	78	5.78 (3.70)	4.94 – 6.62	1.4 – 19.30	4.85
Broken Hill	28	2.70 (1.32)	2.18 – 3.21	1.0 – 5.20	2.38
Total Sample	106	4.97 (3.52)	4.29 – 5.64	1.0 – 19.3	4.02

Note. N: sample size; *SD*: standard deviation.

PbB concentrations in each centre and the total sample exhibited skewed distributions (see Figures 12, 13 & 14) as only a small number of children (n = 3) recorded PbB concentrations equal to or greater than 15 µg/dL (all of these children were from Port Pirie). For skewed distributions, using a log transformation of the data can prevent a small number of outliers from exerting disproportionate influence on analyses of associations between variables (Tong, 1995). Since this study is seeking to use regression analyses to investigate the relationship between PbB concentration and cognitive abilities, preliminary analyses tested whether log transformations reduced skewness. This revealed that the use of log transformed and untransformed data resulted in no change on Spearman's correlation coefficient, the statistic of choice. Hence, untransformed data will be used in analyses.

When the sample was divided by gender, it was noted that males (mean PbB = 5.6 µg/dL, SD = 4.04) tended to have higher mean untransformed PbB levels than females (mean PbB = 4.4 µg/dL, SD = 2.84). While this 1.2 µg/dL difference was not statistically significant ($t_{(1, 104)} = 1.7$, $p = 0.09$), it represents a moderate effect size (d = 0.34).

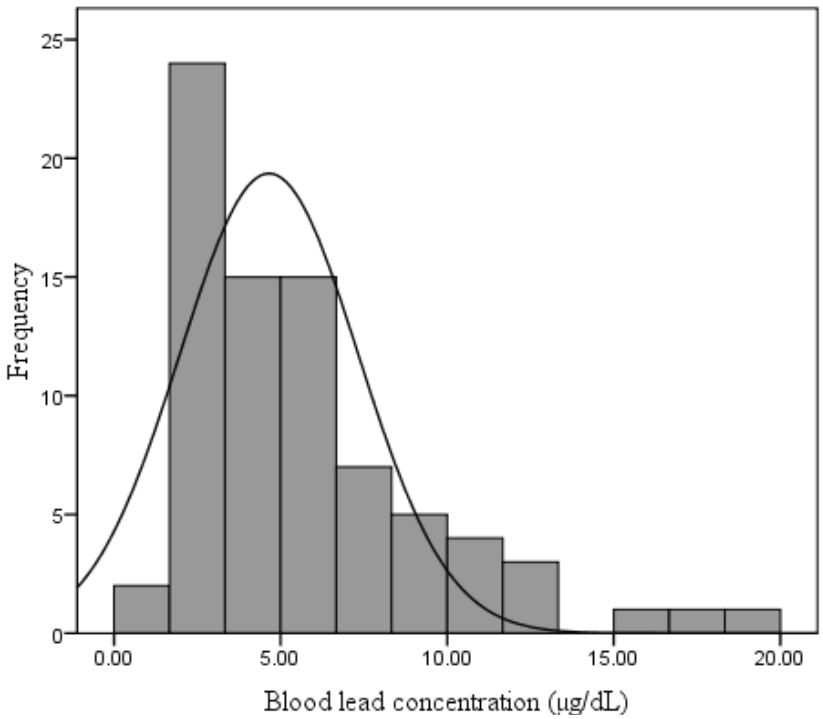

Figure 12

Distribution of PbB levels in Port Pirie sample (n = 79)

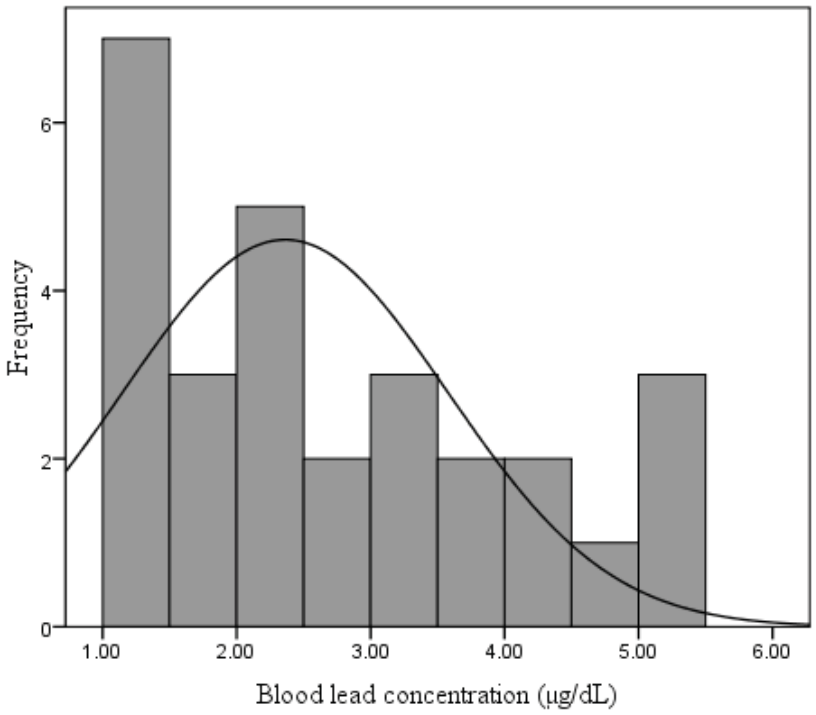

Figure 13

Distribution of PbB levels in Broken Hill sample (n = 28).

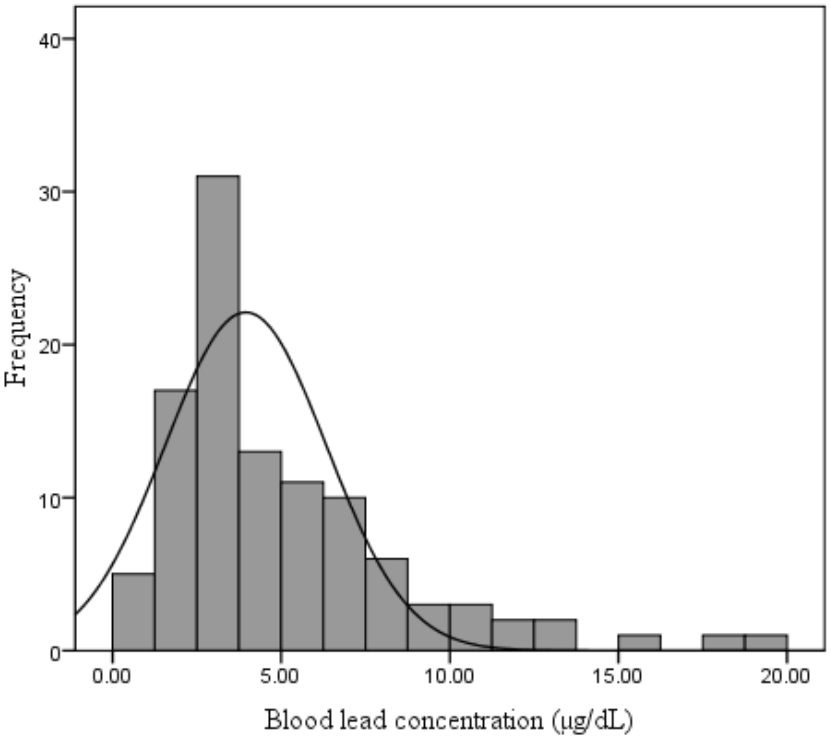

Figure 14

Distribution of PbB levels in Total sample (N = 106)

6.3 Children's Cognitive Abilities

The distributions of WISC-IV FSIQ, VCI, PRI, WMI and PSI scores are presented in Appendix J. The mean scores of the WISC-IV scale and subscales are presented in Table 25. Subscales for WISC-IV Australian have been designed with mean = 10.0 (*SD* = 3). Subscale scores ranged from 8.8 (*SD* = 3.79; 95% CI = 8.1, 9.6) for the Letter-numbering task to 10.9 (*SD* = 3.08; 95% CI = 10.3, 11.5) for Block Design.

The WISC-IV Australian was designed to have a mean FSIQ of 100 and a *SD* of 15; according to the test classifications, the current sample performed in the average range on all subscales. The sample's FSIQ was estimated at 100.2 (14.59; 95% CI = 97.4, 103.0). Mean scores for the WISC-IV scale scores ranged from a low of 94.5 (*SD* = 15.31; 95% CI = 91.6, 97.5) for the WMI to 102.2 (*SD* =14.97; 95% CI = 99.3, 105.0) for the PRI.

WISC-IV scale scores were compared on the basis of Port Pirie and Broken Hill residency. On the whole, children from Broken Hill performed better than children from Port Pirie with mean differences ranging from 3.96 points for PRI, to 6.0 points for FSIQ. No single mean difference reached statistical significance at the $p < 0.05$ level, but differences for VCI (mean difference = 5.8 points) and FSIQ approached statistical significance at the $p = 0.06$ level and had moderately large effects sizes (Cohen's $d = 0.42$ for both VCI and FSIQ).

Table 25

Mean scores for the WISC-IV subscales and IQ scales for the sample of 106 children aged 7 and 8 years.

Index/subtest score	Mean (*SD*)	*SE*	Range
Full-Scale IQ	**100.2 (14.59)**	**1.42**	**69 - 134**
Verbal Comprehension Index	**100.8 (13.95)**	**1.36**	**71 - 144**
Similarities	10.2 (3.30)	0.32	3 - 18
Vocabulary	10.1 (2.34)	0.23	5 - 16
Comprehension	10.4 (2.85)	0.28	4 - 19
Perceptual Reasoning Index	**102.2 (14.97)**	**1.45**	**69 - 133**
Block Design	10.9 (3.08)	0.30	3 -18
Picture Concepts	9.9 (3.10)	0.30	3 - 20
Matrix Reasoning	10.3 (3.12)	0.30	3 - 18
Working Memory Index	**94.5 (15.31)**	**1.49**	**50 - 129**
Digit Span	9.5 (2.60)	0.25	1 - 17
Letter-number sequencing	8.8 (3.79)	0.37	1 - 15
Processing Speed Index	**100.5 (13.65)**	**1.33**	**65 - 141**
Coding	10.5 (3.01)	0.29	1 - 18
Symbol search	9.7 (2.61)	0.25	1 - 19

Note. Scale scores are in **bold.** *SE*: Standard error; *SD*: Standard deviation; WISC-IV: Wechsler Intelligence Scale for Children-Fourth Edition.

Mean scores for the WJ-III and the electronic battery are summarised in Table 26. WJ-III scores are normed with a mean of 100 and *SD* of 15 (Mather & Woodcock, 2001). Hence, according to the WJ-III classification system, participants scored in at least the average range (scaled score = 90 - 110) on all subscales, with performance ranging from 97.0 for Incomplete Words (*SD* =14.97; 95% CI = 94.3, 99.7) to above average for Auditory attention (mean = 114.6, *SD* =14.97; 95% CI = 112.1, 117.1). For the WJ-III cluster scores (each is an average across all subscales amalgamous to a broad ability score), participants' mean performance was also in the average range; 103.5 (*SD* =14.53; 95% CI = 100.7, 106.4) for Glr and 108.8 (*SD* =14.53; 95% CI = 106.0, 111.6) for Ga.

A modified version of Raven's progressive matrices was administered as a supplementary measure of Gf. There are no normative data available for this modified version but in this sample, the mean number of correct answers was 7.0 (*SD* = 4.08).

Picture Swaps was included in the cognitive assessment battery as a measure of Working Memory. Picture Swaps has been used extensively in the research literature (Burns, Lee & Vickers, 2006; Martin, Wittert, Burns & McPherson, 2008; Nettelbeck & Burns, 2010) but, to date, no normative data are available. The mean number of correct Picture Swaps was 6.8 items (*SD* = 2.89).

Gs Invaders has only previously been administered to University students (McPherson & Burns, 2007) and hence there are currently no normative data for children. In this sample, mean performance was 33.6 (*SD* = 7.50) correct items.

Inspection time is a measure which does not currently have accompanying normative data. The mean IT of the participants was 88 milliseconds (m/secs; *SD* = 25.74; 95% CI = 83, 93), indicating that the mean time that participants required to accurately make a judgement about the IT stimuli was 88 m/secs.

Table 26

Mean scores for the WJ-III scales and cluster scores, Raven's matrices, Picture Swaps, Gs Invaders and Inspection Time for 104 children aged 7 to 8 years.

Scale/test	Mean Scaled Score (*SD*)	*SE*	Range
Long-term storage and retrieval (Glr)	**103.5 (14.53)**	**1.42**	**63 – 158**
Auditory Processing (Ga)	**108.8 (14.53)**	**1.43**	**79 – 140**
Visual-auditory Learning	102.0 (13.99)	1.37	61 – 161
Retrieval Fluency	104.4 (12.61)	1.24	74 – 132
Sound Blending	102.6 (13.67)	1.34	72 – 134
Incomplete Words	97.0 (13.79)	1.35	66 – 131
Auditory Attention	114.6 (12.78)	1.25	79 – 146
Spatial Relations	105.2 (8.81)	0.86	82 – 129
Raven's Matrices[a]	7.0 (4.08)	0.40	1 – 16
Picture Swaps[a]	6.8 (2.89)	0.74	1 – 14
Gs Invaders	33.6 (7.50)	0.28	19 – 58
Inspection Time (m/sec)	88.0 (25.74)	2.52	36 – 206

Note. Cluster scores are in **bold.** *SE*: Standard error; *SD*: Standard deviation; WJ-III: Woodcock Johnson-III Tests of Cognitive Abilities.
[a] $n = 103$.

6.4 Summary of the characteristics of the study population

Having described the demographic characteristics of the children and their families, in general the sample can be described as a group of 7 - 8 year olds (*N* = 106; mean age = 7.96 years, *SD* = 0.59 years) with mean arithmetic PbB concentration of 4.97 µg/dL (*SD* = 3.52) and average FSIQ and Glr and Ga cluster scores. The majority of children in the sample lived in two- parent families with at least one sibling. The families living in Broken Hill tended to have a higher annual income than those in Port Pirie and Broken Hill parents had higher levels of educational attainment than parents in Port Pirie. The majority of parents in the sample did not currently smoke cigarettes.

The description of the sample will now turn to an overview of the distribution of potential covariate variables and their association with PbB concentration and cognitive ability measures.

Chapter 7: Distribution of potential covariate variables and their association with cognitive ability measures

Chapter Summary

This chapter summarises the distribution of familial, psycho-social and environmental and pre- and post-natal variables that were assessed as potential covariates to the association between Pb exposure and children's cognitive abilities.

As a secondary issue, this chapter seeks to identify which potential covariates should be included in subsequent statistical analyses of the association between Pb and cognitive abilities. Potential covariates were identified for inclusion in subsequent multiple regression models as follows.

The continuous variables with the largest Spearman's correlation with FSIQ and the categorical variables that showed significant differences in WISC-IV FSIQ across categories were considered the most important covariates. The continuous and categorical variables meeting these criteria for inclusion in multiple regression models were: mother's WAIS-III FSIQ, birth weight, MC HOME Total, number of recent stressful life events in family, annual combined family income (low, middle or high income), current maternal smoking (yes or no), smoking during pregnancy (yes or no), duration of breastfeeding (no breastfeeding, breastfeeding for ≤ 6 months duration, or breastfeeding for ≥ 7 months duration).

Data summarised in this section were obtained via cognitive assessment batteries administered to the mother and father in-person and questionnaire batteries completed by each parent and returned by mail to the Adelaide-based research team.

7.1 Distribution of potential covariate variables

In order to explore the study hypotheses, ANALYSIS 1 (associations between WISC-IV cognitive abilities and PbB concentration) and ANALYSIS 2 (associations between the *g* and CHC factor scores and PbB concentration) require the identification of potential covariates to the associations between children's cognitive abilities and PbB exposure. This chapter will explore the distribution of potential covariates and identify variables to be entered into multiple regression analyses alongside PbB concentration.

7.1.1 Familial

Maternal Cognitive Abilities

Maternal IQ was assessed using the WAIS-III and scores are summarised in Table 27. The distribution of VIQ, PIQ and FSIQ are presented in Appendix K. These scores were reasonably normally distributed and subsequent analyses utilised untransformed WAIS-III scale and subscale data. According to WAIS-III classifications, mean maternal FSIQ (Mean = 105. 7, *SD* = 11.57, 95% CI = 103.8, 108.2), VIQ (Mean = 102.2, *SD* = 12.13, 95% CI = 100.2, 104.9) and PIQ (Mean = 109.1, *SD* = 12.20, 95% CI = 107.1, 111.8) were all in the average range, as were individual subscale scores. Mother's mean IT was 52 m/sec (*SD* = 14.51, 95% CI = 49.0, 55.2).

Table 27

Mean maternal WAIS-III (n = 98) and IT scores (n = 97).

WAIS-III Scales and subscales	Mean	*SD*	*SE*	Range
Full-Scale IQ	**105.7**	**11.57**	**1.17**	**74 - 137**
Verbal IQ	**102.2**	**12.13**	**1.22**	**71 - 134**
Similarities	10.8	2.81	0.28	3 - 18
Information	9.9	2.29	0.23	4 - 14
Vocabulary	11.1	2.72	0.28	1 - 17
Arithmetic	9.9	2.40	0.24	3 - 15
Digit span	9.9	2.82	0.29	4 - 16
Comprehension	11.0	2.90	0.29	4 - 19
Performance IQ	**109.1**	**12.20**	**1.23**	**77 - 136**
Block Design	11.8	2.47	0.25	6 - 18
Picture Completion	11.4	2.81	0.28	6 - 18
Digit Symbol	10.8	2.51	0.25	4 - 18
Picture arrangement	10.4	2.70	0.23	5 - 18
Matrix Reasoning	12.5	2.44	0.25	6 - 17
Inspection Time (m/sec)	52	14.5	1.47	16 - 110

Note. Scale scores are **bold**. IT; Inspection time; *n*: subsample size; *SE*: Standard error; *SD*: Standard deviation; WAIS-III: Wechsler Adult Intelligence – Third Edition.
[a] *n* = 103.

Paternal Cognitive Abilities

Father's IT and SPM performance is summarised in Table 28. Father's mean IT was 56 m/sec (*SD* = 23.23, 95% CI = 50.6, 60.2).

Table 28

Mean paternal Standard Progressive Matrices and Inspection Time scores.

Test	*N*	Mean	*SD*	*SE*	Range
Inspection Time (m/sec)	83	56	23.23	2.55	32 - 202
Raven's Progressive Matrices Total	86	44.5	6.49	0.79	21 – 58

Note. N: sample size; *SE*: Standard error; *SD*: Standard deviation.

For the SPM, the mean number of correct items for the fathers was 44.5 (*SD* = 6.49; 95% CI = 43.5, 46.1). While the Raven's family of tests are widely administered, it was not possible to identify age normed data for this sample of fathers (mean age = 40.5 years, *SD* = 6.31). The Australian Council of Educational Research published a table of Australian norms collected for 18 year old Victorian National Service trainees entering the Australian army, navy or air force between June 1952 and June 1953. According to these norms the data collected for this sample is in the average IQ range (99 – 111; Australian Council for Educational Research, n.d). However, as Raven (2000) states, it is "appropriate to draw attention to the seriousness of the errors which stem from the use of outdated norms" (p.35) due to the phenomenon of the Flynn effect (Flynn, 2006) which has documented a steady increase in scores on cognitive tests, such as the SPM, over time – a trend that has been insufficiently accounted for by explanations proposed such as the increased proliferation of

matrix-like puzzles in pop culture and the use of computers and technology (Raven, 2000). Hence, the normative standing of the performance of fathers in this sample will not be commented on further but their raw scores will be used as a measure of paternal cognitive ability in subsequent analyses.

Highest level of parental education and p*arent occupation*.

Data relating to highest level of parental education and Parent Occupation are summarised in Chapter 6 in Tables 22 and 23.

7.1.2 Psycho-social and environmental

Markers of Socioeconomic Status

Combined annual income, current exposure to parental smoking, family size (number of siblings) and parent's period of residence in Port Pirie or Broken Hill are possible psycho-social and environmental factors which are summarised in Chapter 6, Tables 22 and 23.

Care giving environment

The care giving environment was assessed using the MC HOME (see Table 29). There were no statistically significant differences between the MC HOME ratings of mothers and fathers and these differences had small effect sizes ($d \leq 0.2$). Hence for analyses, maternal and paternal scores have been aggregated (see Table 29). In addition to the Total MC HOME score (Mean = 10.4, *SD* = 1.61), two scale scores were calculated; provision of Cognitive Support (Mean = 6.8, *SD* = 1.40) and Emotional Support (Mean = 3.55, *SD* = 0.88).

Table 29

Distribution of results for psycho-social and environmental questionnaires completed by mothers and father.

Questionnaire		*N*	Mean (*SD*)	*SE*	Range
MC HOME Total[a]		86	10.2 (1.69)	0.18	4 - 13
Recent Life Events Questionnaire [b, c]					
Number of stressful recent life events		171	1.9 (2.20)	0.17	0 - 15
Stressful recent life events still affecting respondent		171	0.65 (1.19)	0.09	0 - 9
Dyadic Adjustment Scale [b, c]					
Overall Dyadic Adjustment		128	115.6 (15.88)	1.40	55 - 148
Dyadic Consensus		136	52.0 (7.39)	0.63	31 - 65
Affectional Expression		142	7.6 (1.97)	0.17	2 - 10
Dyadic Satisfaction		142	39.7 (5.62)	0.32	19 - 49
Dyadic Cohesion		147	15.36 (3.88)	0.32	3 – 24
Beck Depression Inventory –II	Mother	79	7.0 (8.01)[c]	0.90	0 - 36
	Father	76	3.3 (4.16)[c]	0.48	0 - 20

Note. MC HOME: Middle child Home Observation for Measurement of the Environment Inventory*; N*: sample size; *SE*: Standard error; *SD*: Standard deviation.
[a] MC HOME Total scores per family.
[b] Aggregated maternal and paternal scores
[c] Scores are classified in the normal range.

Stressful Life events in family

Cox and Benovitin (2000) report that in their pilot study of the Recent Life Events Questionnaire (RLE) the mean number of recent stressful events experienced by their sample was between 7 and 8 events and about half of these events were rated as still affecting the respondent. The RLE does not have cut-off scores for classification and it is conceptualised such that the more stressful life events experienced, the greater the chance of an impact upon the caregiver, their children and the family as a whole. Possible psychological or functional repercussions are heightened if the caregiver reports that the event is still 'affecting' them

For this sample, both the mothers (n = 91) and fathers (n = 80) reported relatively few recent stressful events and the mean for each group was approximately two recent events (see Table 29). When mothers and fathers were asked to indicate whether these recent life events were still causing them psychological distress, the mean number of events still causing distress was less than one. There were no statistically significant differences between the recent life event rating of mothers and fathers and these differences had small effect sizes ($d \leq$ 0.13). Hence, maternal and paternal RLE scores will be aggregated for further analyses.

Quality of the relationship between parents (or partners)

The Dyadic Adjustment Scale (DAS) was used to assess the quality of the relationship between parents (or partners). There were no statistically significant differences identified between maternal and paternal ratings on all subscales of the DAS and the effect sizes for these differences were small in magnitude ($d \leq 0.23$), hence maternal and paternal scores will be aggregated for use in subsequent analyses (see Table 29).

There was some concern about the rate of response that would be achieved for the DAS, given the personal and sensitive nature of some questions relating to dyadic relationships. In terms of the rate of reporting for the DAS, more dyadic adjustment total scores were available for fathers (n = 68) than mothers (n = 60). For seven of nine single mother families, there was no DAS score available, suggesting that these mothers may not

currently be in a relationship or that they chose not to respond to this component. The remaining missing data for mothers were accounted for by 14 cases where missing data in the scale scores meant that a total score could not be calculated and, in 10 cases, mothers did not respond at all. For fathers, five provided incomplete data such that a total dyadic scale could not be calculated and nine fathers did not respond.

Parent's depressive symptomology

Parent's mental health was assessed using the BDI, a tool which gauges depressive symptomology. As illustrated in Table 29, both mother (mean = 7.0, *SD* = 8.01) and father (mean = 3.30, *SD* = 4.16) self-reported depressive symptomology was classified in the normal range. There was a significant difference between these scores when comparisons were made using an independent samples t-test, where mother's rated their depressive symptomology 3.72 points higher than fathers ($t_{(1, 153)} = 3.61$, $p = 0.001$). The magnitude of this difference ($d = 0.58$) was moderate. Given the significant difference between maternal and paternal ratings on the BDI, these scores will not be aggregated when included in exploratory correlational analyses with PbB concentration and cognitive abilities.

The mean scores of both parents seem quite low given research suggesting that mental health difficulties, such as depression, are disproportionately higher in Australian rural and remote communities as compared to city-dwellers (Kilkkinen, Kao-Philpot, O'Neil, Philpot, Reddy, Bunker et al., 2007; Rajkumar & Hoolahan, 2004) it is possible that the self-report nature of this measure may have led to an underestimation of depressive symptomology in this sample.

7.1.3 Pre- and Post-natal

Data relating to a range of pre- and post natal factors were reported by the target child's mother and are summarised in Table 30. These data will be discussed in terms of maternal, delivery, and birth and neonatal characteristics of the sample.

Table 30

Summary of pre- and post-natal variables.

Pre- and post-natal factors		Total sample (*N* = 106)
Mother's mean age at birth (years) (*SD*)		28.6 (5.01)
Gravidity – no. (%)	0	29 (31.9)
	1,2 or 3	65 (56.1)
	≥4	8 (8.8)
	Missing	4 (3.2)
	Smoked around time of conception[a] – no. (%)	21 (21.7)
	Smoked during pregnancy – no. (%)	16 (16.5)
	Consumed alcohol around time of conception[a] – no. (%)	36 (37.1)
	Consumed alcohol during pregnancy– no. (%)	11 (11.3)
Mode of Delivery	Vaginal delivery	62 (63.9)
	Caesarean section	33 (34.0)
	Missing	3 (2.1)
Birth order (%)[b]	First child	32.6
	Second child	32.6
	Third child	15.8
	≥ fourth child	5.3
	Missing	13.7
	Mean birth order of sample (*SD*)	2.0 (1.0)
	Gestational age at birth (week) – mean (*SD*)	35.3 (10.32)
	Mean Birth weight (g) (*SD*)	3360.8 (589.54)
	Neonatal intensive care unit admission	17 (17.5)
Birth and neonatal complications – no. (%)	Emergency caesarean section	11 (11.3)
	Jaundice	10 (10.3)
	Fetal distress	6 (6.2)
	Extended labour	4 (4.1)
	Forcep extraction/venteuse delivery	4 (4.1)
	Multiple pregnancies	3 (3.1)
	Foetal death in multiple births	2 (2.1)
	High maternal blood pressure	2 (2.1)
	Neonatal ventilation	2 (2.1)
	Gestational diabetes	2 (2.1)
	Other [c]	11(11.3)

Note. g: grams; *N*: sample size; *n*: subsample size; no.: Number; *SD*: Standard deviation.
[a] Data quantifying consumption of alcohol and cigarettes 'around time of conception' will not be considered as potential covariates due to reliance upon memory and difficulty in pinpointing conception.
[b] Data for three sets of twins and seven only children (*n* = 13) were excluded.
[c] Single reported cases of breech birth, perineal tears, maternal coccyx fracture, induction, neonatal oxygen, nasal tube, low apgar scores, umbilical cord wrapped around infant's neck, toximia and hip dysplasia.

Maternal characteristics: *maternal age at child's birth, gravidity and pre-natal exposure to neurotoxic agents*

Using data taken from 96 mothers, mean maternal age at child's birth was 28.6 years (*SD* = 5.01). For 31.9% of the sample, conception of the target child was their first pregnancy, while 56.1% had previously been pregnant one to three times and 8.8 % had previously been pregnant four or more times.

Of the 93 mothers providing data about their smoking behaviours prior to and during pregnancy (see Table 30), 16.5% reported that they smoked during their pregnancy. Likewise of the women reporting their alcohol consumption behaviour (*n* = 92), 11.3% reported consuming alcohol during pregnancy. As illustrated in Table 30, women's use of cigarettes and alcohol declined following confirmation of pregnancy but about a third of the women were not abstinent from smoking or drinking alcohol leading up to, or around the time of conception.

Delivery and birth factors*: mode of delivery, birth and neonatal complications and NICU admission.*

Of the 95 mothers who reported the mode of their child's birth, 62 reported a vaginal delivery and 33 reported a caesarean section birth. Forty one mothers reported complications associated with their child's birth and/or the post-natal period. Of these 41 mothers, 14 reported more than one birth and/or post-natal complication. The most frequent complications reported by the mothers were emergency caesarean section (11%), jaundice (10.3%) and fetal distress (6.2%; see Table 30). Further, 17.5% of mothers reported that their baby was admitted to NICU for more than a few hours post birth.

Neonatal characteristics: birth order, gestational age and birth weight.

As summarised in Table 30, 32.6 % of children in the sample were the first born and 32.6 % were the second born child. A smaller percent were third born children (15.8%) and

5.3 % were the fourth born child and beyond. Data documenting birth order were missing for 13.7 % of the sample.

Only 55 mothers provided an estimate of their child's gestational age, the mean of which was 35.3 weeks (*SD* = 10.32 weeks). According to these data 11 children (11.3%) were born preterm (< 37 weeks gestation).

Mean birth weight of the sample (*n* = 89) was 3088 g (*SD* = 1092 g). As can be seen from Figure 15, the range of birth weights tended to be normally distributed. According to these data, eleven (11.1%) children had a low birth weight (less than 2500 g) and 13 (13.1%) children were large for gestational age (greater than 4000 g).

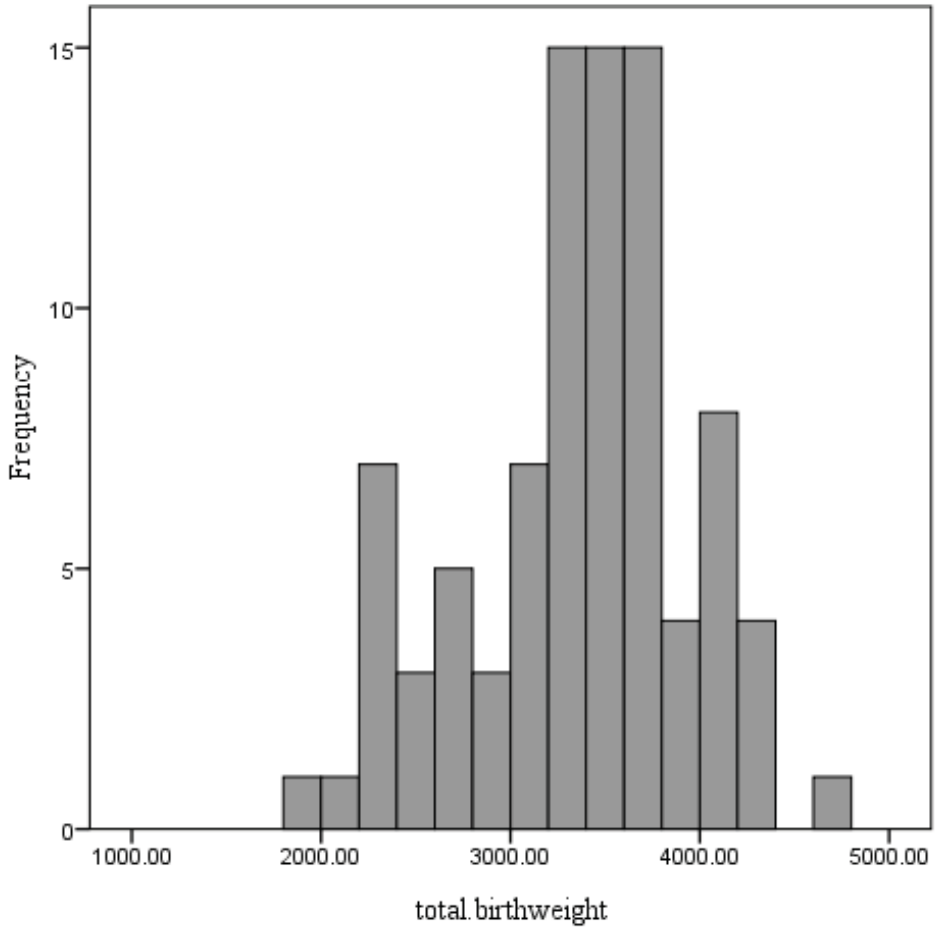

Figure 15

Distribution of birth weight (grams) in 89 children.

Incidence and Duration of breast-feeding

Ninety-four mothers provided data about their breastfeeding with the target child (see Table 31). Mothers reported the mean duration of breastfeeding as 8.7 months (*SD* = 11.59). Of the total sample, 11.3% of children were never breastfed, 36.1% of children were breastfed up to and including 6 months of age and 49.4 % of children were breastfed for 7 months duration and beyond.

Table 31

Incidence and Duration of breastfeeding (N = 106)

Provision of infant nutrition	Total sample
Mean duration (months) of breastfeeding (*SD*)	8.7 (11.59)
Not breastfed	11.3 %
Breastfed for ≤ 6 months	36.1 %
Breastfed for ≥ 7 months	49.4 %
Not reported	3.2 %

Note. N: Sample size; *SD*: Standard Deviation.

7.2 Decision-making strategy for entry of potential covariates into multiple regression modelling

As stated in Chapter 2, the cognitive abilities measured in this study will be explored in two ways using multiple regression; firstly, the associations between the primary cognitive measure, WISC-IV and PbB concentration will be investigated and secondly, the associations between PbB concentration and the *g* factor and generated CHC clusters (estimated from

factor scores for seven broad cognitive abilities: Gs; Gf, Glr, Ga, Gv, Gc and Gsm) will be examined. In order to undertake these analyses the associations between children's cognitive abilities and potential covariates will be explored; it is possible that extraneous factors may confound the associations between PbB concentration and cognitive abilities and hamper the ability to identify the specific impacts of Pb upon cognition. Hence, to address this possibility, information about a number of variables that are theorised to impact cognitive development were collected, with the view that factors that significantly associated with cognitive abilities would be identified for entry into multiple regression alongside PbB concentration, so that contributions to the model could be assessed. Given the number of potential covariates collected, a strategy was required to determine the most pertinent covariates to the relationship between children's cognitive abilities (primarily, WISC-IV FSIQ and subscales) and PbB levels. To inform decision-making, the approaches to covariate selection utilised in previous research were reviewed.

In general the strategies documented in previous research were informed by "empirical and subject matter considerations" (Bellinger et al., 1992, p. 856). While some studies entered all of the covariate data collected into their multiple regression modelling (Canfield et al., 2003; Cho et al., 2010; Kim et al., 2009; Schnaas et al., 2000; Sovcikova et al., 1997; Wasserman et al., 1998), due to the limited sample size of this study, we favoured approaches which employed empirical pretesting of covariate candidates (Dietrich et al., 1987). Indeed, Cooney et al. (1989) explain that the advantage of covariate pretesting is that it can "increase [statistical] power by reducing error variance without underestimating any lead effect by overcorrection" (p. 97) and Bellinger et al. (1992) support that these approaches can increase the precision of a study.

Specifically, a number of research groups (Després et al., 2005), Dietrich et al., 1987) and Hu et al., 2006[21]) included potential covariates that associated with outcomes at the $p \leq$

[21] Hu et al. (2006) also included variables with "biological plausibility" (p. 1731) regardless of the level of significance reached in associations with outcomes variables.

0.10 level. Taking a slightly different approach, Surkan et al. (2007), identifying covariates that significantly ($p < 0.2$) associated with IQ in bivariate analyses and included these in multivariate analysis of covariance model, then variables that were statistically significant ($p < 0.2$) in multivariate analysis were included in subsequent models of the associations between cognitive measures and PbB levels.

In this study it was important to identify covariates sparingly (due to a small sample size) so that the number of variables to be entered into the regressions was not over-ambitious. Hence stringent covariate selection guidelines were set in terms of the relationships between WISC-IV FSIQ and continuous and categorical potential covariates:

- Continuous variables with the largest Spearman's correlation with FSIQ were identified for inclusion in multiple regression modelling. The intercorrelations between the continuous covariate variables are presented in Appendix L.
- Categorical variables that showed significant differences in WISC-IV FSIQ across categories were considered the most important covariates; mean ability level for each category was calculated, with one-way ANOVAs used to identify significant differences between categories.

The relationships between WISC-IV FSIQ and continuous and categorical potential covariates are discussed in further detail in the following sections and the variables identified for inclusion in subsequent multiple regression modelling are presented.

7.2.1 Spearman correlations between WISC-IV FSIQ and subscales and continuous potential covariates

The Spearman (ρ) correlations between untransformed WISC-IV FSIQ and subscales and each of the continuous demographic, familial, psycho-social, environmental, biomedical, and pre- and post-natal variables (summarised in Chapters 3 and 4), are presented in Table 32. Given the large amount of data presented in Table 32, statistically significant associations will be the focus.

As seen in Table 32, no significant associations were identified between the continuous demographic variable parent's years of residence in each centre and cognitive abilities.

For familial variables quantifying parental cognitive ability, significant inverse associations were identified between subscales of the WAIS-III maternal assessment and WISC-IV child assessment such that:

- WAIS-III VIQ correlated significantly with WISC-IV measures of FSIQ ($\rho = 0.24$, $p = 0.01$), VCI ($\rho = 0.30$, $p = 0.01$) and WMI ($\rho = 0.20$, $p = 0.05$).
- WAIS-III PIQ correlated significantly with WISC-IV measures of FSIQ ($\rho = 0.24$, $p = 0.01$), VCI ($\rho = 0.24$, $p = 0.01$), PRI ($\rho = 0.24$, $p = 0.01$) and WMI ($\rho = 0.24$, $p = 0.01$).
- WAIS-III FSIQ correlated significantly with WISC-IV measures of FSIQ ($\rho = 0.26$, $p = 0.01$), VCI ($\rho = 0.30$, $p = 0.01$) and WMI ($\rho = 0.21$, $p = 0.05$).
- Small non-significant associations were identified between child cognitive measures and maternal and paternal IT and paternal SPM.

Continuous pre-and post-natal variables that significantly correlated with cognitive measures were maternal age at child's birth (FSIQ: $\rho = 0.21$, $p = 0.05$; PSI: $\rho = 0.20$, $p = 0.05$) and total birth weight ($\rho = 0.24$ to 0.36, $p \leq 0.01$ for FSIQ, PRI and PSI).

Significant moderate ($\rho = 0.21$ to 0.32) associations were identified between child cognitive measures and the continuous psycho-social and environmental factor MC HOME scores total (with FSIQ, VCI, WMI). Significant inverse associations were identified between number of recent stressful events reported by parents and FSIQ ($\rho = -0.25$, $p = 0.05$), PRI ($\rho = -0.25$) and WMI ($\rho = -0.24$, $p = 0.05$). Small non significant correlations were identified between total Dyadic Adjustment Scale and WISC-IV subscales.

Table 32

Unadjusted Spearman correlations between cognitive measures and potential covariates.

Potential continuous covariates			FSIQ	VCI	PRI	WMI	PSI
Demographic	Parent's years of residence in each centre		- 0.01	0.10	- 0.04	- 0.11	- 0.03
Familial variables	*Maternal abilities*						
	WAIS-III VIQ		0.24*	0.30**	0.12	0.20*	0.09
	WAIS-III PIQ		0.27**	0.26**	0.21*	0.23*	0.04
	WAIS-III FSIQ		0.26**	0.30**	0.15	0.22*	0.04
	Maternal IT		- 0.03	0.07	- 0.11	- 0.09	0.03
	Paternal abilities						
	Paternal IT		0.02	0.10	0.06	- 0.03	- 0.16
	Raven's Standard Progressive Matrices		0.14	0.07	0.18	0.11	0.12
Pre- and post natal variables	Maternal age at child's birth		0.21*	0.17	0.14	0.17	0.20*
	Birth weight		0.33**	0.19	0.36**	0.18	0.30**
Psycho-social and environmental factors	MC HOME Total		0.26*	0.24*	0.18	0.25*	0.16
	BDI-II	Maternal	0.03	0.07	0.06	0.06	- 0.12
		Paternal	- 0.04	0.07	- 0.07	- 0.07	- 0.15
	Dyadic Adjustment Total		0.16	0.19	0.09	- 0.07	0.14
	Number of recent stressful life events		- 0.25*	- 0.09	- 0.25*	- 0.24*	- 0.13
	Recent stressful life events still causing distress		0.00	0.03	- 0.05	- 0.06	0.07

Note. BDI-II: Beck Depression Inventory - Second Edition; FSIQ: Full Scale IQ; IT; Inspection Time; PIQ: Performance IQ; PRI: Perceptual Reasoning Index; PSI: Perceptual Speed Index; VCI: Verbal Comprehension Index; VIQ: Verbal IQ; WAIS-III: Wechsler Adult Intelligence Scale, Third Edition; WMI: Working Memory Index.

* Correlation is significant at the 0.05 level, two-tailed.

** Correlation is significant at the 0.01 level, two-tailed.

7.2.2 Mean WISC-IV FSIQ and subscale scores for categorical potential covariates

Tables 33 and 34 summarise the mean WISC-IV ability level for each group of categorical demographic and pre- and post-natal potential covariates. One-way ANOVAs were used to identify significant differences between categories and this information is also presented. Given the large amount of data presented in Tables 33 and 34, categorical variables which differed significantly across categories will be the focus of discussions.

In terms of demographic variables (see Table 33), there were no significant differences between children's WISC-IV FSIQ and subscale scores based on gender, number of children in the family, highest level of parental education and current paternal smoking. Some trends were noted, such that females tended to have lower scores than males; children from families with two or three children tended to perform better than singletons or those that came from a family with four or more children; WISC-IV scores tended to increase with increasing level of parental education.

WISC-IV FSIQ and subscale score showed a significant ($p \leq 0.05$ for FSIQ, VCI, WMI and PRI, $p = 0.06$ for PSI) increasing trend as family income increased from ≤ $ 20,000 to $50,000, to in excess of $81,000. Children's whose parents reported annual income in the lowest category had mean FSIQs which were 14.7 IQ points lower than children from families in the highest annual income bracket.

It was found that the children of mothers who reported current smoking scored significantly lower than the children of mothers who report no current smoking for FSIQ, PRI, WMI and PSI (the VCI difference approached significance, $p = 0.09$). Specifically, children whose mother currently smoked had a mean FSIQ 10.4 points lower than children whose mothers did not smoke at the time of the assessment.

Table 33

Mean WISC-IV FSIQ and subscale scores for the potential categorical demographic covariates.

Potential covariates	Categories (*n*)	Mean FSIQ	Mean VCI	Mean PRI	Mean WMI	Mean PSI
Gender	Female (54)	99.8	99.9	101.5	93.4	102.7
	Male (52)	100.6	101.7	102.9	95.6	98.3
	F (1, 104) (*p*-value)	0.06 (0.80)	0.47 (0.50)	0.24 (0.63)	0.52 (0.47)	2.92 (0.09)
Number of children in family	One child (7)	96.7	97.1	98.6	85.4	104.6
	Two children (36)	101.1	102.5	101.3	96.6	101.1
	Three children (33)	101.1	101.1	104.3	95.3	99.5
	Four or more children (19)	95.2	93.1	98.6	93.6	98.9
	F (3, 91) (*p*-value)	0.94 (0.42)	2.27 (0.09)	0.69 (0.56)	1.09 (0.36)	0.38 (0.77)
Highest level parental education	Some years of high school (11)	98.0	93.6	99.8	99.5	101.4
	Ceased at Year 12 matriculation (13)	97.8	99.5	101.9	89.7	100.6
	Technical, Trade or TAFE certificate (44)	99.1	100.7	101.5	93.0	98.3
	A University degree (29)	103.2	102.5	103.7	98.2	103.8
	F (3, 93) (*p*-value)	0.65 (0.58)	1.10 (0.35)	0.20 0.89)	1.49 (0.22)	0.96 (0.41)

Note. Significant differences between groups are **bold**. Full Scale IQ; *n*: subsample size; PRI: Perceptual Reasoning Index; PSI: Perceptual Speed Index; TAFE: Technical and Further Education; VCI: Verbal Comprehension Index; WISC-IV: Wechsler Intelligence Scale for Children-Fourth Edition; WMI: Working Memory Index.

Table 33

Continued.

Potential covariates	Categories (*n*)	Mean FSIQ	Mean VCI	Mean PRI	Mean WMI	Mean PSI
Family annual income	≤ $20,000 to $50,000 (29)	91.6	94.2	94.1	87.5	96.4
	$51,000 to $80,000 (30)	101.3	102.6	102.1	94.7	100.6
	More than $81,000 (31)	106.3	104.6	107.7	100.5	104.8
	F (2, 87) (*p*-value)	8.66 **(<0.001)**	4.81 **(0.01)**	4.28 **(<0.001)**	5.73 **(0.005)**	2.97 (0.06)
Current maternal smoking	No (73)	101.6	100.8	103.4	96.3	102.7
	Yes (22)	91.2	95.2	94.4	87.3	92.0
	F(1, 93) (*p*-value)	9.63 **(0.003**)	2.87 (0.09)	6.30 **(0.01)**	6.13 **(0.02)**	11.97 **(<0.001)**
Current paternal smoking	No (67)	101.6	101.3	103.0	96.6	102.2
	Yes (12)	99.1	101.3	101.9	93.1	95.9
	F(1, 77) (*p*-value)	0.34 (0.56)	0.00 (0.99)	0.06 (0.81)	0.54 (0.46)	2.56 (0.11)

Note. Significant differences between groups are **bold**. Full Scale IQ; *n*: subsample size; PRI: Perceptual Reasoning Index; PSI: Perceptual Speed Index; VCI: Verbal Comprehension Index; WMI: Working Memory Index.

For the pre- and post-natal categorical variables (see Table 34), significant differences across WISC-IV scales were identified for smoking during pregnancy and duration of breastfeeding. Women who reported smoking during their pregnancy had children with significantly ($p \leq 0.02$) lower FSIQ, VCI, PRI and PSI. When breastfeeding practices were investigated, there was a significant ($p = 0.03$) difference between the FSIQ scores of each group, such that FSIQ rose with duration of breastfeeding from no breastfeeding (mean FSIQ

= 89.5) to breastfeeding for less than or equal to 6 months duration (mean FSIQ = 89.97) to breastfed for equal to or greater than 7 months duration (mean FSIQ = 102.40). A similar significant (p = 0.04) difference across breastfeeding categories was identified for PRI scores and the difference approached significance for VCI and WMI.

Table 34

Mean WISC-IV FSIQ and subscale scores for the potential categorical pre- and post-natal covariates.

Potential Covariates	Categories (*n*)	Mean FSIQ	Mean VCI	Mean PRI	Mean WMI	Mean PSI
Gravidity	0 (29)	103.9	103.5	104.7	99.6	102.0
	1 (26)	99.2	99.9	98.8	94.5	102.1
	2 (16)	96.3	96.4	102.8	90.4	94.8
	3 (13)	97.3	98.8	99.5	91.7	99.0
	4 or more (10)	97.1	97.2	99.5	91	101.2
	F (4, 89) (*p*-value)	0.99 (0.42)	0.89 (0.48)	0.64 (0.63)	1.29 (0.28)	0.96 (0.43)
Birth order	First child (31)	103.5	105.0	102.6	100.1	100.3
	Two child (31)	99.7	100.2	102.3	93.4	101.0
	Third or later child (20)	98.4	96.8	101.3	93.9	100.8
	F (2, 79) (*p*-value)	0.95 (0.39)	2.43 (0.10)	0.05 (0.95)	1.77 (0.18)	0.03 (0.97)
Gestational age	Less than 37 weeks (4)	99.5	98.8	104.0	99.3	95.8
	37 – 40 weeks (33)	97.2	98.2	97.9	94.0	98.8
	More than 40 weeks (8)	104.3	102.5	104.6	98.5	103.5
	F (2, 42) (*p*-value)	0.79 (0.46)	0.38 (0.69)	0.85 (0.43)	0.36 (0.70)	0.84 (0.44)

Note. Significant differences between groups are **bold**. FSIQ: Full Scale IQ; *n*: subsample size; PRI: Perceptual Reasoning Index; PSI: Perceptual Speed Index; VCI: Verbal Comprehension Index; WISC-IV: Wechsler Intelligence Scale for children: Fourth Edition; WMI: Working Memory Index.

Table 34

Continued.

Potential Covariates	Categories (*n*)	Mean FSIQ	Mean VCI	Mean PRI	Mean WMI	Mean PSI
Mode of delivery	Vaginal delivery (62)	99.5	99.1	101.4	95.4	100.6
	Caesarean (33)	99.7	101.2	102.0	93.1	99.6
	F (1, 93) (*p*-value)	0.00 (0.95)	0.49 (0.48)	0.04 (0.84)	0.45 (0.50)	0.12 (0.73)
NICU admission (more than a few hours)	No (76)	99.8	99.8	101.8	94.8	100.9
	Yes (17)	97.5	99.7	99.6	94.1	95.5
	F (1, 91) (*p*-value)	0.35 (0.55)	0.00 (0.99)	0.28 (0.60)	0.02 (0.88)	2.29 (0.13)
Smoking during pregnancy	No (77)	101.6	101.2	103.6	96.2	101.7
	Yes (16)	90.9	92.9	93.2	89.6	93.3
	F (1, 91) (*p*-value)	8.04 **(0.01)**	5.33 **(0.02)**	6.70 **(0.01)**	2.60 (0.11)	5.53 **(0.02)**
Alcohol consumption during pregnancy	No (81)	99.2	99.3	101.5	94.3	100.5
	Yes (11)	106.3	105.6	106.7	102.0	98.8
	F (1, 90) (*p*-value)	2.47 (0.12)	2.32 (0.13)	1.19 (0.28)	2.58 (0.11)	0.14 (0.71)
Duration of breast-feeding	Not breastfed (10)	89.5	91.2	92.3	85.6	96.7
	Breastfed for ≤ 6 months (35)	99.0	99.8	100.6	93.6	100.1
	Breastfed for ≥ 7 months (48)	102.4	102.2	104.8	97.4	100.3
	F (2, 90) (*p*-value)	3.49 **(0.03)**	2.77 (0.07)	3.27 **(0.04)**	2.56 (0.08)	0.32 (0.73)

Note. Significant differences between groups are **bold**. FSIQ: Full Scale IQ; n: subsample size; NICU: Neonatal Intensive Care Unit; PRI: Perceptual Reasoning Index; PSI: Perceptual Speed Index; VCI: Verbal Comprehension Index; WMI: Working Memory Index.

No other significant differences were identified for the pre- and post-natal categorical variables although some showed notable trends; children admitted to NICU tended to have lower WISC-IV scores and counter-intuitively, the children of mothers who reported drinking alcohol tended to have higher WISC-IV scores (except for PSI) than the children of mothers who abstained from alcohol during pregnancy.

7.2.3 Final covariate selection

The final selection of covariates is presented in Table 35 and it is evident that the covariates that met the selection criteria for this study were demographic, familial, psycho-social and environmental and pre- and post-natal in nature.

Table 35

Covariates identified for inclusion in regression with WISC-IV FSIQ and subscales and Pb concentration

Variable domain	Covariate
Continuous covariates	
Familial	WAIS-III FSIQ
Pre- and post natal	Birth weight
Psycho-social and environmental factors	MC HOME Total
Psycho-social and environmental factors	Number of recent stressful life events
Categorical covariates	
Demographics	Annual combined family income [a]
Demographics	Current maternal smoking
Pre- and post natal	Smoking during pregnancy
Pre- and post natal	Duration of breast-feeding [a]

Note. FSIQ: Full Scale IQ; MC HOME: Middle child Home Observation for Measurement of the Environment Inventory; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition; WISC-IV: Wechsler Intelligence Scale for Children-Fourth Edition.

[a] Three-level categorical variables were recoded into 'dummy' variables in SPSS so that 'Annual combined family income' was coded as either 'middle income' or 'high income;' 'Duration of breast-feeding' was coded as 'breastfeeding for ≤ 6 months duration' or 'breastfeeding for ≥ 7 months duration.'

Chapter 8: Associations between blood lead concentration and WISC-IV subscales.

Chapter Summary

Simple and covariate-adjusted multiple regression analyses were used to explore the relationship between PbB concentration and the WISC-IV FSIQ and its subscales (VCI, PSI, WMI and PRI). Simple (unadjusted) analyses confirmed the first hypothesis that there would be an inverse association between FSIQ and PbB concentration across the exposure range of Port Pirie and Broken Hill children. The Spearman correlation between FSIQ and PbB concentration was significant ($\rho = -0.30$, $p = 0.002$) and this pattern of association was also seen in Spearman correlations between PbB concentration and each of the WISC-IV subscales.

Following from Chapter 7, which identified the most important potential covariates that might confound an association between cognitive abilities and PbB concentration, multiple regression analyses were conducted with FSIQ and each of the WISC-IV subscales considered as dependent variables. Ten variables (see Table 35) were entered for each model at the first step and then the blood lead terms (linear and quadratic terms) were entered at the second step.

These analyses confirmed Hypothesis 2, in part; the apparent associations of blood lead with FSIQ, VCI, PRI and PSI were attenuated when a range of demographic, familial, psycho-social and environmental and pre- and post-natal factors were also considered in the models. The variables that consistently explained the most variance in cognitive performance were linked to breastfeeding and family income level. However, the change in F-statistic (ΔF (2, 59) = 3.51, $p = 0.04$) for the WMI model indicated that the addition of the blood lead terms (PbB + PbB2) significantly increased the amount of variance in WMI already explained by the model. Relative importance regressions confirmed that the blood lead terms together accounted for 27% of the explained variance in WMI. The contribution of the blood lead terms to the PSI model also approached statistical significance ($p = 0.08$).

8.1. Unadjusted relationship between blood lead concentration and WISC-IV subscales

In unadjusted correlations, a significant inverse association was observed between WISC-IV FSIQ and PbB concentration (i.e., as PbB levels increased, FSIQ decreased; see Table 36). This confirmed the first hypothesis that there would be an inverse association between FSIQ and PbB concentration across the exposure range of Port Pirie and Broken Hill children. Figure 16 illustrates that the unadjusted relationship between WISC-IV FSIQ and PbB concentration is non-linear in shape. In order to best capture the non-linear curve observed in Figure 16, linear and quadratic PbB terms were included in subsequent multiple regression models.

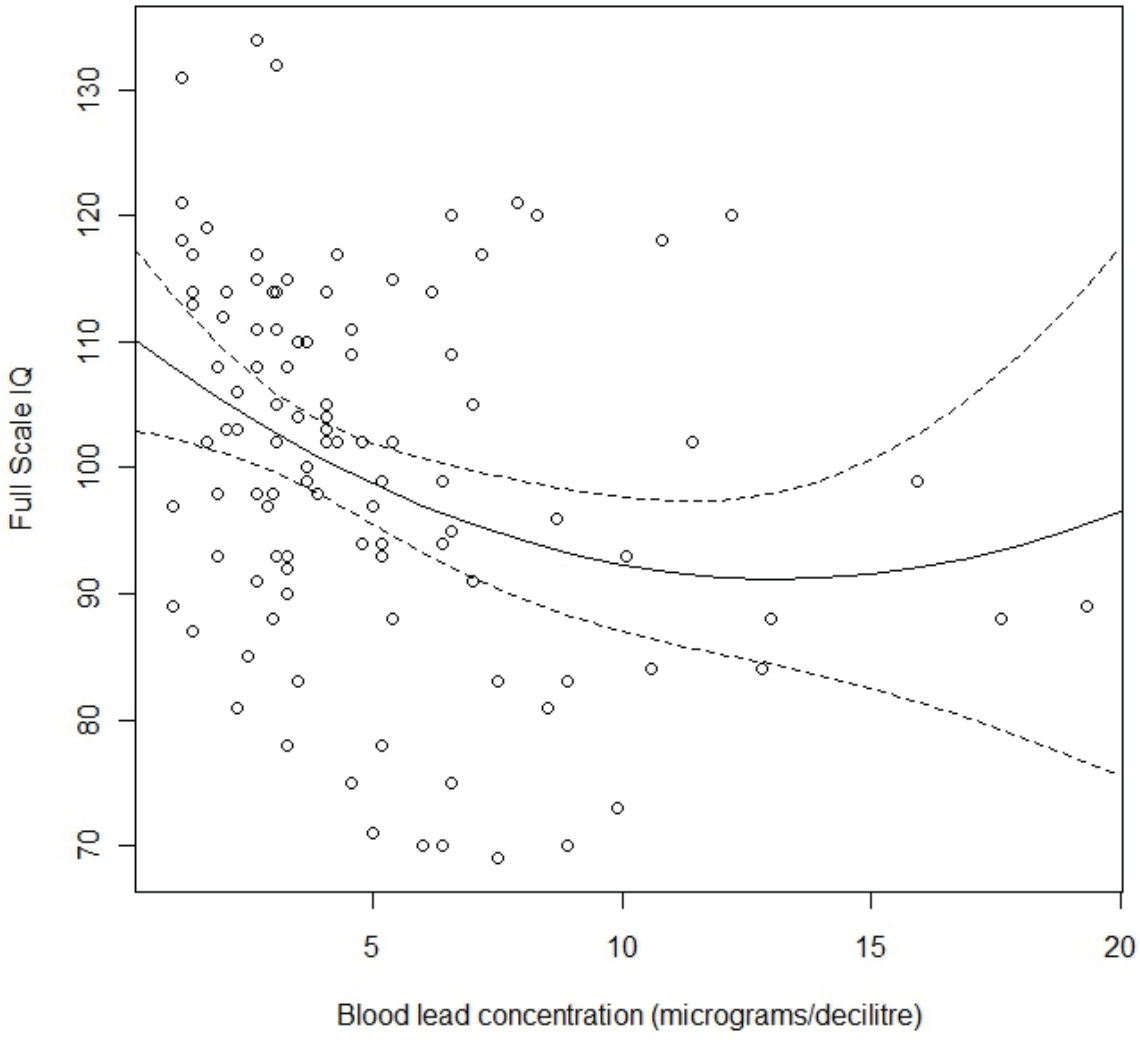

Figure 16

Unadjusted association between PbB concentration and FSIQ.

As shown in Table 36 unadjusted inverse spearman correlations between mean PbB levels and WISC-IV scale and subscale scores ranged from - 0.13 for Matrix Reasoning to - 0.30 for FSIQ. Moderate significant correlations were identified between PbB concentration and all scale scores. Subscales of the VCI correlate the most consistently ranging from - 0.20 to - 0.27.

8.2 Multiple regression modelling

Multiple regression analyses were conducted to explore the impact of various covariates on the relationship between PbB concentration and WISC-IV FSIQ.

Multiple regression analyses with FSIQ as the dependent variable will be presented and discussed first, followed by regressions using the VCI, PRI, WMI and PSI subscales as dependent variables. For all regression models, mother's WAIS-III FSIQ, current maternal smoking, birth weight, MC HOME total, total stressful life events, smoking during pregnancy, income (low, middle, high), breastfeeding (none, breastfeeding for ≤ 6 months duration, breastfeeding for ≥ 7 months duration; see Table 35) were entered first and the apparent 'effects' of Pb exposure were then assessed by entering the linear and quadratic terms of PbB concentration. These analyses address hypothesis 2 of the study which seeks to confirm that the association between children's cognitive abilities (WISC-IV performance in this case) and PbB concentration will be attenuated by demographic, familial, psycho-social and environmental and pre- and post-natal factors.

Table 36

Unadjusted Spearman correlations between PbB concentration and the WISC-IV

WISC-IV subscales	Correlation coefficient	*P*-level
Full-Scale IQ	- 0.30	0.00
Verbal Comprehension Index	- 0.25	0.01
Similarities	- 0.20	0.04
Vocabulary	- 0.22	0.02
Comprehension	- 0.27	0.01
Perceptual Reasoning Index	- 0.21	0.03
Block Design	- 0.17	0.08
Picture Concepts	- 0.18	0.07
Matrix Reasoning	- 0.13	0.20
Working memory Index	- 0.29	0.00
Digit Span	- 0.18	0.06
Letter-number sequencing	- 0.28	0.00
Processing Speed Index	- 0.24	0.02
Coding	- 0.24	0.01
Symbol search	- 0.19	0.05

Note. Subscale and cluster scores are **bold**. WISC-IV: Wechsler Intelligence Scale for Children-Fourth Edition

8.2.1 FSIQ as the dependent variable

Table 37 summarises the multiple regression run with FSIQ as the dependent variable. The final model was statistically significant (F (12, 59) = 4.36, $p < 0.0001$) and the adjusted R^2 indicated that the full model accounted for 36% of the variance in FSIQ scores.

In step 1 of the model, the variables that significantly contributed to the model were breastfeeding (children breastfed for ≤ 6 months duration scored on average 12.7 points more than children who were never breastfed; children breastfed for ≥ 7 months duration scored 11.4 points more than children who were never breastfed) and income (children from high income families scored on average 10.0 points higher than children from low income families; children from middle income families scored 7.1 points higher and this difference approached statistical significance).

As can be seen in Table 37, the variables that significantly contributed to the full model were breastfeeding (children breastfed ≤ 6 months duration scored 11.0 points more than children who were never breastfed; children breastfed ≥ 7 months duration scored 10.7 points more) while the contribution of the income variables and PbB concentration approached statistical significance.

The change in F-statistic (ΔF (2, 59) = 1.90, $p = 0.16$) for the FSIQ model indicated that the addition of the blood lead terms (PbB and PbB^2) did not significantly increase the amount of variance in FSIQ already explained by the model.

Table 37

Multiple regression model with FSIQ as the dependent variable (n = 74).

Model		Unstandardised Coefficient β (Std. Error)	*P*-level
Step 1[a]	(Constant)	64.91 (22.88)	0.01
	WAIS-III FSIQ	0.12 (0.16)	0.46
	Current maternal smoking	- 5.30 (4.95)	0.29
	Birth weight	0.00	0.62
	MC HOME total	0.33 (0.99)	0.74
	Total stressful life events	- 0.84 (0.82)	0.31
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 4.41 (5.38)	0.42
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	12.74 (4.99)	0.01
	Breastfeeding for ≥ 7 months duration	11.43 (5.12)	0.03
	Low income	0.00	
	Middle Income	7.09 (3.99)	0.08
	High Income	9.96 (4.53)	0.03
Step 2[b]	(Constant)	74.45 (23.44)	<0.001
	WAIS-III FSIQ	0.11 (0.16)	0.49
	Current maternal smoking	- 4.27 (5.15)	0.41
	Birth weight	0.00 (0.00)	0.49
	MC HOME total	0.14 (1.02)	0.89
	Total stressful life event	- 0.69 (0.86)	0.43
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 4.52 (5.34)	0.40
	No breastfeeding	0	
	Breastfeeding for ≤ 6 months duration	11.00 (5.00)	0.03
	Breastfeeding for ≥ 7 months duration	10.68 (5.22)	0.05
	Low income	0.00	
	Middle Income	7.19 (4.02)	0.08
	High Income	8.57 (4.53)	0.06
	PbB	**- 2.26 (1.26)**	**0.08**
	PbB^2	**0.10 (0.08)**	**0.17**

Note. Blood lead terms are **bold**. FSIQ: Full Scale IQ; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; *n*: subsample size; PbB: blood lead; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition.

[a] $R^2 = 0.44$, Adjusted $R^2 = 0.34$.

[b] $R^2 = 0.47$, Adjusted $R^2 = 0.36$, $\Delta R^2 = 0.03$. ΔF (2, 59) = 1.90, $p = 0.16$.

8.2.2 VCI as the dependent variable

Table 38 summarises the multiple regression calculated with VCI as the dependent variable. The final model was statistically significant (F (12, 59) = 2.49, $p < 0.01$) and the Adjusted R^2 indicated that the full model accounted for 20% of the variance in VCI scores.

In step 1 of the model, the only variables that significantly contributed to the model were mother's WAIS-III FSIQ and the breastfeeding ≤ 6 months duration (children breastfed ≤ 6 months duration scored on average 11.0 points higher than children who were not breastfed; children breastfed ≥ 7 months duration scored 8.6 points more than children who were never breastfed and this difference approached statistical significance).

As can be seen in Table 38, the only variable that significantly contributed to the full model was the quadratic PbB^2 variable which has limited explanatory power when not considered with the PbB term. Aside from this, breastfeeding ≤ 6 months duration and middle income approached statistical significance.

The change in F-statistic (ΔF (2, 59) = 1.01, $p = 0.37$) for the VCI model indicated that the addition of the blood lead terms (PbB and PbB^2) did not significantly increase the amount of variance in VCI already explained by the model.

Table 38

Multiple regression model with VCI as the dependent variable (n = 74).

Model		Unstandardised Coefficient β (Std. Error)	*P*-level
Step 1[a]	(Constant)	48.24 (23.05)	0.04
	WAIS-III FSIQ	0.29 (0.16)	0.01
	Current maternal smoking	- 4.66 (4.98)	0.35
	Birth weight	0.00 (0.00)	0.74
	MC HOME total	0.92 (1.0)	0.36
	Total stressful life events	1.00 (0.82)	0.23
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 0.98 (5.42)	0.86
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	11.01 (5.02)	0.03
	Breastfeeding for ≥ 7 months duration	8.57 (5.25)	0.11
	Low income	0.00	
	Middle Income	6.65 (4.02)	0.10
	High Income	6.70 (4.56)	0.15
Step 2[b]	(Constant)	55.84 (23.95)	0.02
	WAIS-III FSIQ	0.28 (0.17)	0.09
	Current maternal smoking	- 4.10 (5.26)	0.44
	Birth weight	0.00 (0.00)	0.84
	MC HOME total	0.75 (1.04)	0.47
	Total stressful life event	1.15 (0.88)	0.20
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 0.98 (5.46)	0.86
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	9.74 (5.12)	0.06
	Breastfeeding for ≥ 7 months duration	8.12 (5.33)	0.13
	Low income	0.00	
	Middle Income	6.83 (4.11)	0.10
	High Income	5.71 (4.63)	0.22
	PbB	**- 1.61 (1.29)**	**0.22**
	PbB^2	**0.07 (0.08)**	**0.04**

Note. Blood lead terms are **bold**. FSIQ: Full Scale IQ; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; *n*: subsample size; PbB: blood lead; VCI: Verbal Comprehension Index; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition.
[a] $R^2 = 0.31$, Adjusted $R^2 = 0.20$.
[b] $R^2 = 0.34$, Adjusted $R^2 = 0.20$, $\Delta R^2 = 0.02$, ΔF (2, 59) = 1.01, $p = 0.37$.

8.2.3 PRI as the dependent variable

Table 39 summarises the multiple regression with PRI as the dependent variable. The final model was statistically significant (F (12, 59) = 2.71, p = 0.01) and the Adjusted R^2 indicated that this model accounted for 22% of the variance in PRI scores.

In step 1 of the model, the only variable that significantly contributed to the model was breastfeeding (children breastfed ≤ 6 months duration scored on average 11.5 points more than children who were never breastfed; children breastfed longer ≥ 7 months duration scored 10.1 points more, although this difference only approached statistical significance). Other variables approaching statistical significance in the model were total stressful life events and maternal smoking during pregnancy; the negative regression coefficients of these variables indicated that children whose families experienced more stressful recent life events and whose mothers were current smokers, had lower PRI scores when a number of other variables were controlled.

The change in F-statistic (ΔF (2, 59) = 0.06, p = 0.94) for the PRI model indicated that the addition of the blood lead terms (PbB and PbB^2) did not significantly increase the amount of variance in PRI already explained by the model.

Table 39

Multiple regression model with PRI as the dependent variable (n = 74)

Model		Unstandardised Coefficient β (Std. Error)	*P*-level
Step 1[a]	(Constant)	65.76 (26.01)	0.01
	WAIS-III FSIQ	0.12 (0.19)	0.52
	Current maternal smoking	0.95 (5.64)	0.87
	Birth weight	0.00 (0.00)	0.16
	MC HOME total	0.03 (1.13)	0.98
	Total stressful life events	- 1.68 (0.93)	0.08
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 9.94 (6.13)	0.11
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	11.52 (5.69)	0.05
	Breastfeeding for ≥ 7 months duration	10.60 (5.95)	0.08
	Low income	0.00	
	Middle Income	1.64 (4.55)	0.72
	High Income	5.30 (5.16)	0.31
Step 2[b]	(Constant)	67.99 (27.55)	0.02
	WAIS-III FSIQ	0.12 (0.19)	0.54
	Current maternal smoking	0.44 (6.05)	0.94
	Birth weight	0.00 (0.00)	0.21
	MC HOME total	- 0.09 (1.20)	0.94
	Total stressful life event	- 1.56 (1.02)	0.13
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 9.71 (6.28)	0.13
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	11.46 (5.88)	0.06
	Breastfeeding for ≥ 7 months duration	10.85 (6.13)	0.08
	Low income	0.00	
	Middle Income	1.96 (4.73)	0.68
	High Income	5.32 (5.33)	0.32
	PbB	**0.02 (1.48)**	**0.99**
	PbB^2	**- 0.01 (0.09)**	**0.89**

Note. Blood lead terms are **bold**. FSIQ: Full Scale IQ; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; *n*: subsample size; PbB: blood lead; PRI: Perceptual Reasoning Index; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition.

[a] $R^2 = 0.35$, Adjusted $R^2 = 0.25$.

[b] $R^2 = 0.36$, Adjusted $R^2 = 0.22$, $\Delta R^2 = 0.001$, ΔF (2, 59) = 0.06, $p = 0.94$.

8.2.4 WMI as the dependent variable

Table 40 summarises the multiple regression with WMI as the dependent variable. The final model was statistically significant (F (12, 59) = 3.17, $p < 0.001$) and the Adjusted R^2 indicated that this model accounted for 27% of the variance in WMI scores.

In step 1 of the model, only the breastfeeding variable significantly contributed to the model (children breastfed ≥ 7 months duration scored on average 13.6 points more than children not breastfed; children breastfed ≤ 6 months duration scored 11.3 points more than children who were never breastfed although this difference only approached statistical significance). In addition the contribution of the high income variable also approached statistical significance.

As can be seen in Table 40, the variables that significantly contributed to the full model were breastfeeding ≥ 7 months duration (children breastfed ≥ 7 months duration scored 11.88 points more than children not breastfed) and linear and quadratic PbB terms; the negative regression coefficient for linear PbB term indicated that children with higher PbB levels had significantly lower WMI scores.

The change in F-statistic (ΔF (2, 59) = 3.51, $p = 0.04$) for the WMI model indicated that the addition of the blood lead terms (PbB and PbB^2) significantly increased the amount of variance in WMI already explained by the model.

Table 40

Multiple regression model with WMI as the dependent variable (n = 74).

Model		Unstandardised Coefficient β (Std. Error)	*P*-level
Step 1[a]	(Constant)	74.19 (26.51)	0.01
	WAIS-III FSIQ	0.07 (0.19)	0.71
	Current maternal smoking	- 5.18 (5.73)	0.37
	Birth weight	0.00 (0.00)	0.69
	MC HOME total	0.43 (1.15)	0.71
	Total stressful life events	- 1.44 (0.95)	0.13
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	1.33 (6.23)	0.83
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	11.32 (5.78)	0.06
	Breastfeeding for ≥ 7 months duration	13.55 (6.04)	0.03
	Low income	0.00	
	Middle Income	5.31 (4.63)	0.26
	High Income	8.62 (5.24)	0.11
Step 2[b]	(Constant)	85.71 (26.48)	<0.001
	WAIS-III FSIQ	0.06 (0.18)	0.76
	Current maternal smoking	- 2.56 (5.82)	0.66
	Birth weight	0.00 (0.00)	0.99
	MC HOME total	0.35 (1.15)	0.76
	Total stressful life event	- 1.42 (0.98)	0.15
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	0.71 (6.03)	0.91
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	8.58 (5.65)	0.13
	Breastfeeding for ≥ 7 months duration	11.88 (5.89)	0.05
	Low income	0.00	
	Middle Income	4.90 (4.54)	0.29
	High Income	6.31 (5.12)	0.22
	PbB	**- 3.71 (1.42)**	**0.01**
	PbB^2	**0.19 (0.08)**	**0.03**

Note. Blood lead terms are **bold**. FSIQ: Full Scale IQ; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; *n*: subsample size; PbB: blood lead; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition; WMI: Working Memory Index.

[a] $R^2 = 0.32$, Adjusted $R^2 = 0.21$.

[b] $R^2 = 0.39$, Adjusted $R^2 = 0.27$, $\Delta R^2 = 0.07$, ΔF (2, 59) = 3.51, $p = 0.04$.

8.2.4.1 Relative importance linear regression

Relative importance regression was used to explore further the contribution of the blood lead variables (PbB and PbB^2) to the multiple regression models with WISC-IV WMI as the dependent variable.

Johnson and Lebreton (2004) define relative importance as "the proportionate contribution each predictor makes to R^2, considering both its direct effect (i.e, its correlation with the criterion) and its effect when combined with the other variables in the regression equation" (p.240). According to Grömpling (2006), of the six different methods for assessing relative importance in linear regression, the method proposed by Lindeman, Merenda and Gold (denoted "lmg") which averages the contribution of each regressor over the different possible orderings of regressors, is a recommended approach (Grömpling, 2006). The lmg method will be used here to explore the relationship between the blood lead variables (PbB and PbB^2) and the WISC-IV WMI. The relative importance metrics were normalised to sum to 1.0 and can be interpreted as the proportion of explained variance attributable to each variable.

The data for the relative importance model using WMI as the dependent variable is summarised in Table 41. The proportion of variance explained by the model presented in Table 41 was 38.3%.

As shown in Table 41, using the lmg method, the relative importance metric for the blood lead terms (PbB relative importance metric = 0.19; PbB^2 relative importance metric = 0.11) together account for 30% of the explained variance in WMI. Other notable contributors were Total stressful life events terms (relative importance metric = 0.14), income level (relative importance metric = 0.17) and duration of breastfeeding (relative importance metric = 0.17).

Table 41

Relative importance metrics (WMI is the dependent variable; n = 72).

Regressors	Proportion of explained variance
PbB	**0.19**
PbB^2	**0.11**
WAIS-III FSIQ	0.07
Current maternal smoking	0.06
Birth weight	0.02
MC HOME total	0.06
Total stressful life events	0.14
Smoking during pregnancy	0.02
Income level	0.17
Duration of breastfeeding	0.17

Note. Blood lead terms are **bold**. FSIQ: Full Scale IQ; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; *n*: subsample size; PbB: blood lead; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition; WMI: Working Memory Index.

8.2.5 PSI as the dependent variable

Table 42 summarises the multiple regression with PSI as the dependent variable. The final model was statistically significant (F (12, 59) = 3.12, p = 0.02) and the Adjusted R^2 indicated that this model accounted for 26% of the variance in PSI scores.

In step 1 of the model the income variable significantly contributed to the model; children from high income families scored, on average, 11.5 points higher than children from low income families.

Table 42

Multiple regression model with PSI as the dependent variable (n = 74).

Model		Unstandardised Coefficient β (Std. Error)	*P*-level
Step 1[a]	(Constant)	124.97 (23.31)	<0.001
	WAIS-III FSIQ	- 0.25 (0.17)	0.14
	Current maternal smoking	- 9.98 (5.04)	0.05
	Birth weight	0.00 (0.00)	0.68
	MC HOME total	- 0.71 (1.01)	0.49
	Total stressful life events	- 1.20 (0.83)	0.16
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 3.91 (5.48)	0.48
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	4.66 (5.08)	0.36
	Breastfeeding for ≥ 7 months duration	1.99 (5.31)	0.71
	Low income	0.00	
	Middle Income	6.80 (4.07)	0.10
	High Income	11.51 (4.61)	0.02
Step 2[b]	(Constant)	136.07 (23.61)	<0.001
	WAIS-III FSIQ	- 0.26 (0.16)	0.11
	Current maternal smoking	- 8.68 (5.19)	0.10
	Birth weight	0.00 (0.00)	0.51
	MC HOME total	- 0.91 (1.03)	0.38
	Total stressful life event	- 1.04 (0.87)	0.24
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 4.07 (5.38)	0.45
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	2.60 (5.04)	0.61
	Breastfeeding for ≥ 7 months duration	1.07 (5.25)	0.84
	Low income	0.00	
	Middle Income	6.89 (4.05)	0.09
	High Income	9.84 (4.57)	0.04
	PbB	**- 2.69 (1.27)**	**0.04**
	PbB^2	**0.12 (0.08)**	**0.10**

Note. Blood lead terms are **bold**. FSIQ: Full Scale IQ; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; *n*: subsample size; PbB: blood lead; PSI: Processing Speed Index; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition.

[a] $R^2 = 0.33$, Adjusted $R^2 = 0.23$.

[b] $R^2 = 0.39$, Adjusted $R^2 = 0.26$, $\Delta R^2 = 0.05$, ΔF (2, 59) = 2.61, $p = 0.08$.

In the full model, significant contributors were high income (children from high income families scored 9.8 points higher than children from low income families) and the linear and quadratic PbB terms; the negative regression coefficient for linear PbB term indicated that children with higher PbB levels had significantly lower PSI scores.

The change in F-statistic (ΔF (2, 59) = 2.61, p = 0.08) for the PSI model indicated that the addition of the blood lead terms (PbB and PbB^2) did not significantly increase the amount of variance in PSI explained by the model.

8.2.5.1 Relative importance linear regression

Given the statistically significant coefficient for PbB in the full model, relative importance regression was used to further explore the contribution of the blood lead variables (PbB and PbB^2) to the multiple regression models with WISC-IV PSI as the dependent variable.

The data for the relative importance model using PSI as the dependent variable is summarised in Table 43. The proportion of variance explained by the model presented in Table 43 was 37.65%.

As shown in Table 43, for the blood lead terms (PbB relative importance metric = 0.16; PbB^2 relative importance metric = 0.09), together account for 25% of the explained variance in PSI. Other notable contributors were current maternal smoking (relative importance metric = 0.19), total stressful life events (relative importance metric = 0.11) and the income variable (relative importance metric = 0.20).

Table 43

Relative importance metrics (PSI is the dependent variable; n = 72).

Regressors	Proportion of explained variance
PbB	**0.16**
PbB^2	**0.09**
WAIS-III FSIQ	0.06
Current maternal smoking	0.19
Birth weight	0.10
MC HOME total	0.03
Total stressful life events	0.11
Smoking during pregnancy	0.06
Income level	0.20
Duration of breastfeeding	0.01

Note. Blood lead terms are **bold**. FSIQ: Full Scale IQ; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; *n*: subsample size; PbB: blood lead; PSI: Processing Speed Index; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition.

8.3 Summary of multiple regression analyses using FSIQ and WISC-IV subscales as the dependent variables

Multiple regression analyses were conducted with WISC-IV FSIQ and subscale scores as dependent variables in order to explore the contribution of Pb to variance in children's WISC-IV performance when a range of potential covariates were controlled.

Table 44 summarises the relevant statistics for each model. In sum, in multiple regression analyses for children's WISC-IV performance at ages 7 to 8 years, the overall variance attributable to Pb was modest. The addition of the Pb terms (PbB and PbB^2) to a model with ten covariates only resulted in a significant change in the *F* statistic when WMI

was the dependent variable. The contribution of the PbB terms also approached statistical significance in the PSI model. Hence these analyses support hypothesis 2, in part, since the associations between FSIQ, VCI, PRI and PSI and PbB were attenuated by demographic, familial, psycho-social and environmental and pre- and post-natal factors, but not for WMI.

It is evident from Table 44, that the models accounted for between 22% and 36% of the explained variance in children's WISC-IV FSIQ and subscale scores. Hence, it follows that there is a large amount of variance in children's WISC-IV FSIQ and subscale scores (between 64% and 78%) which cannot be explained by any of the variables considered in this study, whether they be familial, socio-environmental, pre-and post-natal covariates or the blood lead terms.

Using the example of the WMI model where the addition of the blood lead terms did significantly improve the explanatory power of the model, it is evident that 73% of the variance in WMI is not accounted for by the model, that familial, socio-environmental, pre- and post-natal covariates accounted for 20% of the variance and that the blood lead terms account for 7% of the variance in WMI.

The amount of variance that remained unaccounted for by the model suggests that there may be other important influences upon cognitive development that have not been addressed in the current study; as Tong (1995) says of unaccounted variance, "unravelling the complexity of genotype-environmental influence on IQ still poses a great challenges to neurobehavioral science researchers" (p. 167).

Table 44

Summary of statistics for full models using the using WISC-IV subscales as the dependent variables

Subscales	R^2	Adjusted R^2	With the addition of the PbB terms		
			ΔR^2	ΔF (2, 59) =	*P*- level
FSIQ	0.47	0.36	0.03	1.90	0.16
VCI	0.34	0.20	0.02	1.01	0.37
PRI	0.36	0.22	0.001	0.06	0.94
WMI	0.39	0.27	0.07	3.51	0.04
PSI	0.39	0.26	0.05	2.61	0.08

Note. FSIQ: Full Scale IQ; PbB: blood lead; PRI: Perceptual Reasoning Index; PSI: Perceptual Speed Index; VCI: Verbal Comprehension Index; WISC-IV: Wechsler Intelligence Scale for Children – Forth Edition; WMI: Working Memory Index.

Chapter 9: Associations between blood lead concentration, the *g* factor and Cattell-Horn-Carroll Factor scores

Chapter Summary

This chapter presents the factor analytic approach to the development of a model of cognitive abilities underpinned by the CHC.

Preliminary analyses confirmed inverse significant association between PbB concentration and *g* (ρ = - 0.31, p = 0.01) and the CHC factors across the exposure range of Port Pirie and Broken Hill children.

Following from Chapter 6 which identified the most pertinent potential covariates to the association between cognitive abilities and PbB concentration, covariate adjusted multiple regression analyses were used to explore the relationship between PbB concentration, the *g* factor and CHC factor scores.

In sum, in multiple regression analyses, the overall variance in factor scores that was attributed to Pb was modest. The addition of the Pb terms (PbB and PbB^2) to the model of ten covariates only resulted in a significant change in the F statistic when Gs was the dependent variable.

In addition to *g* and the six factors from the CHC, when multiple regression was run using the Glr performance score, it was found that the addition of the Pb terms (PbB and PbB^2) to the model of ten covariates resulted in a significant change in the F statistic.

9.1 Fitting a measurement model consistent with Cattell-Horn-Carroll theory

Figure 9 in Chapter 4 showed a conceptual model of seven broad abilities measured by subtests of the WISC-IV, tests from the WJ-III measuring abilities not captured by the WISC-IV, along with computerised tests developed at the University of Adelaide (IT, Gs Invaders,

Swaps) which were included with the aim of better defining the latent variables described in Chapter 4. The model also included estimation of a higher-order general ability factor (*g*).

Prior to fitting the latent variable model, the unadjusted spearman associations between PbB concentration and the subtests of the WISC-IV, WJ-III and the computerised tests (IT, Gs Invaders, Swaps) were explored. In chapter 8, inverse unadjusted inverse spearman correlations were noted between mean PbB levels and WISC-IV subscale scores; see Table 36. The unadjusted spearman correlations between PbB concentration and the WJ-III subscales, mRPM, Picture Swaps, Gs Invaders and Inspection Time are presented in Table 45. On the whole, correlations were inverse and ranged from - 0.11 for Visual-auditory Learning to - 0.32 for Sound Blending. However, the correlation between IT and PbB concentration was near-zero ($\rho = 0.01$, $p = 0.91$). This was an unexpected finding given that Gs Invaders, another measure of Gs, correlated significantly and inversely with PbB concentration ($\rho = - 0.27$, $p = 0.01$). Reflecting upon this disparity, it is possible that the Gs Invaders task is more sensitive to PbB exposure than IT. In addition, the IT data may be unreliable due to administration errors, or due to the young age of participants. Also of note, Gs Invaders is a visually and conceptually engaging task; children's performance may have varied between Gs Invaders and IT. IT was still included in the latent variable model because it is theorised to share variance with the other speed measures used in this study.

At the outset is it acknowledged that the ultimate sample size ($N = 106$) is marginal for fitting such a latent variable model; nonetheless the model fit statistics (see below) suggest that the analyses presented in this chapter are reliable. Latent variable models were estimated using MPlus 6.1 (Muthén & Muthén, 2010); Full Information Maximum Likelihood estimates were used to deal with the small number of missing observations on several variables (minimum covariance coverage was 0.95). The fit of these types of models should be assessed using a range of fit criteria; specifically, goodness-of-fit and model complexity should be considered (Kline, 2005). Here, we have used the Root Mean Square Error of Approximation (RMSEA; Steiger & Lind, 1980), along with its 90 percent confidence interval, and the

likelihood ratio chi-square. The RMSEA is a parsimony-adjusted index where values less than about 0.05 indicate close approximate fit; and RMSEA greater than or equal to 0.10 suggests poor fit. The likelihood ratio chi-square tests the hypothesis that the model is correct but it is sensitive to the size of correlations and to sample size. Commonly, to overcome these problems, it is divided by the model degrees of freedom and a rule-of thumb is that this value should be less than about two for a good fitting model (Kline, 2005).

Table 45

Unadjusted Spearman correlations between PbB concentration and WJ-III subscales, Raven's matrices, Picture Swaps, Gs Invaders and Inspection Time (n =104)

WJ-III Subscales and computerised tests	Correlation coefficient	*P*-level
WJ-III Subscales		
Visual-auditory Learning	- 0.11	0.26
Retrieval Fluency	- 0.25	0.01
Sound Blending	- 0.32	0.001
Incomplete Words	- 0.21	0.04
Auditory Attention	- 0.16	0.11
Spatial Relations	- 0.24	0.02
Raven's Matrices	- 0.12	0.22
Picture Swaps	- 0.21	0.03
Gs Invaders	- 0.27	0.01
Inspection Time	- 0.01	0.91

Note. WJ-III: Woodcock Johnson-III Tests of Cognitive Abilities.

The model shown in Figure 9 was estimated and the fit statistics were good, χ^2 (163) = 241.4, $p < 0.001$, RMSEA = 0.07, 90% CI = 0.05, 0.09. However, the Glr factor was near indistinguishable from the higher-order g and this is not acceptable on theoretical grounds (unlike, for example, Gf being near equivalent to g (e.g., Undheim & Gustafsson, 1987). Because Glr was defined by two tests from the WJ-III and the computer scoring of that instrument provides an age-normed Glr score, it was decided to omit these variables and the Glr factor from the proposed measurement model. Furthermore, the Gsm factor was ill-defined but by allowing Swaps to load on this factor rather than Gf produced a better model and the Gsm factor was redefined as a latent working memory variable (hereafter WM).

The model shown in Figure 17 was therefore estimated (note the theoretically justifiable correlated residuals for WISC-IV Vocabulary and WJ-III Sound Blending added on the basis of examination of modification indices).

Again, the fit statistics for this model were good, χ^2 (129) = 190.2, $p < 0.001$, RMSEA = 0.06, 90% CI = 0.05, 0.09. Table 46 shows the standardised parameter estimates. Scores on the latent variables were calculated and used as dependent variables in regression analyses that parallel those presented in Chapter 8.

Of note in Table 46 is that the loadings are all statistically significant and in the expected direction. The loadings of the first-order factors on the higher-order g are all high, with that for WM being particularly high; this latter result is consistent with the literature on WM and general intelligence (see e.g., Kyllonen, & Christal, 1990). It is reasonable to observe that abilities in children of the age of the current sample are not as differentiated as for adults which is consistent with the high *g*-loadings of the first-order factors on *g*.

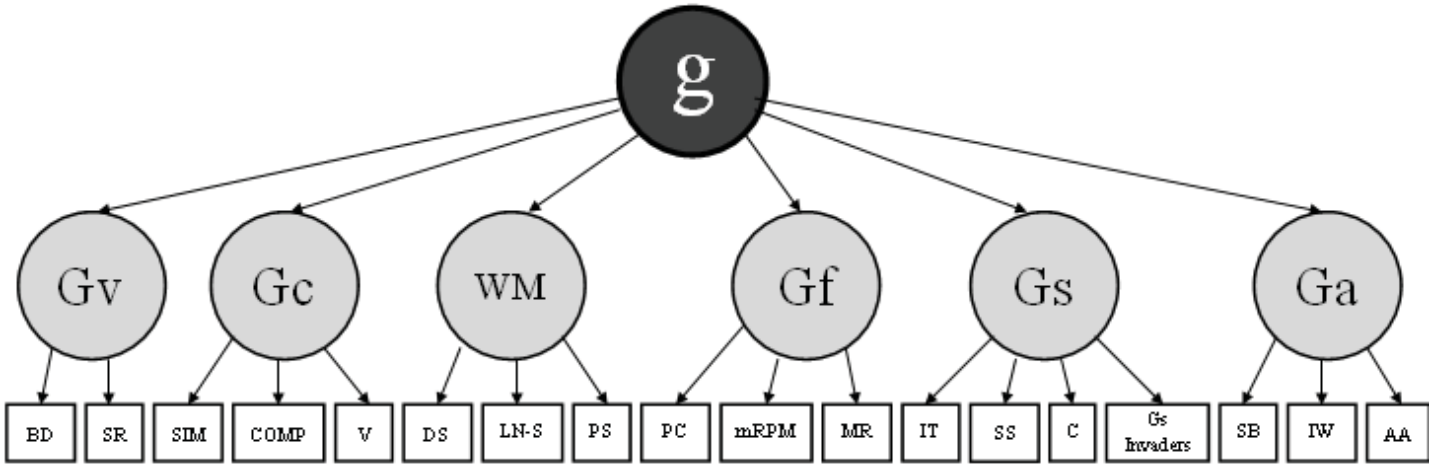

Figure 17

Factor structure of tests administered to assess child cognition.

Note. AA: Auditory Attention from the WJ-III; BD: Block Design from the WISC-IV; C: Coding from the WISC-IV; COMP: Comprehension from the WISC-IV; DS: Digit Symbol from the WISC-IV; IT: Inspection Time; IW: Incomplete Words from the WJ-III; LNS: Letter-number Sequencing from the WISC-IV; MR: Matrix Reasoning from the WISC-IV; mRPM: modified Raven's Progressive Matrices; *g*: general intelligence; Ga: Auditory ability factor; Gc: Crystallised ability factor; Gf: Fluid ability factor; Gs: Speed of information processing factor; Gv: Visuo-spatial ability factor; SR: SIM: Similarities from the WISC-IV; V: Vocabulary from the WISC-IV; RF: Retrieval Fluency from the WJ-III; PC: Picture Concepts from the WISC-IV; PS: Picture Swaps; SS: Symbol Search from the WISC-IV; SB: Sound Blending from the WJ-III; WM: Working Memory factor

Table 46

Standardised maximum likelihood parameter estimates and their standard errors for a model with six first-order latent variables and one second-order latent variable for 18 cognitive abilities measures

	Loading (*SE*)
1. Coding → Gs	0.560 (0.089)
2. Symbol Search→ Gs	0.728 (0.079)
3. IT→ Gs	- 0.399 (0.102)
4. Gs Invaders→ Gs	0.495 (0.095)
5. Picture Concepts → Gf	0.520 (0.085)
6. Matrix Reasoning → Gf	0.789 (0.062)
7. modified Raven → Gf	0.686 (0.068)
8. Sound Blending → Ga	0.609 (0.084)
9. Incomplete words → Ga	0.506 (0.092)
10. Auditory Attention → Ga	0.575 (0.089)
11. Block Design → Gv	0.952 (0.069)
12. Spatial Relations → Gv	0.498 (0.042)
13. Similarities → Gc	0.840 (0.041)
14. Vocabulary → Gc	0.870 (0.039)
15. Comprehension → Gc	0.713 (0.055)
16. Digit Symbol → WM	0.600 (0.077)
17. Letter-Number Sequencing → WM	0.739 (0.071)
18. Picture Swaps → WM	0.485 (0.088)
g → Gs	0.710 (0.090)
g → Gf	0.889 (0.069)
g → Ga	0.839 (0.085)
g → Gv	0.721 (0.090)
g → Gc	0.703 (0.067)
g → WM	0.924 (0.074)

Note. *g*: *g* factor: Generalised ability; Ga: Auditory ability; Gc: Crystallised ability; Gf: Fluid ability; Gs: Speed of information processing; Gsm: Short-term memory; Gv: Visuo-spatial ability; IT: Inspection Time; *N*: sample size; *SE*: standard error; WM: Working Memory factor.

9.2 Unadjusted relationship between blood lead concentration and the factor model

In unadjusted correlations, a significant inverse association ($\rho = -0.31$, $p < 0.01$) was observed between the *g* factor and PbB concentration, such that, as PbB levels increased, the *g* factor decreased (see Table 47). Figure 18 illustrates that the unadjusted relationship between the *g* factor and PbB concentration is non-linear in shape. In order to best capture the non-linear curve observed in Figure 18 (and similarly observed by Lanphear et al. (2005) in Figure 1), in addition to PbB, a quadratic PbB^2 term was included in subsequent multiple regression analyses.

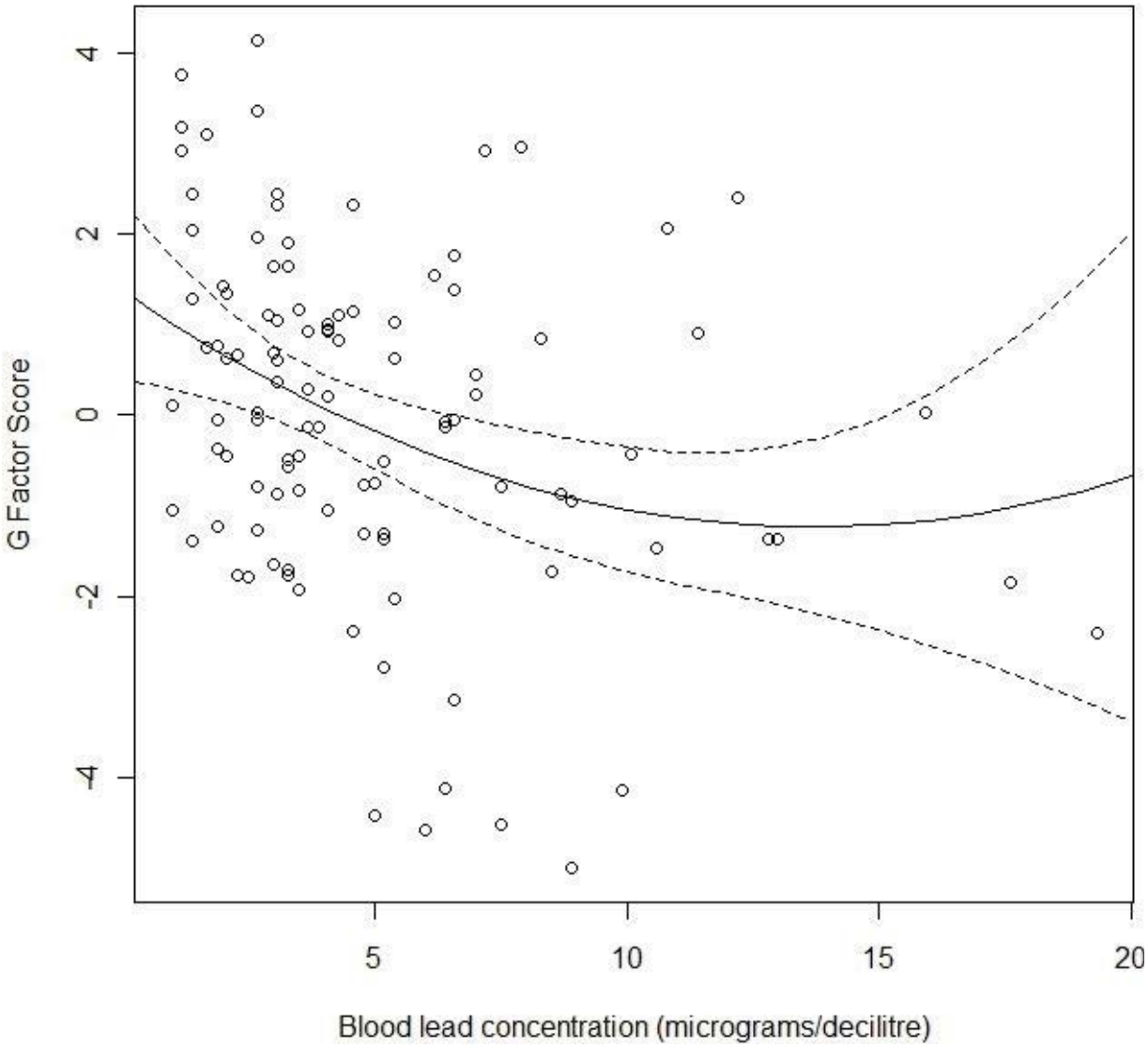

Figure 18

Unadjusted association between PbB concentration and the g factor. The fitted line is the regression of g factor scores on PbB and PbB^2; the dashed lines are the 95% confidence intervals for the regression line.

As shown in Table 47, unadjusted inverse correlations between mean PbB levels and CHC factor scores ranged from - 0.25 for Gf and Gc, to - 0.33 for Ga.

Table 47

Unadjusted Spearman correlations between PbB concentration*, the g factor and CHC factor scores (N = 106).*

g factor and CHC factor scores	Correlation coefficient	*P*-level
g factor	- 0.31	0.001
Gv	- 0.27	0.004
Gc	- 0.25	0.01
WM	- 0.31	0.001
Gf	- 0.25	0.01
Gs	- 0.30	0.002
Ga	- 0.33	0.001

Note. CHC: Cattell-Horn-Carroll model of intelligence; *g* factor: Generalised ability; Ga: Auditory ability; Gc: Crystallised ability; Gf: Fluid ability; Gs: Speed of information processing; Gsm: Short-term memory; Gv: Visuo-spatial ability; *N*: sample size; PbB: blood lead; WM: Working Memory factor.

9.3 Multiple regression modelling

Multiple regression analyses were conducted to examine the relationship between CHC factors and various potential predictors, respectively. Multiple regression analyses with *g* as the dependent variable will be presented and discussed primarily, followed by regressions using Gv, Gc, WM, Gf, Gs, Ga and Glr factors as dependent variables. For each regression model, mother's WAIS-III FSIQ, current maternal smoking, birth weight, MC HOME total, total stressful life events, smoking during pregnancy, income (low, middle, high), breastfeeding (none, breastfeeding for ≤ 6 months duration, breastfeeding for ≥ 7 months duration; see Table 35), were entered at Step 1 and PbB and PbB^2 were entered at Step 2.

9.3.1 *g* factor as the dependent variable

Table 48 summarises the multiple regression with *g* as the dependent variable. The final model was statistically significant (F (12, 59) = 2.95, p = 0.003) and the Adjusted R^2 indicated that this model accounted for 25% of the variance in *g* factor scores.

In step 1 of the model, the variable that significantly contributed to the model was breastfeeding (children breastfed ≤ 6 months duration had higher *g* factor scores than children who were never breastfed; children breastfed ≥ 7 months duration had higher *g* factor scores).

As can be seen in Table 48, the only variable that significantly contributed to the full model was breastfeeding ≥ 7 months duration while the contribution of the breastfeeding up ≤ 6 months duration and PbB (children with higher PbB levels had lower *g* factor scores) approached statistical significance.

The change in F-statistic (ΔF (2, 59) = 1.82, p = 0.17) for the *g* factor model indicated that the addition of the blood lead terms (PbB + PbB^2) did not significantly alter the amount of variance in the *g* factor which was explained by the model.

Table 48

Multiple regression model with the g factor as the dependent variable (n = 74).

Model		Unstandardised Coefficient β (Std. Error)	*P*-level
Step 1[a]	(Constant)	- 2.50 (3.38)	0.46
	WAIS-III FSIQ	0.00 (0.02)	0.97
	Current maternal smoking	0.02 (0.73)	0.98
	Birth weight	0.00 (0.00)	0.67
	MC HOME total	0.05 (0.15)	0.75
	Total stressful life events	- 0.19 (0.12)	0.12
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 1.09 (0.80)	0.18
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	1.47 (0.74)	0.05
	Breastfeeding for ≥ 7 months duration	1.75 (0.77)	0.03
	Low income	0.00	
	Middle Income	0.52 (0.59)	0.38
	High Income	0.99 (0.67)	0.14
Step 2[b]	(Constant)	- 1.01 (3.47)	0.77
	WAIS-III FSIQ	- 0.03 (0.02)	0.91
	Current maternal smoking	0.13 (0.76)	0.87
	Birth weight	0.00 (0.00)	0.57
	MC HOME total	0.01 (0.15)	0.93
	Total stressful life event	- 0.16 (0.13)	0.21
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 1.09 (0.79)	0.18
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	1.23 (0.73)	0.10
	Breastfeeding for ≥ 7 months duration	1.67 (0.77)	0.04
	Low income	0.00	
	Middle Income	0.56 (0.60)	0.36
	High Income	0.80 (0.67)	0.24
	PbB	**- 0.31 (0.19)**	**0.10**
	PbB^2	**0.01 (0.01)**	**0.23**

Note. Blood lead terms are **bold**. FSIQ: Full Scale IQ; *g* factor: Generalised ability; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; *n*: subsample size; PbB: blood lead; PSI: Processing Speed Index; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition.

[a] $R^2 = 0.33$, Adjusted $R^2 = 0.23$.

[b] $R^2 = 0.38$, Adjusted $R^2 = 0.25$, $\Delta R^2 = 0.04$, ΔF (2, 59) = 1.82, $p = 0.17$.

9.3.2 Gv factor as the dependent variable

Table 49 summarises the multiple regression with Gv as the dependent variable. The final model was statistically significant (F (12, 59) = 2.55, p = 0.01) and the Adjusted R^2 indicated that this model accounted for 21% of the variance in FSIQ scores.

In step 1 of the model, the variables that significantly contributed to the model were breastfeeding (children breastfed ≤ 6 months duration had higher Gv factor scores than children who were never breastfed; children breastfed ≥ 7 months duration had higher Gv factor scores) and maternal smoking during pregnancy (children whose mothers reported smoking during pregnancy had lower Gv factor scores than children whose mothers did not smoke during pregnancy).

As can be seen in Table 49, the only variable that significantly contributed to the full model was breastfeeding ≥ 7 months duration, while the contribution of the breastfeeding ≤ 6 months duration and smoking during pregnancy approached statistical significance.

The change in F-statistic (ΔF (2, 59) = 0.83, p = 0.44) for the Gv model indicated that the addition of the blood lead terms (PbB and PbB^2) did not significantly alter the amount of variance in Gv explained by the model.

Table 49

Multiple regression model with the Gv factor as the dependent variable (n = 74)

Model		Unstandardised Coefficient β (Std. Error)	*P*-level
Step 1[a]	(Constant)	- 3.58 (4.12)	0.39
	WAIS-III FSIQ	- 0.01 (0.03)	0.75
	Current maternal smoking	0.47 (0.89)	0.60
	Birth weight	0.00 (0.00)	0.22
	MC HOME total	0.05 (0.18)	0.80
	Total stressful life events	- 0.14 (0.15)	0.35
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 1.91 (0.97)	0.05
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	1.81 (0.90)	0.05
	Breastfeeding for ≥ 7 months duration	2.36 (0.94)	0.02
	Low income	0.00	
	Middle Income	0.710.72)	0.33
	High Income	0.83 (0.82)	0.31
Step 2[b]	(Constant)	- 2.09 (4.30)	0.63
	WAIS-III FSIQ	- 0.01 (0.03)	0.70
	Current maternal smoking	0.39 (0.94)	0.68
	Birth weight	0.00 (0.00)	0.26
	MC HOME total	- 0.01 (0.19)	0.97
	Total stressful life event	- 0.09 (0.16)	0.58
	No smoking during pregnancy		
	Smoked during pregnancy	- 1.84 (0.98)	0.07
	No breastfeeding		
	Breastfeeding for ≤ 6 months duration	1.65 (0.92)	0.08
	Breastfeeding for ≥ 7 months duration	2.38 (0.96)	0.02
	Low income		
	Middle Income	0.82 (74)	0.27
	High Income	0.73 (0.83)	0.39
	PbB	**- 0.18 (0.23)**	**0.45**
	PbB^2	**0.00 (0.01)**	**0.75**

Note. Blood lead terms are **bold**. FSIQ: Full Scale IQ; Gv: Visuo-spatial ability; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; *n*: subsample size; PbB: blood lead; PSI: Processing Speed Index; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition.

[a] $R^2 = 0.32$ Adjusted $R^2 = 0.21$

[b] $R^2 = 0.34$ Adjusted $R^2 = 0.21$ $\Delta R^2 = 0.02$, ΔF (2, 59) = 0.83, $p = 0.44$.

9.3.3 Gc factor as the dependent variable

Table 50 summarises the multiple regression with Gc as the dependent variable. The final model was statistically significant (F (12, 59) = 2.65, p = 0.01) and the Adjusted R^2 indicated that this model accounted for 22% of the variance in FSIQ scores.

In step 1 of the model, the variable that significantly contributed to the model were breastfeeding ≤ 6 months duration (children breastfed ≤ 6 months duration had higher Gc factor scores than children who were never breastfed), while the contributions of breastfeeding ≥ 7 months duration (children breastfed ≥ 7 months duration had higher Gc factor scores than children who were never breastfed) and the income variable (children in middle income families had Gc factor scores higher than children in low income families; children in high income families had Gc factor scores higher than children in low income families) approached statistical significance.

As can be seen in Table 50, the only variable that significantly contributed to the full model was breastfeeding ≤ 6 months duration, while the contributions of breastfeeding ≥ 7 months duration and middle income approached statistical significance.

The change in F-statistic (ΔF (2, 59) = 2.10, p = 0.13) for the Gc model indicated that the addition of the blood lead terms (PbB and PbB^2) did not significantly alter the amount of variance in the Gc factor explained by the model.

Table 50

Multiple regression model with the Gc factor as the dependent variable (n = 74)

Model		Unstandardised Coefficient β (Std. Error)	*P*-level
Step 1[a]	(Constant)	- 9.45 (4.38)	0.04
	WAIS-III FSIQ	0.05 (0.03)	0.14
	Current maternal smoking	- 0.85 (0.95)	0.37
	Birth weight	0.00 (0.00)	0.97
	MC HOME total	0.15 (0.19)	0.44
	Total stressful life events	0.17 (0.16)	0.27
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 0.38 (1.03)	0.71
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	2.14 (0.95)	0.03
	Breastfeeding for ≥ 7 months duration	1.76 (1.00)	0.08
	Low income	0.00	
	Middle Income	1.46 (0.76)	0.06
	High Income	1.46 (0.87)	0.10
Step 2[b]	(Constant)	- 8.29 (4.58)	0.08
	WAIS-III FSIQ	0.05 (0.03)	0.15
	Current maternal smoking	- 0.77 (1.01)	0.45
	Birth weight	0.00 (0.00)	0.95
	MC HOME total	0.12 (0.20)	0.55
	Total stressful life event	0.20 (0.17)	0.25
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 0.38 (1.04)	0.72
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	1.95 (0.98)	0.05
	Breastfeeding for ≥ 7 months duration	1.69 (1.02)	0.10
	Low income	0.00	
	Middle Income	1.48 (0.79)	0.06
	High Income	1.31 (0.89)	0.15
	PbB	**- 0.25 (0.25)**	**0.32**
	PbB^2	**0.01 (0.02)**	**0.47**

Note. Blood lead terms are **bold**. FSIQ: Full Scale IQ; Gc: Crystallised ability; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; *n*: subsample size; PbB: blood lead; PSI: Processing Speed Index; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition.

[a] $R^2 = 0.30$ Adjusted $R^2 = 0.19$

[b] $R^2 = 0.35$ Adjusted $R^2 = 0.22$ $\Delta R^2 = 0.05$, ΔF (2, 59) = 2.10, $p = 0.13$.

9.3.4 WM factor as the dependent variable

Table 51 summarises the multiple regression with WM as the dependent variable. The final model was statistically significant (F (12, 59) = 2.80, p = 0.004) and the Adjusted R^2 indicated that this model accounted for 21% of the variance in FSIQ scores.

In step 1 of the model, the variable that significantly contributed to the model were breastfeeding ≥ 7 months duration (children breastfed ≥ 7 months duration had higher WM factor scores than children who were never breastfed), while the contributions of breastfeeding ≤ 6 months duration (children breastfed ≤ 6 months duration had higher Gc factor scores than children who were never breastfed) and total stressful life events (children whose families experienced more stressful life events had lower WM scores) approached significance.

As can be seen in Table 51, the only variable that significantly contributed to the full model was breastfeeding ≥ 7 months duration while the contribution of PbB (children with higher PbB levels had lower WM factor scores) approached statistical significance.

The change in F-statistic (ΔF (2, 59) = 2.21, p = 0.12) for the WM model indicated that the addition of the blood lead terms (PbB and PbB^2) did not significantly alter the amount of variance in WM explained by the model.

Table 51

Multiple regression model with the WM factor as the dependent variable (n = 74)

Model		Unstandardised Coefficient β (Std. Error)	*P*-level
Step 1[a]	(Constant)	- 1.91 (2.63)	0.47
	WAIS-III FSIQ	0.00 (0.00)	0.98
	Current maternal smoking	0.05 (0.57)	0.94
	Birth weight	0.00 (0.00)	0.74
	MC HOME total	0.05 (0.11)	0.68
	Total stressful life events	- 0.15 (0.09)	0.11
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 0.75 (0.62)	0.23
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	1.07 (0.57)	0.07
	Breastfeeding for ≥ 7 months duration	1.33 (0.60)	0.03
	Low income	0.00	
	Middle Income	0.34 (0.46)	0.46
	High Income	0.69 (0.52)	0.19
Step 2[b]	(Constant)	- 0.71 (2.68)	0.79
	WAIS-III FSIQ	0.00 (0.02)	0.92
	Current maternal smoking	0.16 (0.59)	0.78
	Birth weight	0.00 (0.00)	0.59
	MC HOME total	0.02 (0.12)	0.84
	Total stressful life event	- 0.13 (0.10)	0.19
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 0.76 (0.61)	0.22
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	0.86 (0.57)	0.14
	Breastfeeding for ≥ 7 months duration	1.24 (0.60)	0.04
	Low income	0.00	
	Middle Income	0.36 (0.46)	0.44
	High Income	0.52 (0.52)	0.32
	PbB	**- 0.28 (0.14)**	**0.06**
	PbB^2	**0.01 (0.01)**	**0.15**

Note. Blood lead terms are **bold**. FSIQ: Full Scale IQ; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; PbB: blood lead; *n*: subsample size; PSI: Processing Speed Index; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition; WM: Working Memory factor.

[a] $R^2 = 0.32$ Adjusted $R^2 = 0.20$

[b] $R^2 = 0.36$ Adjusted $R^2 = 0.23$ $\Delta R^2 = 0.05$, ΔF (2, 59) = 2.21, $p = 0.12$.

9.3.5 Gf factor as the dependent variable

Table 52 summarises the multiple regression with Gf as the dependent variable. The final model was statistically significant (F (12, 59) = 3.10, p = 0.002) and the Adjusted R^2 indicated that this model accounted for 21% of the variance in FSIQ scores.

In step 1 of the model, the variable that significantly contributed to the model was total stressful life events (children whose families experienced recent stressful life events had lower Gf factor scores). The contributions of a number of variables approached statistical significance; breastfeeding (children breastfed ≤ 6 months duration had higher Gf factor scores than children who were never breastfed; children breastfed ≥ 7 months duration had higher Gf factor scores than children who were never breastfed), income (children from high income families had higher Gf factor scores than children from low income families) and smoking during pregnancy (children whose mothers smoked during pregnancy had lower Gf scores than children whose mothers did not smoke during pregnancy).

As can be seen in Table 52, while no variables significantly contributed to the full model, a number approached statistical significance; breastfeeding ≥ 7 months duration, smoking during pregnancy and total stressful life events.

The change in F-statistic (ΔF (2, 59) = 0.30, p = 0.75) for the Gf factor model indicated that the addition of the blood lead terms (PbB and PbB^2) did not significantly alter the amount of variance in the Gf factor explained by the model.

Table 52

Multiple regression model with the Gf factor as the dependent variable (n = 74)

Model		Unstandardised Coefficient β (Std. Error)	*P*-level
Step 1[a]	(Constant)	- 2.43	0.34
	WAIS-III FSIQ	0.00	0.86
	Current maternal smoking	0.18	0.75
	Birth weight	0.00	0.49
	MC HOME total	0.05	0.66
	Total stressful life events	- 0.18	0.05
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 1.01	0.09
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	0.92	0.10
	Breastfeeding for ≥ 7 months duration	1.01	0.08
	Low income	0.00	
	Middle Income	0.39	0.38
	High Income	0.86	0.09
Step 2[b]	(Constant)	- 2.01	0.45
	WAIS-III FSIQ	0.00	0.88
	Current maternal smoking	0.23	0.70
	Birth weight	0.00	0.46
	MC HOME total	0.04	0.73
	Total stressful life event	- 0.17	0.08
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 1.01	0.10
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	0.84	0.14
	Breastfeeding for ≥ 7 months duration	0.98	0.10
	Low income	0.00	
	Middle Income	0.39	0.39
	High Income	0.80	0.13
	PbB	**- 0.10**	**0.48**
	PbB^2	**0.01**	**0.58**

Note. Blood lead terms are **bold**. FSIQ: Full Scale IQ; Gf: Fluid ability; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; *n*: subsample size; PbB: blood lead; PSI: Processing Speed Index; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition.

[a] $R^2 = 0.38$ Adjusted $R^2 = 0.28$

[b] $R^2 = 0.39$ Adjusted $R^2 = 0.26$ $\Delta R^2 = 0.01$, $\Delta F\ (2, 59) = 0.30$, $p = 0.75$.

9.3.6 Gs factor as the dependent variable

Table 53 summarises the multiple regression with Gs as the dependent variable. The final model was statistically significant (F (12, 59) = 3.17, p = 0.002) and the Adjusted R^2 indicated that this model accounted for 27% of the variance in FSIQ scores.

In step 1 of the model, the only variable that significantly contributed to the model was high income (children from high income families had higher Gs factor scores than children from low income families), while the contribution of middle income (children from middle income families had higher Gs factor scores than children from low income families) approached statistical significance.

As can be seen in Table 53, the variables that significantly contributed to the full model were high income and PbB (children with higher PbB levels had lower Gs factor scores), while the contributions of the middle income variable approached statistical significance.

The change in F-statistic (ΔF (2, 59) = 3.39, p = 0.04) for the Gs model indicated that the addition of the blood lead terms (PbB and PbB^2) did significantly alter the amount of variance in Gs explained by the model.

9.3.6.1 Relative importance linear regression

Given the statistically significant coefficient for PbB in the full model, relative importance regression was used to further explore the contribution of the blood lead variables (PbB and PbB^2) to the multiple regression models with Gs as the dependent variable.

The data for the relative importance model using Gs as the dependent variable is summarised in Table 54. The proportion of variance explained by the model presented in Table 54 was 40%.

Table 53

Multiple regression model with the Gs factor as the dependent variable (n = 74)

Model		Unstandardised Coefficient β (Std. Error)	*P*-level
Step 1[a]	(Constant)	1.27 (2.48)	0.61
	WAIS-III FSIQ	- 0.02 (0.02)	0.39
	Current maternal smoking	- 0.69 (0.54)	0.20
	Birth weight	0.00 (0.00)	0.93
	MC HOME total	- 0.08 (0.11)	0.48
	Total stressful life events	- 0.12 (0.09)	0.17
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 0.41 (0.58)	0.48
	No breastfeeding	0.77 (0.54)	0.16
	Breastfeeding for ≤ 6 months duration	0.00	
	Breastfeeding for ≥ 7 months duration	0.86 (0.57)	0.13
	Low income	0.00	
	Middle Income	0.75 (0.43)	0.09
	High Income	1.26 (0.49)	0.01
Step 2[b]	(Constant)	2.67 (2.48)	0.29
	WAIS-III FSIQ	- 0.02 (0.02)	0.32
	Current maternal smoking	- 0.57 (0.55)	0.30
	Birth weight	0.00 (0.00)	0.74
	MC HOME total	- 0.11 (0.11)	0.33
	Total stressful life event	- 0.10 (0.09)	0.29
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 0.42 (0.57)	0.46
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	0.53 (0.53)	0.32
	Breastfeeding for ≥ 7 months duration	0.77 (0.55)	0.17
	Low income	0.00	
	Middle Income	0.77 (0.43)	0.07
	High Income	1.06 (0.48)	0.03
	PbB	**- 0.31 (0.13)**	**0.02**
	PbB^2	**0.01 (0.01)**	**0.08**

Note. Blood lead terms are **bold**. FSIQ: Full Scale IQ; Gs: Speed of information processing; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; *n*: subsample size; PbB: blood lead; PSI: Processing Speed Index; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition.

[a] $R^2 = 0.32$ Adjusted $R^2 = 0.21$

[b] $R^2 = 0.39$ Adjusted $R^2 = 0.27$ $\Delta R^2 = 0.07$, ΔF (2, 59) = 3.39, $p = 0.04$.

As shown in Table 54, for the blood lead terms (PbB relative importance metric = 0.18; PbB^2 relative importance metric = 0.09), together account for 27% of the explained variance in Gs. The other most notable contributor was income level (relative importance metric = 0.28).

Table 54

Relative importance metrics (Gs is the dependent variable; n = 72).

Regressors	Proportion of explained variance
PbB	**0.18**
PbB^2	**0.09**
WAIS-III FSIQ	0.03
Current maternal smoking	0.11
Birth weight	0.06
MC HOME total	0.03
Total stressful life events	0.09
Smoking during pregnancy	0.06
Income level	0.28
Duration of breastfeeding	0.07

Note. Blood lead terms are **bold**. FSIQ: Full Scale IQ; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; *n*: subsample size; PbB: blood lead; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition; WMI: Working Memory Index.

9.3.7 Ga factor as the dependent variable

Table 55 summarises the multiple regression with Ga as the dependent variable. The final model was statistically significant (F (12, 59) = 2.65, p = 0.01) and the Adjusted R^2 indicated that this model accounted for 22% of the variance in FSIQ scores.

In step 1 of the model, the only variable that significantly contributed was breastfeeding (children breastfed ≤ 6 months duration had higher Ga factor scores than children who were never breastfed; children breastfed ≥ 7 months duration had higher Ga factor scores than children who were never breastfed) and total stressful life events (children whose family reported more stressful life events had lower Ga factor scores).

As can be seen in Table 55, the variable that significantly contributed to the full model was breastfeeding ≥ 7 months duration, while the contributions of breastfeeding ≤ 6 months duration and the linear PbB variable (children with higher PbB levels had lower Ga factor scores) approached statistical significance.

The change in F-statistic (ΔF (2, 59) = 2.10, p = 0.13) for the Ga factor model indicated that the addition of the blood lead terms (PbB and PbB^2) did not significantly alter the amount of variance in the Ga factor explained by the model.

Table 55

Multiple regression model with the Ga factor as the dependent variable (n = 74)

Model		Unstandardised Coefficient β (Std. Error)	*P*-level
Step 1[a]	(Constant)	- 3.42 (11.51)	0.77
	WAIS-III FSIQ	- 0.02 (0.08)	0.80
	Current maternal smoking	0.26 (2.49)	0.92
	Birth weight	0.00 (0.00)	0.87
	MC HOME total	0.05 (0.50)	0.92
	Total stressful life events	- 0.84 (0.41)	0.05
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 3.63 (2.70)	0.19
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	5.13 (2.51)	0.05
	Breastfeeding for ≥ 7 months duration	6.10 (2.62)	0.02
	Low income	0.00	
	Middle Income	0.60 (2.01)	0.77
	High Income	2.65 (2.28)	0.25
Step 2[b]	(Constant)	2.31 (11.75)	0.85
	WAIS-III FSIQ	- 0.03 (0.08)	0.73
	Current maternal smoking	0.49 (2.58)	0.85
	Birth weight	0.00 (0.00)	0.78
	MC HOME total	- 0.10 (0.51)	0.85
	Total stressful life event	- 0.70 (0.43)	0.11
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 3.56 (2.68)	0.19
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	4.27 (2.51)	0.09
	Breastfeeding for ≥ 7 months duration	5.87 (2.62)	0.03
	Low income	0.00	
	Middle Income	0.81 (2.02)	0.69
	High Income	2.00 (2.27)	0.38
	PbB	**- 1.07 (0.63)**	**0.09**
	PbB^2	**0.04 (0.04)**	**0.25**

Note. Blood lead terms are **bold**. FSIQ: Full Scale IQ; Ga: Auditory ability; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; *n*: subsample size; PbB: blood lead; PSI: Processing Speed Index; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition.

[a] $R^2 = 0.30$ Adjusted $R^2 = 0.19$

[b] $R^2 = 0.35$ Adjusted $R^2 = 0.22$ $\Delta R^2 = 0.05$, ΔF (2, 59) = 2.10, $p = 0.13$.

9.3.8 Glr factor as the dependent variable

Although the CHC factor, Glr did not load in the model structure which was developed based on this dataset, the factor could be constructed based on the theoretical underpinnings of the Woodcock, McCrew & Mather (2001). Woodcock et al. (2001) constructed Glr using the WJ-III battery tasks visual-auditory processing and retrieval fluency tasks.

Table 56 summarises the multiple regression with Glr as the dependent variable. The final model approached statistical significant (F (12, 59) = 1.51, p = 0.15) and the Adjusted R^2 indicated that this model accounted for only 8% of the variance in FSIQ scores.

In step 1 of the model, the only variable that approached statistical significance was breastfeeding ≥ 7 months duration (children breastfed ≥ 7 months duration had higher Glr factor scores than children who were never breastfed).

As can be seen in Table 56, the blood lead variables were the only significant contributors to the full model. In particular the negative regression coefficient for PbB indicated that the Glr factor decreased with increasing PbB levels (children with higher PbB levels had lower Glr factor scores).

The change in F-statistic (ΔF (2, 59) = 4.18, p = 0.02) for the Glr factor model indicated that the addition of the blood lead terms (PbB and PbB^2) significantly increased the amount of variance in the Glr factor explained by the model.

9.3.8.1 Relative importance linear regression

Given the statistically significant coefficient for PbB in the full model, relative importance regression was used to further explore the contribution of the blood lead variables (PbB and PbB^2) to the multiple regression models with Glr as the dependent variable.

The data for the relative importance model using Glr as the dependent variable is summarised in Table 57. The proportion of variance explained by the model presented in Table 57 was 24.13 %.

Table 56

Multiple regression model with the Glr factor as the dependent variable (n = 74)

Model		Unstandardised Coefficient β (Std. Error)	*P*-level
Step 1[a]	(Constant)	485.24 (10.23)	< 0.001
	WAIS-III FSIQ	0.03 (0.07)	0.69
	Current maternal smoking	1.23 (2.21)	0.58
	Birth weight	0.00 (0.00)	0.32
	MC HOME total	0.05 (0.44)	0.92
	Total stressful life events	- 0.01 (0.37)	0.99
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 2.29 (2.40)	0.35
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	2.84 (2.23)	0.21
	Breastfeeding for ≥ 7 months duration	4.35 (2.33)	0.07
	Low income	0.00	
	Middle Income	- 0.10 (1.78)	0.96
	High Income	- 0.97 (2.02)	0.63
Step 2[b]	(Constant)	488.63 (10.11)	< 0.001
	WAIS-III FSIQ	0.03 (0.07)	0.71
	Current maternal smoking	2.66 (2.22)	0.24
	Birth weight	0.00 (0.00)	0.12
	MC HOME total	0.09 (0.44)	0.85
	Total stressful life event	- 0.08 (0.37)	0.83
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 2.70 (2.30)	0.25
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	1.73 (1.17)	0.43
	Breastfeeding for ≥ 7 months duration	3.49 (2.25)	0.13
	Low income	0.00	
	Middle Income	- 0.48 (1.74)	0.78
	High Income	- 1.96 (1.96)	0.32
	PbB	**- 1.57 (0.54)**	**0.01**
	PbB^2	**0.09 (0.03)**	**0.01**

Note. Blood lead terms are **bold.** FSIQ: Full Scale IQ; Glr: Long-term storage and retrieval; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; n: subsample size; PbB: blood lead; PSI: Processing Speed Index; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition.

[a] $R^2 = 0.13$, Adjusted $R^2 = - 0.02$

[b] $R^2 = 0.24$, Adjusted $R^2 = 0.08$, $\Delta R^2 = 0.11$, ΔF (2, 59) = 4.18, $p = 0.02$.

As shown in Table 57, for the blood lead terms (PbB relative importance metric = 0.10; PbB^2 relative importance metric = 0.06), together account for 16% of the explained variance in Glr. The other most notable contributors were birth weight (relative importance metric = 0.13) and duration of breastfeeding (relative importance metric = 0.28).

Table 57

Relative importance metrics (Glr is the dependent variable; n = 72).

Regressors	Proportion of explained variance
PbB	**0.10**
PbB^2	**0.06**
WAIS-III FSIQ	0.06
Current maternal smoking	0.04
Birth weight	0.13
MC HOME total	0.08
Total stressful life events	0.11
Smoking during pregnancy	0.10
Income level	0.06
Duration of breastfeeding	0.28

Note. Blood lead terms are **bold**. FSIQ: Full Scale IQ; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; *n*: subsample size; PbB: blood lead; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition; WMI: Working Memory Index.

9.4 Summary of multiple regression analyses using the *g* factor and Cattell-Horn-Carol factor scores as the dependent variables

Multiple regression were conducted with using the *g* factor and CHC factor scores as dependent variables in order to explore the contribution of Pb to variance in children's cognitive performance when a range of potential covariates were controlled.

Table 58 summarises the relevant statistics for each model. In sum, in multiple regression analyses, the overall variance in factor scores that was attributed to Pb was modest. The addition of the Pb terms (PbB and PbB^2) to the model of ten covariates only resulted in a significant change in the F statistic when Gs was the dependent variable.

In addition to *g* and the six factors from the CHC, the analyses were also run with the Glr factor which could not be delineated from the data using factor analysis, but for which measures were available to construct an averaged performance score. When multiple regression was run using the Glr performance score, it was found that the addition of the Pb terms (PbB and PbB^2) to the model of ten covariates resulted in a significant change in the F statistic.

It is evident from Table 58 that the model accounted for between 21% and 37% of the explained variance in children's factor scores. Hence, as stated for the multiple regressions presented in Chapter 8, it follows that there is a large amount of variance in children's factor scores (between 73% and 79%) which cannot be explained by any of the variables considered in this study, whether they be familial, socio-environmental, pre-and postnatal covariates or the blood lead terms. The amount of variance that remained unaccounted for by the model suggests that there may be other important influences upon cognitive development that have not been addressed in the current study.

Table 58

Summary of statistics for models using the using the g factor and CHC factor scores as the dependent variables

Factors	R^2	Adjusted R^2	With the addition of the PbB terms		
			ΔR^2	ΔF (2, 59) =	*P*-level
g	0.38	0.25	0.04	1.82	0.17
Gv	0.34	0.21	0.02	0.83	0.44
Gc	0.35	0.22	0.05	2.10	0.13
WM	0.36	0.23	0.05	2.21	0.12
Gf	0.39	0.26	0.01	0.30	0.75
Gs	0.39	0.27	0.07	3.39	0.04
Ga	0.35	0.22	0.05	2.10	0.13
Glr	0.24	0.08	0.11	4.18	0.02

Note. *g* factor: Generalised ability; Ga: Auditory ability; Gc: Crystallised ability; Gf: Fluid ability; Glr: Long-term storage and retrieval; Gs: Speed of information processing; Gsm: Short-term memory; Gv: Visuo-spatial ability; PbB: blood lead; WM: Working Memory factor.

Chapter 10: Exploratory investigations

Chapter Summary

Chapter 10 presents the results of exploratory investigations of the effects of Pb on some contemporary measures of cognitive abilities; Gs Invaders and Picture Swaps.
To explore further the correlations between PbB concentration and Gs Invaders and Picture Swaps (presented in Chapter 9), respectively, multiple regression modelling was conducted with these cognitive abilities as the dependant variables and the same group of variables identified as potential covariates as in previous analyses. In sum, the overall variance in Gs Invaders and Picture Swaps scores that was attributed to Pb, was modest and **t**he addition of the Pb terms (PbB and PbB^2) to the model of ten covariates only resulted in a significant change in the *F*-statistic for Gs Invaders.

In order to provide insights into factors which may significantly impact child PbB levels, Chapter 10 also presents the results of investigations in to the associations between PbB levels and the range of covariates measured in this study. In analyses it was noted that PbB concentration significantly decreased with higher paternal cognitive performance on the SPM and better HOME scores. Furthermore, PbB concentration significantly decreased as family income and parent education increased and as numbers of children in the family decreased; PbB levels significantly decreased with birth order: first born children had lower PbB levels than children born into families with siblings. In summary, it was noted that demographic, familial, psycho-social and environmental and pre - and post-natal variables were differentially and significantly associated with PbB level.

10.1 Exploratory investigations of the effects of lead on some contemporary measure of cognitive abilities

Having established significant inverse associations between PbB concentration and Gs Invaders ($\rho = -0.27$, $p = 0.01$) and Picture Swaps ($\rho = -0.21$, $p = 0.03$; see Table 45) multiple regression analyses were conducted to explore the impact of various covariates on the relationship between PbB concentration and Gs Invaders, and PbB concentration and Picture Swaps.

For each regression model, mother's WAIS-III FSIQ, current maternal smoking, birth weight, MC HOME total, total stressful life events, smoking during pregnancy, income (low, middle, high), breastfeeding (none, breastfeeding for ≤ 6 months duration, breastfeeding for ≥ 7 months duration; see Table 35), were entered first and the apparent 'effects' of Pb exposure were then assessed by entering the linear and quadratic terms of PbB concentration.

10.1.1 Multiple regression with Gs Invaders as the dependent variable

Table 59 summarises the multiple regression with Gs Invaders as the dependent variable. The final model approached statistical significance (F (12, 58) = 1.80, $p = 0.07$) and the Adjusted R^2 indicated that this model accounted for 12% of the variance in Gs Invaders.

In step 1 of the model, the only variable that significantly contributed to variance in Gs Invaders performance was the high income variable (children from high income families scored 7.0 more items correct that children from low income families).

As can be seen in Table 59, in the full model significant contributors were MC HOME total (as the richness of the home environment increased, performance on Gs Invaders decreased; this finding is unexpected), income (children from high income families scored 5.9 more items correct than children from low income families) and PbB concentration (as children's PbB levels increased their performance on Gs Invaders decreased).

Table 59

Multiple regression model with the Gs Invaders as the dependent variable (n = 71)

Model		Unstandardised Coefficient β (Std. Error)	*P*-level
Step 1[a]	(Constant)	51.87 (14.68)	< 0.001
	WAIS-III FSIQ	- 0.06 (0.11)	0.60
	Current maternal smoking	- 3.78 (3.20)	0.21
	Birth weight	0.00 (0.00)	0.20
	MC HOME total	- 1.02 (0.64)	0.12
	Total stressful life events	- 0.16 (0.54)	0.76
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	2.66 (3.41)	0.44
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	4.12 (3.17)	0.20
	Breastfeeding for ≥ 7 months duration	4.71 (3.33)	0.16
	Low income	0.00	
	Middle Income	2.38 (2.60)	0.36
	High Income	6.98 (2.90)	0.02
Step 2[b]	(Constant)	62.5 (14.66)	< 0.001
	WAIS-III FSIQ	- 0.08 (0.10)	0.44
	Current maternal smoking	- 3.55 (3.28)	0.28
	Birth weight	0.00 (0.00)	0.22
	MC HOME total	-1.27 (0.64)	0.05
	Total stressful life event	0.07 (0.56)	0.90
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	2.99 (3.30)	0.37
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	2.91(3.08)	0.35
	Breastfeeding for ≥ 7 months duration	4.65(3.23)	0.16
	Low income	0.00	
	Middle Income	2.70 (2.56)	0.30
	High Income	5.89 (2.84)	0.04
	PbB	-1.58 (0.80)	0.05
	PbB^2	0.06 (0.05)	0.24

Note. Blood lead terms are **bold**. FSIQ: Full Scale IQ; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; *n*: subsample size; PbB: blood lead; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition.

[a] R^2 = - 0.18., Adjusted R^2 = 0.04

[b] R^2 = 0.27, Adjusted R^2 = 0.12, ΔR^2 = 0.09, ΔF (2, 58) = 3.62, p = 0.03.

The change in *F*-statistic (ΔF (2, 58) = 3.62, p = 0.03.) for the Gs Invaders model indicated that the addition of the blood lead terms (PbB and PbB^2) significantly increased the amount of variance in the Gs Invaders performance that was explained by the model.

10.1.2 Multiple regression with Picture Swaps as the dependent variable

Table 60 summarises the multiple regression with Picture Swaps as the dependent variable. The final model was not statistically significant (F (12, 58) = 1.03, p = 0.44) and the Adjusted R^2 indicated that this model accounted for only 1% of the variance in Picture Swaps scores.

Table 60

Multiple regression model with the Picture Swaps as the dependent variable (n = 71)

Model		Unstandardised Coefficient β (Std. Error)	*P*-level
Step 2[b]	(Constant)	10.26 (6.03)	0.09
	WAIS-III FSIQ	- 0.03 (0.04)	0.56
	Current maternal smoking	2.20 (1.35)	0.11
	Birth weight	0.00 (0.00)	0.83
	MC HOME total	0.30 (0.27)	0.26
	Total stressful life event	- 0.47 (0.23)	0.05
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 0.76 (1.36)	0.58
	No breastfeeding	0.00	
	Breastfeeding for ≤ 6 months duration	- 0.90 (1.27)	0.48
	Breastfeeding for ≥ 7 months duration	- 0.37 (1.33)	0.79
	Low income	0.00	
	Middle Income	- 1.02 (1.06)	0.34
	High Income	0.07 (1.17)	0.96
	PbB	- 0.64 (0.33)	0.06
	PbB^2	0.04 (0.02)	0.06

Note. Blood lead terms are **bold**. FSIQ: Full Scale IQ; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; *n*: subsample size; PbB: blood lead; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition.

[a] R^2 = - 0.12., Adjusted R^2 = - 0.03.

[b] R^2 = 0.18, Adjusted R^2 = 0.01, ΔR^2 = 0.06, ΔF (2, 58) = 1.92, p = 0.16.

10.1.3 Summary of investigation of the effects of lead on contemporary measure of cognitive abilities

In sum, in multiple regression analyses, the overall variance in Gs Invaders and Picture Swaps scores that was attributed to Pb was modest. The addition of the Pb terms (PbB and PbB^2) to the model of ten covariates only resulted in a significant change in the F statistic for Gs Invaders. These models only accounted for a small amount of the variance in performance on Gs Invaders and Picture Swaps. This as stated previously, there is a large amount of variance in children's performance on these measures that cannot be explained by any of the variables considered in this study, whether they be familial, socio-environmental, pre-and post-natal covariates or blood lead terms. The amount of variance that remained unaccounted for by the model suggests that there may be other important influences upon cognitive development that have not been addressed in the current study.

10.2 Correlational analyses of associations between potential covariate variables and blood lead concentration

The correlations between untransformed PbB concentration and potential covariate variables (summarised in Chapters 3 and 4) are discussed as an exploratory exercise which contributes to knowledge about factors that may influence children's PbB levels.

10.2.1 Correlations between blood lead concentration and subscales and continuous potential covariates

In summary, the constellation of significant associations between PbB concentration and the continuous variables (presented in Table 61) points to the relevance of familial and care giving factors in children's PbB level. Specifically, PbB concentration was significantly inversely associated with the familial variable of SPM, a measure of paternal cognitive abilities (ρ = - 0.25, p = 0.05). Other significant inverse associations were identified between PbB level and the psycho-social and environmental measure Total MC HOME score (ρ = -

0.35, $p = 0.01$). The remaining correlations between PbB concentration and the potential covariate variables were in the very small to small range, varied in direction and did not reach statistical significance.

Table 61

Unadjusted Spearman correlations between PbB concentration and potential covariates.

Potential covariate		Correlation Coefficient
Demographics		
Parent's years of residence in centre		0.02
Familial		
Maternal cognitive abilities	WAIS-III FSIQ	- 0.15
	Maternal Inspection Time	0.11
Paternal cognitive abilities	Paternal Inspection Time	0.07
	Raven's Standard Progressive Matrices	- 0.25 *
Psycho-social and environmental		
MC HOME Total		- 0.35 **
BDI - II	Maternal	0.04
	Paternal	- 0.01
Total Dyadic Adjustment Scale		- 0.07
Number of recent stressful life		0.17
Recent stressful life events still causing distress		0.06
Pre- and post-natal		
Maternal age at child's birth		- 0.12
Birth weight		- 0.08

Note. BDI-II: Beck Depression Inventory – Second Edition; FSIQ: Full Scale IQ; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; WAIS-III: Wechsler Adult Intelligence Scale – Third Edition.
* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).

10.2.2 Mean blood lead concentration levels for categorical potential covariates

Significant differences in PbB level were identified across the categories of highest level of parental education, family income and birth order (see Table 62 and 63). The difference between categories approached statistical significant for the number of children in family.

It is evident from Table 62 that, for the demographic categorical variable number of children in family, PbB levels increased as the number of children in a family increased. For highest level of parental education, as parents years of education increased from some years of high school (mean PbB = 7.13 µg/dL), through to Year 12 matriculation (mean PbB = 6.05 µg/dL), completion of Technical, Trade or TAFE certificates (mean PbB = 5.19 µg/dL) and to the highest level reported, a University degree (mean PbB = 3.12) µg/dL, children's PbB levels significantly ($\chi^2 = 18.30$, $p < 0.001$) decreased. It was also noted that as annual combined family income increased, children's PbB levels significantly decreased ($\chi^2 = 15.26$, $p < 0.001$).

Of the pre- and post-natal variables summarised in Table 63, only categorical differences for birth order significantly differed ($\chi^2 = 9.70$, $p = 0.01$) where PbB levels increased with birth order. Mechanistically, it is possible that with an increasing number of pregnancies there is increasing accumulated maternal Pb exposure and subsequent bone Pb mobilisation through pregnancy.

No significant differences in child PbB level were identified for the remainder of the demographic and pre- and post-natal categorical variables. Children whose mothers reported current smoking had higher PbB levels than those that do not currently smoke and this difference approached statistical significance ($\chi^2 = 2.99$, $p = 0.08$) and similarly, children whose mothers reported smoking during pregnancy had higher mean PbB levels that children whose mothers did not report smoking during pregnancy but this difference was not significant.

Table 62

Mean PbB levels for each of the demographic categorical variables

Categorical Variables	Categories (*n*)	Mean PbB level (µg/dL; 95% CI)	Difference between categories χ^2 with 1 d.f (*p* value)
Gender	Female (54)	4.40 (3.63, 5.18)	1.62 (0.20)
	Male (52)	5.55 (4.43, 6.68)	
Number of children in family	One child (7)	4.64 (1.09, 8.20)	**7.50 (0.06)**
	Two children (36)	4.08 (3.02, 5.14)	
	Three children (33)	5.22 (3.90, 6.55)	
	Four or more children (19)	6.57 (4.71, 8.43)	
Highest level parental education	Some years of high school (11)	7.13 (4.13, 10.13)	**18.30 (<0.001)**
	Year 12 matriculation (13)	6.05 (3.85, 8.26)	
	Technical, Trade or TAFE certificate (44)	5.19 (4.18, 6.20)	
	A University degree (29)	3.12 (2.39, 3.85)	
Family annual income	≤$20,000 to $50,000 (29)	6.10 (4.64, 7.55)	**15.26 (<0.001)**
	$51,000 to $80,000 (30)	5.56 (4.21, 6.91)	
	More than $81,000 (31)	3.25 (2.56, 3.93)	
Current maternal smoking	No (73)	4.86 (3.98, 5.75)	2.99 (0.08)
	Yes (22)	5.46 (4.23, 6.69)	
Current paternal smoking	No (67)	4.75 (3.85, 5.64)	1.65 (0.20)
	Yes (12)	5.12 (3.69, 6.54)	

Note. Significant differences between groups are **bold**. CI; Confidence Interval; d.f.: degrees of freedom; *n*: subsample size; PbB: Blood lead; TAFE: Technical and Further Education; µg/dL: micrograms per deciliter.

Table 63

Mean PbB levels for each of the pre- and post-natal categorical variables

Categorical Variables	Categories (*n*)	Mean PbB level (µg/dL; 95% CI)	Difference between categories χ^2 with 1 d.f (*p* value)
Birth order	First born child (31)	3.66 (2.84, 4.49)	**9.70 (0.01)**
	Second born child (31)	5.26 (3.69, 6.83)	
	Third born or later child (20)	6.68 (4.85, 8.50)	
Gravidity	0 (29)	4.24 (3.06, 5.43)	4.32 (0.36)
	1 (26)	5.21 (3.49, 6.93)	
	2 (16)	5.14 (3.91, 6.37)	
	3 (13)	5.84 (3.30, 8.38)	
	4 or more (10)	5.12 (3.52, 6.72)	
Gestational age	Less than 37 weeks (4)	6.28 (1.04, 13.59)	0.84 (0.66)
	37 – 40 weeks (33)	5.21 (3.96, 6.45)	
	More than 40 weeks (8)	6.44 (3.10, 9.77)	
Mode of delivery	Vaginal delivery (62)	4.70 (3.94, 5.46)	0.05 (0.81)
	Caesarean (33)	5.40 (3.94, 6.86)	
NICU admission (more than a few hours)	No (76)	5.04 (4.23, 5.85)	0.26 (0.61)
	Yes (17)	4.44 (2.95, 5.92)	
Smoking during pregnancy	No (77)	4.82 (4.02, 5.63)	1.59 (0.21)
	Yes (16)	5.37 (3.86, 6.85)	
Alcohol consumption during pregnancy	No (81)	4.98 (4.19, 5.77)	0.02 (0.90)
	Yes (11)	4.60 (2.94, 6.26)	
Duration of breastfeeding	Not breastfed (10)	5.44 (3.05, 7.83)	0.58 (0.75)
	Breastfed for ≤ 6 months (35)	4.39 (3.48, 5.31)	
	Breastfed for ≥ 7 months (48)	5.02 (3.91, 6.13	

Note. Significant differences between groups are **bold**. CI; Confidence Interval; d.f.: degrees of freedom*; n*: subsample size; NICU: Neonatal Intensive Care Unit; PbB: Blood lead; µg/dL: micrograms per deciliter.

10.2.3 Summary of variables that may impact children's blood lead concentration

The associations between child PbB levels and the range of demographic, familial, psycho-social and environmental and pre- and post-natal variables collected in this study were explored in order to provide insights into which factors may significantly impact child PbB levels. In summary, it was noted that demographic, familial, psycho-social and environmental and pre - and post-natal variables differentially and significantly associated with PbB level, further illustrating the diverse and intersecting range of factors which impact the interaction of Pb and the human body.

Specifically, it was noted that PbB concentration was:

- Significantly inversely associated with *paternal cognitive abilities* (SPM: $\rho = -0.25$, $p = 0.05$).
- Significantly differed across categories for the *demographic* variables number children in family (approached significance as $p = 0.06$), highest level of parental education and family income, such that PbB concentration significantly decreased, as family income and parent education increased and PbB concentration increased as number of children in family increased.
- Significantly inversely associated with the *psycho-social and environmental* measure Total MC HOME score ($r = -0.35$, $p = 0.01$).
- Significantly differed based on the birth order of a child such that PbB levels increased with birth order.

DISCUSSION AND CONCLUSIONS

Chapter 11: Discussion

Chapter Summary

Chapter 11 provides a discussion of the results of this study. First, the study objectives, aims and hypotheses will be reviewed in conjunction with previous research findings. Second, the study is evaluated in terms of its strengths and limitations. Third, the implications of this research will be considered. Fourth, opportunities for future research are discussed.

11.1 Overview of study objectives and findings

Extensive research has confirmed the deleterious impacts of Pb on childhood development. This study responded to recent findings that have suggested that there may be a non-linear relationship between Pb and children's cognitive abilities (Lanphear et al., 2005; Canfield et al., 2005); specifically, Lanphear et al. (2005) identified a steeper dependence of IQ on PbB concentration in the range 1 to 10 µg/dL than in the ranges above 10 µg/dL. While this may seem counterintuitive, a number of potential biological mechanisms to explain such an effect have been proposed (Altmann et al., 1998; Basha et al., 2003; Canfield et al., 2003; Hubbs-Tait et al., 2005; Mudge, 1996; Pilsner et al., 2009; Schwartz et al., 1994; Zawia et al., 2009; Zhou & Suszkiw, 2004). Further investigation of the effects of low-level Pb exposure on children's cognitive performance was warranted to understand the nature of the relationship.

This study sought to determine whether there was an inverse association between children's cognitive abilities and Pb exposure at levels previously thought to be inconsequential (i.e., approximately 10 µg/dL and less); to characterise any association identified between PbB concentration and cognitive abilities; and describe any confounding effects of factors (e.g., demographic, familial, psycho-social and environmental, pre- and

postnatal) that influence the development of children's cognitive abilities; and to determine if certain cognitive abilities were more vulnerable to the deleterious impacts of Pb exposure. Hence children's cognitive abilities were measured through a battery which included the WISC-IV as the primary outcome measure and which was supplemented with tools that measure CHC abilities not measured by the WISC-IV. Factor analytic methods were applied to these data to estimate factor scores based on the CHC model.

Cognitive, demographic, familial, psycho-social and environmental and pre- and post-natal cross-sectional data were collected from 106 families with 7 and 8 year old children (mean age = 7.96 years, *SD* = 0.59) living in the Australian communities of Port Pirie and Broken Hill. Residents of Port Pirie and Broken Hill are exposed to Pb via the smelting and mining industries and children in the sample had mean PbB levels of 4.97 µg/dL (*SD* = 3.52, range = 1.0 – 19.3) and average WISC-IV FSIQ. The majority of children in the sample lived in two parent families with at least one sibling. The families living in Broken Hill tended to have a higher annual income than those in Port Pirie; Broken Hill parents had higher levels of education than parents in Port Pirie. At the time of assessment, the majority of parents in the sample did not smoke cigarettes.

The results of this study will be synthesised and discussed in terms of the main findings, as follows.

Non-linear inverse unadjusted associations between PbB concentration and generalised ability measures and specific abilities were identified.

In unadjusted analyses, as PbB level increased, performance on both the WISC-IV and the CHC factor scores decreased. The magnitudes of these associations were moderate in size. These findings align with previous research that reported significant inverse univariate associations between Pb exposure and a range of cognitive measures (paralleling those measured here) across early to middle childhood (Bellinger et al., 1987; Canfield et al., 2003;

Ernhart et al., 1989; Ernhart et al., 1989; Fergusson & Horwood, 1993; Kordas et al., 2004; Pocock et al., 1987; Pocock et al., 1994; Sovcihova et al., 1997).

The most controversial contemporary issue in our understanding of the effects of Pb in children is around the shape of the curve relating neurodevelopmental outcomes to Pb exposure (as estimated by PbB concentration). The shape of the dose-response of a generalised 'outcome' to a generalised 'toxin' might be expected to be quite flat over a range of very low exposures that are insufficient to have any perceptible effect on the outcome and with adverse impacts only becoming apparent when exposure exceeds some threshold exposure level; moreover as exposure to the toxin increases further, these effects might typically be expected to intensify (see the blue curve in Figure 19).

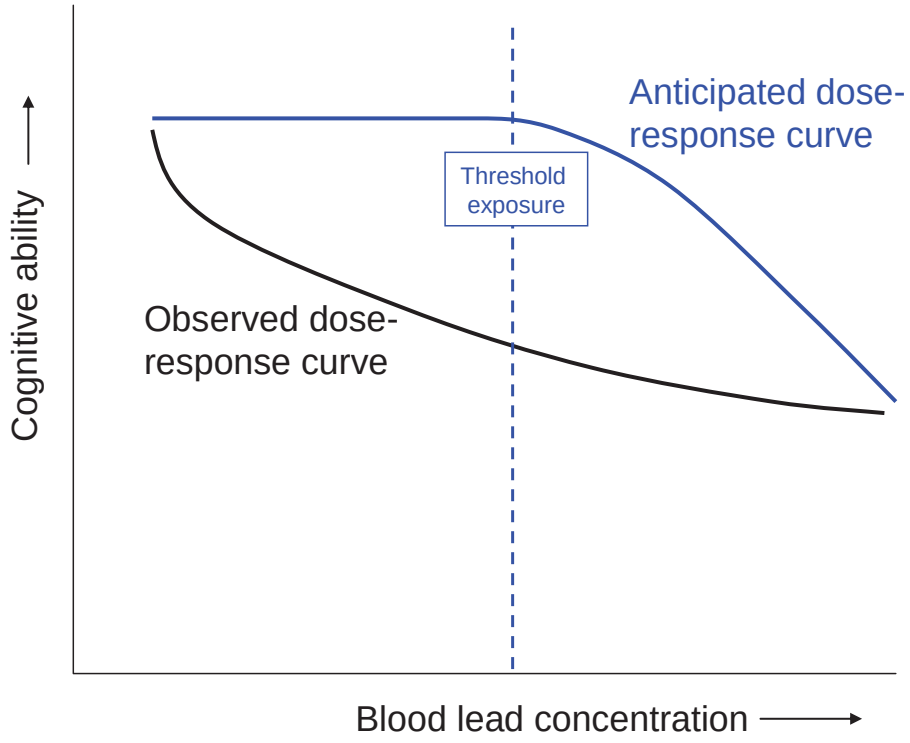

Figure 19

Anticipated dose-response curve between children's cognitive abilities and blood lead concentration (blue curve) and observed dose-response curve between children's cognitive abilities and blood lead concentration (black curve; based on the findings of Canfield et al. (2003) and Lanphear et al. (2005)).

As discussed in the introductory chapters, however, more recent studies (Canfield et al., 2003; Lanphear et al., 2005) have observed an unexpected dose-response in which the apparent effect of exposure to Pb is greatest at very low PbB concentration; and, furthermore, there is no threshold (Chiodo et al., 2004; Schwartz, 1993, 1994); and, the apparent incremental effects of Pb become *less* as exposure increases (see the black curve in the Figure 19).

In this study the shape of the curves of the unadjusted association between PbB concentration and FSIQ and the *g* factor, respectively, were non-linear. The shapes of the curves observed in Figures 16 and 18 were similar to those observed by Lanphear et al. (2005; Figure 1; although Lanphear et al.'s figure was adjusted for HOME score, maternal education, maternal IQ and birth weight) and Canfield et al. (2003; Figure 6); and these curves suggested that the associations between Pb exposure and cognitive performance were steeper at lower Pb exposure levels. The findings of this study add weight to the view that all Pb levels, no matter how low, may detrimentally impact children's cognitive function and that, lower levels of Pb exposure may produce proportionally more insult to cognitive abilities than higher levels of Pb exposure.

Speed of information processing abilities are vulnerable to low-level Pb exposure.

Consistent findings emerged that suggest that low-level Pb may detrimentally impact children's speed of information processing capabilities.

Speed of information processing was gauged initially through the PSI subscale from the WISC-IV (comprised of the Coding and Symbol Search tasks). The contribution of the PbB terms to explained variance in PSI approached statistical significance; however, when relative importance regression was conducted, PbB concentration accounted for the largest amount of explained variance in PSI (25% of explained variance). In addition to administration of the WISC-IV PSI, other measures of speed of information processing (IT and Gs Invaders) were collected allowing estimation of the CHC factor score Gs via

confirmatory factor analysis. In a model using Gs as the dependent variable and including a range of factors believed to impact cognitive development, the addition of the PbB terms significantly increased the amount of explained variance in Gs. Not surprisingly, when multiple regression was run with performance on Gs Invaders as the dependent variable and with a range of variables considered to impact cognitive development included in the model, the addition of the PbB terms significantly increased the explained variance in children's performance on Gs Invaders.

While speed of information processing has been measured previously in the context of Pb-related deficits, it has not been estimated as a broad latent variable. Rather, previous research has centred on the use of RT as a measure of speed of information processing and a significant positive relationship between RT and indices of Pb exposure has been established (Chiodo et al., 2004; Després et al., 2005; Hunter et al., 1985; Lanphear et al., 2000; Minder et al., 1994; Needleman et al, 1979, 1990; Winnecke et al., 1983) such that RT slowed with increasing Pb exposure levels. However, the use of RT is limited by difficulties in distinguishing between cognitive and motor speed; there is some evidence that motor speed is detrimentally impacted by Pb exposure (Dietrich et al., 1993) and this further confounds interpreting any association between RT and Pb levels. The IT task used in this study ameliorates the limitations of motor speed because the stimuli exposure time varies, but participants have unlimited responding time. Minder et al. (1994) have also identified significant associations between performance on the Trail Making Task (viewed as measure of Gs) and Pb exposure. The likelihood that speed of information processing is important as demonstrated by these psychometric evaluations is also supported by previous investigations of the associations between nerve conduction velocity and Pb exposure (Araki & Honma, 1976; Feldman, Haddow, Kopito & Schachman, 1973; Landrigan, Baker Jr., Feldman, Cox, Eden, Orenstein, et al., 1976).

The findings presented here build upon earlier work by using contemporary measures of speed of information processing; our findings indicate that speed of information processing is a cognitive ability which is detrimentally impacted by Pb exposure.

Memory (both working memory and short term memory) are deleteriously impacted by low-level Pb exposure.

When the PbB terms were added to models of the WISC-IV WMI and the WJ-III Glr subscales, the PbB variables contributed significantly more variance in children's memory performance above and beyond the variance already explained by variables considered to impact cognitive development.

WISC-IV WMI is a subscale comprised of children's performance on the Letter-Number Sequencing and Digit Span tasks. Previous research has not reported findings on the WISC-IV WMI subscale (because WMI was not specified as a WISC subscale until the development of WISC-IV), but the Freedom from Distractibility subscale (comprised of Digit Span and Arithmetic subtests from the WISC-III) is arguably similar to WMI. Hence, previous research supports our finding by noting significant inverse associations between PbB concentration and the WISC-III Freedom from Distractibility subscale (Wassermen et al., 1992), as well as tasks such as Digit Span (Chiodo et al., 2004; Lanphear et al. 2000), a 'sequential' factor (comprising Arithmetic, Digit Span and Coding; Caldéron et al., 2001) and Seashore Rhythm Task (Chiodo et al., 2004).

Thorough discussions about models of memory are beyond the scope of this thesis; theoretical models of memory are complex, varied and numerous (Raaijmaker & Shiffrin, 2002). One dominant view defines working memory as "the simultaneous storage and processing of information" (Baddeley, 1992, p. 556). Specifically, working memory is understood to facilitate the processes of language comprehension, learning, and reasoning by providing capacity for temporary storage and active manipulation of information (Baddeley, 1992). Baddeley (1998) also suggested that working memory may include an attentional

control system, referred to as the central executive. This is supported in Mirsky et al.'s (1991) four domain conceptualisation of attention where 'encoding or working memory' is described as a component of attention along with sustained, focused, and shifting attention. Previous research supports the possibility that Pb may detrimentally impact the conceptualisation of working memory offered by Baddeley (1992, 1998); evidence has delineated a detrimental effect of Pb on attentional and cognitive control abilities (Cho et al., 2010; Davis et al., 2004; Nigg et al., 2008), executive functions (Minder et al., 1994), and measures of working memory (Seashore Rhythm Task and the WISC-III Digit Span subtest; Chiodo et al., 2004).

The distinction between 'working memory' and 'short term memory' is equivocal; indeed, Baddeley and Hitch (1974) indicated that short term memory has at times been assigned the role of an "organisational or working memory" (p. 48); short term memory and working memory may be similar or even identical constructs. Mather & Woodcock (2001) defined Glr using the WJ-III battery tasks Visual-Auditory Processing and Retrieval Fluency and while the confirmatory factor analysis undertaken in this study could not estimate this factor based on the data, the Glr subscale could be used. The tasks used by Mather & Woodcock (2001) to comprise Glr are learning and retrieval, and retrieval tasks, respectively, and are comparable to previous research that has shown detrimental impacts of Pb levels on performance on the K-ABC (especially the SIM score; Dietrich et al., 1991), Sternberg Memory Test (Kordas et al., 2006), the Story Memory subtest of the Wide Range Assessment of Memory and Learning (Chiodo et al., 2004) and the Benton Visual Retention Test (Sovcikova et al. 1997).

Regardless of theoretical issues around the definition of memory types, it is evident that the WISC-IV WMI subscale and the WJ-III Glr subscales are both seeking to capture the proficiency with which children can engage, retain and learn information and then actively use this information. Therefore, the current study provides evidence that Pb exposure negatively impacts children's memory performance. The implications of the memory deficits

identified here are broad; as Baddeley and Hitch (1974) indicated, hypothetical memory systems, regardless of their nomenclature and specific structure, have been shown to be important in numerous tasks pertinent to activities of daily living and educational attainment such as problem solving, language acquisition and learning. More generally, "[m]emory, in one form or another, enters into virtually all cognition" (Conway, 1997, p.1).

On the whole, the variables that consistently explained the most variance in cognitive performance were incidence and duration of breastfeeding and family income level.

As summarised in Chapters 2 and 3, and in Table 14, previous research has investigated the associations between Pb exposure and a range of children's cognitive outcomes, studying potential confounders to this relationship, and identifying various cognitive outcomes of interest. This study has not identified Pb as a significant contributor to variance in *all* cognitive abilities considered here (e.g., in multiple regressions with FSIQ, VCI, PRI, the *g* factor, Ga, Gv, Gc, Gsm, Gf as the dependent variables); a finding which contrasts previous research (see Table 14). However, as in previous research, this study did note that, on the whole, socio-economic and environmental variables explained more variance in cognitive performance than Pb exposure.

In this study, the variables that consistently explained the most variance in cognitive performance were breastfeeding (no breastfeeding, breastfeeding up to 6 months duration, breastfeeding longer than 6 months duration) and family income level (low, middle, high income). Table 64 summarises the unstandardised coefficients for the breastfeeding and income variables for the full multiple regression model using the WISC-IV and CHC factor data as dependent variables; it is evident that the relative contribution of breastfeeding, income and other variables varied somewhat across the models and that breastfeeding and income level were particularly important contributors to variance in FSIQ. Other variables that significantly contributed to the models also presented in Table 64; these variables

included PbB concentration, current maternal smoking, smoking during pregnancy and recent stressful life events.

The observation that, on the whole, sociodemographic variables[22] like the incidence and duration of breastfeeding and family income level consistently explained the most variance in cognitive performance, supports the importance of environmental factors in children's neurodevelopment. The findings presented here quantify the differences in children's cognitive performance across sociodemographic variables and this supports the work of intervention programs which seek to support children's cognitive development by enhancing their environment. As an example, for the FSIQ model, compared to children who were not breastfed, children breastfed for up to 6 months duration and children breastfed for longer than 6 months duration had FSIQ scores on average 11.0 and 10.7 FSIQ points higher, respectively[23]; compared to children from low income families, children from middle and high income families had FSIQ scores 7.2 and 8.6 FSIQ points higher, respectively. This finding also places discussions about the impacts of Pb on children's cognitive ability into a relative context; the insults to IQ attributed to Pb were smaller in magnitude than those linked with other environmental variables.

[22] While acknowledging the potential nutritional benefits of breastfeeding, authors have suggested that breastfeeding may be a proxy for environmental, familial and socioeconomic factors (Daniel & Adair, 2000; Horwood & Fergusson, 1998; Kelly & Watt, 2005); this is further discussed in section '11.2.2.5 Is Breastfeeding a sociodemographic proxy?'

[23] Of note, IQ discrepancies noted in this study are greater than those identified previously in Anderson et al.'s (1999) meta-analysis where breastfed children scored approximately 3.16 (95% CI: 2.35, 3.98) IQ points higher than children who were not breastfed.

Table 64

Summary of the unstandardised coefficients of variables that were statistically significant (≤ 0.05) or approached statistical significance (≤ 0.10) for each full multiple regression model.

WISC-IV subscales & CHC factors		**Breastfeeding**			**Income**		**Other variables** (unstandardised coefficient)
		Breastfeeding up to 6 months duration	Breastfeeding longer than 6 months duration		Middle	High	
FSIQ	**Compared to children who were not breastfed**	11.00	10.68	**Compared to low income families**	7.19	8.57	PbB (- 2.26)
VCI		9.74	-		6.83	-	-
PRI		11.46	10.85		-	-	-
WMI		-	11.88		-	-	PbB (- 3.71)
PSI		-	-		6.89	9.84	Current maternal smoking (- 0.68) PbB (-2.69)
g		1.23	1.67		-	-	PbB (- 0.31)
Gv		1.65	2.38		-	-	Smoked during pregnancy (- 1.84)
Gc		1.95	1.69		1.48	-	-
WM		-	1.24		-	-	PbB (- 0.28)
Gf		-	0.98		-	-	Total stressful life events (- 0.17); Smoked during pregnancy (- 1.01)
Gs		-	-		0.77	1.06	PbB (- 0.31)
Ga		4.27	5.87		-	-	PbB (- 1.07)
Glr		-	-		-	-	PbB (- 1.57)

Note. (-) indicates that the unstandardised coefficients were not significant (≤ 0.05) and did not approach significance (≥ 0.10). FSIQ: Full Scale IQ; *g* factor: Generalised ability; Ga: Auditory ability; Gc: Crystallised ability; Gf: Fluid ability; Glr: Long-term storage and retrieval; Gs: Speed of information processing; Gsm: Short-term memory; Gv: Visuo-spatial ability; PbB: blood lead; PRI: Perceptual Reasoning Index; PSI: Perceptual Speed Index; VCI: Verbal Comprehension Index; WISC-IV: Wechsler Intelligence Scale for Children-Fourth Edition**;** WM: Working Memory factor; WMI: Working Memory Index.

Higher PbB levels were significantly associated with lower paternal cognitive ability, parental education level, combined family income, quality of the home environment, larger family size, and later birth order.

The associations between child PbB levels and the range of demographic, familial, psycho-social, environmental, and pre- and post-natal variables collected in this study were explored in order to provide insights into factors that impact child PbB levels.

Specifically, PbB concentration was significantly inversely associated with paternal cognitive abilities, and MC HOME. In addition, PbB levels significantly differed across categories for the number of children in the family (this association approached significance), highest level of parental education and family income, such that PbB concentration significantly decreased, as family income and parent education increased and PbB concentration increased as number of children in family increased and was related to birth order such that PbB levels increased with birth order. On the whole these variables can be viewed as expressing some characteristics of the sociodemographic profile of families.

These findings further support the idea that Pb exposure is an enviromental pollutant with sociodemographic associations such that disadvantaged families are disproportionately exposed to the toxin. As noted in Chapter 5, the participants in this study are exposed to Pb primarily because they reside in communities built around the mining and smelting of Pb ore. It is interesting that even in the context of these relatively small communities, there is a clear trend where children from more disadvantaged families had significantly higher PbB levels than more advantaged families. For health authorities operating in Port Pirie and Broken Hill this information supports initiatives that have been undertaken to combat Pb exposure by supporting low SES families (e.g., in Port Pirie the South Australian Government's Port Pirie Lead Implementation Program runs initiatives to educate families about the risks of Pb exposure, help families obtain washing machines, ensure children have a nutritious breakfast and provide weekend vacuum cleaner loans for removal of ceiling and carpet dust; see

Appendix A for a summary of efforts to reduce lead exposure in Port Pirie and Broken Hill). These findings further reinforce the idea that Pb exposure is an "environmental injustice" (WHO, 2010, p.35) that continues to warrant consideration.

11.2 Commentary on this study

The strengths and limitations of the current study will be reviewed as both an evaluative process and to highlight opportunities for optimising future research.

11.2.1 Strengths

A strength of this study was the approach to measurement of children's cognitive abilities which was designed to:

1. Be comparable to previous research in the field through the use of the Wechsler Scales to assess children's cognitive abilities; and
2. Build upon previous research by assessing other aspects of children's cognitive function guided by CHC theory. Measures such as the WJ-III subtests, IT, Picture Swaps and Gs Invaders had not been previously used in the context of Pb exposure research, and Ga had only been previously considered in the CLS and by De la Burdé & Choate (1975); hence this study was designed to elaborate knowledge about the impacts of Pb upon a broad range of children's cognitive abilities.

In addition, this study sought to thoroughly measure potential covariates to the association between Pb and children's cognitive abilities. In particular, covariate measurement sought to expand beyond previous research by considering the potential impacts of:

- Paternal cognitive ability (as measured by SPM and IT); a covariate which had only been previously considered by Cooney (1989; using the PPVT).
- Parental mental health (as measured by the BDI-II); only Fulton et al. (1987) had previously considered both maternal and paternal mental health. Other studies focused

on maternal mental health challenges (Després et al, 2005; Pocock et al., 1987).

Quality of dyadic relationship (as measured using the DAS); a variable that had not previously been measured using a validated psychometric tool.

This study had several strengths and innovations in its design; the approach to measurement of children's cognitive abilities allowed comparability to previous research while including measures that had not been administered previously in the context of Pb research and which were guided by the CHC model of intelligence. In addition, this study sought to build upon previous research by measuring potential confounders such as paternal cognitive ability, parental mental health and quality of dyadic relationship.

11.2.2 Methodological and theoretical limitations of the study and resultant dataset

It is important to place the findings from the current research program into the context of factors that have limited or otherwise influenced the dataset. As acknowledged in the introductory chapters of this thesis, cross-sectional research is limited because causal inferences regarding the association between variables cannot be made, temporal changes in Pb levels are not taken into account, and selection biases are possible (Tong, 1995). This section will consider and discuss other potential limitations to this study such as the sample size, covariate selection, whether breastfeeding may be a proxy for other variables and reverse causality

11.2.2.1 Sample size

Given the goal of this study - to investigate the associations between Pb exposure and cognitive abilities using one contemporary view of the taxonomy of intelligence and coupled with thorough assessment of potential covariates, it was recognised that a large sample size would be required to have the statistical power to address these complex questions.

As stated in Chapter 2, it is acknowledged that the smaller than planned sample size in this study diminishes the robustness of conclusions drawn from this study. As Eng (2003) has

emphasised, the power of a statistical test must be sufficient for the detection of an effect to be identified if there truly is one. If sufficient power is not achieved, the importance of issues related to underpowered studies is heightened when non-significant effects are identified. Given the wealth of previous research providing support for the detrimental impacts of Pb exposure on children's cognitive abilities (when covariates are controlled) as summarised in Chapters 2 and 3 and especially in Table 14, it is arguable that there was inadequate sensitivity in this study to capture effects at the traditional $p < 0.05$ level. Therefore, the effect sizes found must also be considered.

Given the poor recruitment rate of participants into this study, it is useful to consider limitations to the study design that may have hindered enrolment into this study.

11.2.2.2 Comment on challenges to study recruitment

Patel, Doku and Tennakoon (2003) describe participant 'recruitment' as a discursive process between the researcher(s) and potential participants, which seeks to facilitate informed consent. Recruitment is driven by the researchers' planning, which follows a stepwise and strategic process; identifying the study population, disseminating information about the study, approaching potential participants and then securing participant's informed consent (Patel et al., 2003). As an evaluative exercise, Patel et al.'s (2003) description of the components of the recruitment process was applied to the experience of this study:

- *Identification of the study population:* This research clearly delineated the population of interest as families residing in Port Pirie and Broken Hill with children in the age range 7-to-8 years. These communities were targeted due to their higher level of Pb exposure than the general population, levels that are more likely to represent exposures up to and beyond 10 µg/dL. Given the *a priori* power projections and the populations of these centres, it was anticipated that there were a sufficient number of families in each region with children in the 7-to-8 year age range to meet the sample size targets of 300 families.

- *Engagement with possible participants and dissemination of information about study*: First and foremost, families in each region were engaged using their child's primary school. This approach was favoured because it offered a comprehensive and efficient way to connect with all families as their child approached the targeted age range. Additionally, approaching families through the school system may have made the study less threatening to them. We did not have access to contact details of families in each school because this would have violated confidentiality. Families could only be contacted through a standard information sheet and invitation letter, which was sent home with the target child. These letters were sent home as each new cohort of children approached the age of interest. It is possible that children may not have delivered letters to their parents but this cannot alone account for the recruitment difficulties that were experienced because over the course of the study a number of additional activities were undertaken to bolster recruitment, including community information sessions run by the research team (these sessions sought to encourage community dialogue and education about the project), the publication of articles in the local newspapers and the distribution of biannual newsletters (these were authored by the principal investigator to the supporting NHMRC grant, P. Baghurst) and were sent to participants to maintain their interest and involvement in the research; see Appendix I).
- *Securing informed consent:* Information letters (as well as information sessions and newspaper articles) invited possible participants to telephone the research assistants to discuss their family's involvement in the study and to answer any questions or address concerns. The research assistants involved in the study were residents of each centre and this was viewed as advantageous because families were approached by community members, rather than 'outsiders' who may have been perceived as not grasping the complexity and contentious nature of issues raised by this research. This advantage may have been offset by the possibility that families felt uncomfortable sharing sensitive information with a local community member; a challenge often necessarily negotiated by

health professionals in regional communities (Australian College of Rural and Remote Medicine, 2011; Warner, Monaghan-Geernaert, Battaglia, Brerns, Johnson & Weiss Roberts, 2005).

Rather than there being specific limitations to the study design, it seems likely that a constellation of historical, community, economic and individual factors, interacted to diminish our study's capability to recruit a sample that provided sufficient sample size and therefore statistical power to address the questions of interest (Patel et al. 2003). A thorough discussion of the historical, community and economic factors impacting study recruitment is presented in Appendix M.

It is worth noting that this study was also challenged by the secondary repercussions of slow recruitment such as evolving changes to timelines and planning, increased funding and resource pressures, a preoccupation of staff with recruitment rather than assessment, and a decline in staff morale. While Patel et al. (2003) have reported that the culmination of pressures linked to recruitment difficulties can often mean that research programs are aborted, this research continued with the view that the data and subsequent analyses obtained are a contribution to the field, albeit a potentially limited one.

11.2.2.3 Identification and inclusion of covariates in multiple regression modelling

This study sought to account for the potential confounding effects of variables known to impact cognitive development. The measurement of potential covariates was informed by previous research and broader theoretical perspectives.

In this study the variables that met the criteria for inclusion in multiple regression were demographic, familial, psycho-social and environmental and pre- and post-natal in nature. These variables were included in multiple regression models based on their significant associations with FSIQ. It is noted that previous research (Bellinger et al., 1992; Chiodo et al., 2004) has taken a more stringent approach to the measurement of confounders to the Pb – cognitive abilities relationship by adjusting for variables that may impact cognitive

development and/or Pb level. While this study did not explicitly undertake such an approach, comparison between variables identified for inclusion in multiple regression modelling (based on their associations with FSIQ) and those identified as significantly associated with PbB levels revealed a substantial overlap; MC HOME significantly correlated with both FSIQ and PbB concentration, as did measures of parental cognitive abilities, demographic variables, and pre- and post-natal variables.

It is recognised that in this study the potential covariates identified for measurement and those included in multiple regression modelling were neither definitive or exhaustive. Using the example of Gs, the model constructed accounts for 27% of the variance in Gs performance and the amount of variance that remained unaccounted for by the model (73% of variance unaccounted for) suggests that there may be other important influences upon cognitive development that have not been addressed in the current study. Bellinger (2004a) has stated that there is "no logical end point" (p. 384) to the plethora and iterations of variables that could be considered as potential covariates in studies of environmental neurotoxicant exposure and children's development. While acknowledging Bellinger's (2004) view, there were a number of variables that were not considered as covariates in this study; in particular children's experiences of stress, nutritional levels and attachment relationships will be discussed as potential contributors to the association between Pb exposure and children's cognitive abilities:

- **Children's experiences of stress**: Children's experiences of stress is a potential covariate that could have been considered in this study; empirical evidence suggests that stress can negatively impact children's cognitive function (see White, Cory-Slechta, Gilbert, Tiffany-Castiglioni, Zawia, Virgolini, et al., 2007, for a thorough discussion) and that the psychological and physiological impacts of stress can actually modify the effects of environmental Pb exposure, in sum that "an equivalent level of exposure causes greater injury in stressed subjects" (WHO, 2010, p.35). While this study used the RLE to measure recent family experiences of trauma and stress (with

the view that these may have impaired family functioning and the availability of caregivers), the RLE did not directly assess children's experiences of stress. Indeed, adults and children not only experience and respond to stress differently but find different experiences and events to be stressful.

- **Children's nutritional levels**: Based on empirical evidence and prior research in the field[24], children's nutritional levels could have been considered as a potential covariate to the association between PbB concentration and children's cognitive abilities. Evidence suggests that poor diets can fail to provide the developing brain with sufficient nutrients for appropriate growth and development (Grantham-McGregor & Ani, 2001). Specifically, Grantham-McGregor and Ani (2001) note associations between iron deficiency (and anaemia) and suboptimal cognitive development, social achievement and poor behaviour. Bryan, Osendarp, Hughes, Calvaresi, Baghurst & van Klinken (2004) also indicate that nutrients such as iodine and folate play important roles in infant and childhood cognitive development and that zinc, vitamin B_{12}, and omega-3 polyunsaturated fatty acids may also be beneficial to cognitive outcomes.
- **Children's attachment relationships**: The role of caregiver attachment[25] is being increasingly recognised as being pertinent to childhood cognitive and emotional development (Binns et al., 2007). The use of the MC HOME in this study captured some components of the relationships between children and their caregivers through sections which address emotional and verbal responsivity of caregivers, 'emotional climate' and parental involvement (see Appendix H); it would, nevertheless, be useful

[24] Children's nutritional status was a variable considered as a potential covariate in the research of Calderón et al. (2001) and Després et al. (2005). More specifically, Calderón et al. (2001) and Canfield et al. (2003) measured children's iron levels, while Cooney et al. (1989), Wasserman et al. (1992) and Rahman et al. (2002) considered growth variables (such as height, weight and head circumference) and the Port Pirie Cohort collected data about maternal Body Mass Index and maternal nutritional practices.

[25] Attachment is defined as a close enduring affectional bond between two people (Ainsworth, 1989) and typically the primary attachment figure develops in parent-child dyads. According to Bowlby (1969) attachment bond development is virtually universal; however, individual differences exist because "attachment behaviours...respond to adverse family conditions in the form of increased insecurity" (Magai, 2001, p.406).

to further explore the potential contribution of attachment relationships to the explained variance in cognitive abilities.

11.2.2.4 Is ‘breastfeeding’ a sociodemographic proxy?

Based on the pattern of unstandardised coefficients summarised in Table 64, an issue for consideration is whether the breastfeeding variable collected in this study may have been a proxy for other factors.

Incidence and duration of breastfeeding have been considered as potential covariates to the association between Pb and cognitive abilities in the research of McMichael et al. (1992) and Fergusson and Horwood (1997). A number of research studies have confirmed the positive impacts of breastfeeding on childhood cognitive development (Anderson et al., 1999; Bartels, van Beijsterveldt & Boomsma, 2009; Daniels & Adair, 2000, Horwood & Fergusson, 1998; Jacobson, Chiodo & Jacobson; 1999). In Chapter 2 of this study, ‘breastfeeding’ was framed as a nutritional variable and, indeed research suggests that early brain development may be enhanced by the uptake of the fatty acids that breastfeeding facilitates (Caspi, Williams, Kim-Cohen, Craig, Milne, Poulton et al., 2007).

However, other authors have suggested that breastfeeding may be a proxy variable for environmental, familial and socioeconomic factors that have been discussed as potentially enhancing cognitive development (see Chapter 5 for an overview). For example, Horwood and Fergusson (1998) observed that compared to mothers who did not initiate breastfeeding with their children, mothers who breastfed could be characterised as:

- Being an older age at child’s birth;
- more highly educated;
- nulliparous;
- from upper SES families, with above average income and living standards;
- in a romantic relationship;
- not having smoked during pregnancy;

- as having higher IQ;
- possessing better parenting skills; and
- giving birth to higher birth weight babies.

Other researchers have hypothesised that breastfeeding may enhance cognitive development by positively impacting mother-child attachment and maternal hormonal responses that counter postnatal depression and, in turn, increase the emotional availability and provision of infant care (Daniel & Adair, 2000). Suggesting that breastfeeding may reflect markers of SES (such as, occupation and family income). Kelly and Watt (2005) also observed that mothers employed in positions that were routine and inflexible were more than four times less likely (OR, 0.22, 95% CI = 0.18, 0.29) to breastfeed their children, as compared to women employed in the professions and managerial positions.

Many of the variables conceptualised as confounders to the breastfeeding and cognitive outcomes association were assessed in this study and included in our cognitive ability multiple regression models – for example, maternal smoking during pregnancy, birth weight, income level, maternal IQ and HOME scores; and in spite of the inclusion of these variables in our models, breastfeeding practices still emerged as a key contributor to variance in children's cognitive performance. The study also collected data on variables such as mother's age at birth of child, parental education, gestation, birth order, but these variables did not meet criteria to be included in multiple regressions.

As an exploratory exercise, multiple regressions using FSIQ as the dependent variable were rerun substituting the breastfeeding variables with mother's age at child's birth, highest level of parental education, gestation and birth order. These models are summarised in Appendix N, and it is evident that while each of the four models was statistically significant; only maternal age at birth contributed significantly to the full model ($p = 0.01$); children's FSIQ increased with maternal age. This investigation suggests that perhaps the breastfeeding variable and maternal age at birth, measure something similar which helps to explain variance in children's FSIQ; older mothers are more likely to be more educated and to make informed

decisions that are beneficial to their child's development and are indicative of some characteristic of maternal care giving that may increase with maternal maturity. The unique contribution of breastfeeding to variance in children's FSIQ is certainly an intriguing finding and one which would be worth further investigation.

11.2.2.5 Reverse Causality

Reverse causality, in which Pb-induced cognitive deficits may increase Pb exposure or further disrupt children's learning and cognitive function, may bias associations between Pb and cognitive abilities. A classic example of reverse causality in the context of Pb research is the scenario where children with diminished cognitive function may engage in behaviour which places them at greater risk of Pb exposure (such as pica and geophila which is inappropriate for their chronological age).

In terms of this study of school-aged children, research has established links between Pb exposure and behavioural problems in children (Dietrich, Ris, Succop, Berger, & Bornschein, 2001), hence it is possible that Pb exposed children may exhibit behaviour which negatively impacts their cognitive development and IQ by disrupting school performance, learning, uptake of information and diligence (Wasserman et al., 1998). In order to address such issues, this study may have considered collecting information about children's behaviour in early childhood (for example, parent reports of incidence of pica) or multi-informant (parent and teacher) ratings of children's current behaviour; such information may have enabled comments about reverse causality to be made for the current dataset.

11.2.2.6 Measurement limitations

Blood lead as an exposure marker

This study utilised capillary PbB concentration as a marker of Pb exposure. Having discussed the limitations of PbB as an exposure marker, his section will also consider the

uncertainty associated with PbB collection and the time lag between cognitive assessment and PbB sampling in this study.

Binns et al. (2007) argued that, as in any biological measure, analysis of PbB sampling is prone to analytical errors and collection contamination which can diminish the integrity of a sample. In terms of the threat of contamination and collection errors at the time of PbB sampling, the Environmental Health Centres in Port Pirie and Broken Hill each abide by strict protocols to maintain the integrity of their sampling. Parsons et al. (1997) documented within and between-collector variability in their study of capillary PbB sampling procedures due to inconsistent adherence to collection protocols; hence it is recognised that even in the context of collection protocols, the capillary PbB samples collected in this study are prone to contamination which diminishes the accuracy of Pb estimates and conclusions about the association between PbB levels and children's cognitive abilities.

As summarised in Chapter 5, the collection of PbB concentration samples in this study was delayed by procedural changes at the major analysis facility in Adelaide, the Institute of Medical and Veterinary Science. Hence, across the sample of 106 children in this study there was variation in:

- The age of children at the time of PbB sampling; and/or
- The time between cognitive assessment and PbB sampling.

It is acknowledged that PbB sampling inconsistencies make this study vulnerable to criticism; indeed, it is possible that children's PbB levels may have fluctuated (increased or decreased) in the period between cognitive assessment and Pb sampling due to environmental exposure changes (e.g., seasonal change, procedural changes at the mine or smelter, Pb remediation programs occurring in the child's environment), changes in nutritional intake, or growth of the child.

In response to this potential limitation a number of comments are made that support the view that the described time lag is not a substantial threat to the study's validity:

- *The deleterious effects of Pb exposure are associated with Pb exposure at any age* (Binns et al., 2007); prospective studies have shown that cognitive performance at a given age is significantly associated with both concurrent PbB levels and PbB levels measured in earlier life.
- *Childhood PbB levels show age-related trends and are relatively stable by 7-to-8 years of age***;** evidence from the prospective studies (Boston, Cincinnati, Port Pirie, Sydney and Mexico City) suggests that PbB levels tend to peak between 18 and 36 months of age due to children's locomotive and exploratory patterns, and then decrease and stabilise in early-to-middle childhood. It can be assumed, therefore that, even in communities where environmental Pb exposure is pervasive such as in Port Pirie and Broken Hill, children's PbB levels follow these normative trends and that PbB levels stabilised by the time of assessment and PbB sampling were conducted.
- *The chronic Pb exposure of children in this sample means that their Pb levels may be more stable than the general population***.** Binns et al. (2007) reported that PbB levels gradually decrease over the weeks and months following exposure, eventually achieving equilibrium with the Pb stored in bone. In particular Binns et al. (2007) indicated that for "children with chronic lead exposure and presumably greater bone lead stores, the decline in [blood lead levels] can take much longer" (p. 1287). Due to the chronic exposure of children in this sample their PbB levels may fluctuate less than in the general population, meaning that the time-lag between Pb measurement and cognitive assessment may not be problematic.
- *Reductions in PbB levels follow a slow trajectory and this time frame would be lengthened in the case of chronic PbB exposure (Roberts, Reighart, Ebeling & Hulskey, 2001).* Roberts et al. (2001) quantified the amount of time required for children's (*N* = 579) PbB levels to fall below 10 µg/dL when case management was implemented. The authors found that PbB levels in the ranges:
    - 25 - 29µg/dL required 24 months to decline to less than 10 µg/dL.

- 20 – 24 µg/dL required 21 months to decline to less than 10 µg/dL.
- 15 – 19 µg/dL required 14 months to decline to less than 10 µg/dL.
- 10 – 14 µg/dL required 9 months to decline to less than 10 µg/dL.

Roberts et al.'s (2001) research quantified that, even with case management, reduction in PbB levels follow a slow trajectory (likely to be slower in the case of chronic exposure).

Even though the mean time elapsed between cognitive assessment and PbB sampling in this study was 21.4 months (*SD* = 12.0; range = approximately 5 months prior to cognitive assessment to 48 months post cognitive assessment), it seems unlikely that children's PbB levels would have varied significantly between cognitive assessment and PbB sampling, especially given the possibility that their kinetic trajectories would be slowed due to chronic Pb exposure.

Measures of cognitive abilities

In designing this study, efforts were made to include cognitive measurement tools that were informed by empirical evidence, had robust psychometric qualities, and strict administrative protocols.

The primary measure of children's cognitive abilities used in this study was the WISC-IV and this was supplemented with measures seeking to capture aspects of CHC theory not captured in the WISC-IV. The Wechsler scales have strict administration standards, which intend to limit variation in test administration. As outlined in Chapter 5, the research assistants employed in this study were trained in the administration protocol of the WISC-IV, WAIS-III and the other measures that comprised the children's cognitive assessment battery, with the intention of ensuring the quality and accuracy of collected data.

While it is possible that administration may have diverged from protocol, the nature of the tests administered meant that there was relatively limited opportunity for interpretative or scoring errors in this study. All non-computerised measures were scored initially by the research assistant and then rescored at the Public Health Unit, at the University of Adelaide.

This cross-checking minimised the threat of calculation and scoring errors. Some subtests of the WISC-IV such as Vocabulary, Similarities and Comprehension, require the scoring of a verbal response. For these subtests it was routine for examiners to record a participant's response verbatim and this allowed the scoring for these subtests to be cross-checked. Hence, efforts were taken to ensure the validity and reliability of the cognitive data collected in this study.

Measurement of potential covariates

As Bellinger (2004a) has indicated, in research investigating the associations between children's cognitive outcomes and toxin exposure, uncertainties and errors associated with the measurement of covariates can be more problematic than choice of confounders to be measured.

Reflecting upon the current study, some limitations in the collection of maternal reports of pre- and post-natal data were identified and inaccuracies in these variables may have reduced the integrity of the models developed to explore the associations between PbB and children's cognitive abilities (e.g., due to inaccurate responding on some pre- and post-natal variables may have been overlooked for inclusion in regression models). For example, analyses revealed discrepancies between maternal reports of:

- Gravidity and parity: Mothers reported higher mean parity than mean gravidity; higher gravidity than parity is possible due to fetal loss, but reports of more live births than pregnancies were not feasible. This discrepancy could have been addressed by wording questionnaire items more clearly especially given that some mother's in the sample gave birth to twins (multiple births are considered a single gestational and parous event).
- Gestational age and preterm birth: Missing gestational age data suggested that either mothers did not remember their child's gestational age or that they may not have understood the term 'gestational age'. Maternal responding also revealed some

confusion about the definition of preterm birth (birth ≤ 37 weeks gestation); some mothers reported a gestational age consistent with delivery at full term but 'ticked' that their child was born preterm. The accuracy of maternal reporting may have been aided by (a) providing further explanation of terminology (such as gestational age and preterm birth), (b) asking mothers to indicate if they were uncertain of the accuracy of their responses, or (c) seeking to verify the information provided by mothers by accessing children's pre- and post-natal data through medical records[26].

Another limitation was identified in the measurement of the breastfeeding variable; while this study asked mothers to record the number of months of breastfeeding undertaken (it was assumed that 'zero' months meant that breastfeeding was not initiated), this approach did not measure the incidence of mixed methods of feeding (combinations of breast milk and/or milk formula and/or solids; Doyle & Timmins, 2008)[27]. This oversight oversimplified the breastfeeding practices of mothers in the sample by not capturing variations in breastfeeding practices. Since the breastfeeding variables were important contributors to the multiple regression models constructed in this study, the inclusion of a breastfeeding variable constructed with more sensitivity and specificity may have differentially contributed to the regression models.

11.2.2.7 Possible Biases

Selection biases

Selection biases can diminish the degree to which a sample is representative of the general population or in the case of this research, the populations of Port Pirie and Broken Hill. Given that this study suffered from recruitment difficulties, it may be especially prone to selection bias because more families were approached to participate than those that actually

[26] Although obtaining information from medical records was beyond the resources of the current study and was complicated by consent issues.

[27] Doyle and Timmins (2008) defined 'exclusive breastfeeding' as the number of weeks the child was exclusively fed breast milk from birth, whereas 'non-exclusive breastfeeding' was defined as the number of weeks the child was fed both breast milk and some other form of supplementary formula or solids.

took part. Specifically, this study suffered from what Patel et al. (2003) deemed "non-response and the resultant selection bias" (p. 229).

Reflecting upon this, it is plausible that this study and its design appealed to some community members but not others. It is recognised that the nature of research into cognitive functioning and Pb exposure is controversial and these topics can be emotionally and politically loaded when considered separately and, even more so, when considered together. It is possible that this study may therefore have attracted:

- Parents with concerns about their child's functioning (e.g., based on their observations and feedback from their school or health professionals);
- Parents who already felt confident about the cognitive abilities of themselves and their child, potentially experiencing the study as an opportunity for positive reinforcement about their family's cognitive functioning; and/or
- Parents involved in the health and education sectors who may understand the intricacies of debates about Pb related detriments to functioning and view research as a worthwhile platform for policy change.

By the same token, this study may have not interested:

- Parents insecure about their own abilities and for whom one-on-one cognitive testing may be threatening;
- Families who rely on the mining or Pb smelting industry for their livelihoods;
- Parents who viewed this research as contentious and families who felt that involvement could compromise their employment and/or community standing;
- Families who could not make the time commitment required for the assessment due to factors such as family structure (e.g., single parent families, large families with competing needs of children) or employment (e.g., parents who were not able to take time off work to participate);
- Parents who did not want their child to spend time away from the classroom during the school day; and/or

- Participants who may have felt uncomfortable because the research assistants collecting the cognitive data were community members.

With hindsight it is recognised that some questions relating to selection bias could have been addressed in the study design by gathering information about the families that declined participation. However, unlike studies based in settings, such as in-patient hospital wards (where consent can be obtained face-to-face, and where follow up questions can be posed to participants who decline involvement), this study was challenged in that it sought to recruit participants from two cities through the organisational infrastructure of the primary school systems. Parents were recruited through information packs and were asked to contact the research assistants if they were interested in participation; thus, in this study it was not feasible to request parents to provide information about their reasons for not participating.

Measurement biases

While the research assistants assessing children in this study were blind to the PbB levels of each child, family members who provided information about their child were not blind to this information. Because routine early childhood screening programs are established in both Port Pirie and Broken Hill in order to identify at-risk children, it is probable that parents may have had prior knowledge of their child's current and past exposure levels. This knowledge could have influenced parents in two ways:

- It is possible that parents may have overstated their child's difficulties due to knowledge of the links between Pb and cognition and behaviours.
- Parents reporting information about their home environment, mental health, and relationships may have underreported or denied difficulties due to a desire to understate the impacts of Pb exposure (perhaps due to some investment in the industry, or exhaustion over the perceived stigma associated with Pb exposure in these communities).

11.3 Implications of the current research

Deleterious effects of low-level Pb exposure on children's cognitive abilities were noted in this study and supported in previous research (Lanphear et al., 2000; Canfield et al., 2003; Bellinger & Needleman, 2003; Wasserman et al., 2003; Lanphear et al., 2005; Hu et al., 2006; Kordas et al., 2006; Schnaas et al., 2006; Surkan et al., 2007). Broadly speaking, evidence that low-level Pb exposure has negative effects on children's cognitive abilities has major implications upon public health and governance because:

- *No human populations are entirely 'lead-free'.* Since the eradication of leaded petrol and paint in developed countries Pb exposure levels have dramatically declined but evidence of low-level Pb effects means that all human populations remain at risk because Pb is ubiquitous and environmentally persistent (Tong, 1995).
- *Population level decreases in IQ can increase the number of people diagnosed with an 'intellectual disability'.*
- *The challenges posed by low-level Pb exposure are not health-centric.* Pb exposure is entwined with issues broader than just health, such as the economy[28], environment[29], education[30], town planning and infrastructure[31]; hence whole-of-government approaches to the management and reduction of low-level Pb exposure require consideration (Homel, 2005).
- *The economic costs linked to Pb exposure are "substantial" (WHO, 2010, p.34) even in low-exposure countries and this is a powerful instigator for policy change.* The economic implications of Pb exposure are both direct (e.g., provision of individual medical intervention for children experiencing acute Pb exposure) and indirect in

[29] Because Pb is persistent in the environment it has the capacity to impact the ecological footprint left by humans because it can hinder the health of animals, plant life (Monkiewicz, Geringer, Bas, 1998) and the marine environment (Demayo, Taylor, Taylor & Hodson, 1982). Pb processing can also produce many emissions and effluent bi-products that are released into the ecological environment; these include sulphur dioxide, arsenic, cadmium, copper, mercury, zinc and other particulates (World Bank Group, 1998).

[30] Pb exposure has been shown to negatively impact educational attainment (Fergusson et al., 1997; Fulton et al., 1987; Stiles & Bellinger, 1993; Wang et al., 2002). The support of students with academic challenges may increase the resource requirements of the educational system.

[31] Pb exposure pathways may be considered by city and town planners in the design of infrastructure and residential placement.

nature. The indirect costs of childhood Pb exposure are less tangible but substantial; for example, WHO (2010) conceptualise diminished intelligence, as a "lost opportunity" (p.34) cost. It is estimated that based on a 0.25 IQ point decrement associated with each 1 µg/dL increase in PbB concentration, that the loss in "lifetime economic productivity associated with each lost IQ point is 2.4%" (WHO, 2010, p.34). Moreover, this estimate is considered conservative because it does not account for the economic cost of support services or repercussions to the health, wellbeing and economic productivity of an individual's family.

- *Pb exposure is a preventable and manageable risk to human health and development (Binns et al., 2007).*

Stemming from these broad points, the following will comment on the potential implications of mounting evidence of negative effects of low-level Pb exposure on children's cognitive abilities. Discussed below are a number of suggested clinical and public health approaches that may be beneficial policy considerations for the management of low-level Pb exposure[32]:

Review of the recommended PbB 'action levels' endorsed by key public health agencies and advisory groups; this thesis advocates for recognition that there is no safe level of paediatric Pb exposure.

PbB 'action levels' have been consistently reconsidered and lowered over the last 40 years as research has accumulated that supported the deleterious effects of Pb exposure.[33]

There is limited evidence that any level of Pb exposure can be considered adequately protective of children's health (a view which is further fuelled by suggestions of a non-linear relationship between Pb and children's cognitive abilities (Lanphear et al., 2000; Canfield et

[32] As Weitzman, Byrdc, Aligne & Moss (2002) cautioned, it is worth noting that the avenues for action and change suggested here are "not meant to be encyclopaedic, but rather to build on the current knowledge base and begin to develop the process by which children and society benefit" (p. 402).

[33] For example, WHO (2010) document that in the 1960's CDC defined elevated PbB levels at 60 µg/dL, in the 1970's, as evidence grew about the deleterious impacts of Pb exposure, childhood Pb poisoning was redefined at 40 µg/dL and subsequently lowered to 30 µg/dL. In the 1980's childhood PbB poisoning was reconceptualised at 25 µg/dL and then in the 1990's the current level of 10 µg/dL was endorsed by the CDC.

al., 2003; Kordas et al., 2006). Although scientists have suggested that 2 µg/dL may be a suitable 'action level' (Gilbert & Weiss, 2006) and in 2009, the German 'action level' was lowered to 3.5 µg/dL for children (Wilhelm et al., 2010), based on my research and background literature, it is difficult to quantify a renewed 'action level.' Indeed it is my opinion that accumulating evidence only further supports the assertion that, for the developing brain, no level of Pb exposure is free from adverse effects and that there is no safe level of Pb exposure. While recognising the utility of 'action levels' in guiding the decision-making of public health agencies, reconceptualisation of Pb as a toxin that is a threat to children's development at any level of exposure, may render the concept of 'action levels' redundant.

Greater investment in developmental surveillance and (early) intervention as the cornerstones of paediatric preventive services (Weistzman, Byrdc, Aligne & Moss, 2002).

Regardless of whether populations live in proximity to a major source of Pb, Pb is part of the mélange of toxins and chemicals to which humans are exposed. The effects of Pb on cognitive abilities may be due to the direct neurotoxic effect of this heavy metal on the developing brain. However, as this thesis has highlighted, there are a number of demographic, familial, psycho-social and environmental, pre- and post-natal factors that may increase a child's susceptibility to the harmful effects of Pb exposure and influence the magnitude of the association between Pb exposure and children's functional outcomes; it appears that the children at most risk of higher Pb exposure, are those whose families experience socio-economic challenges (e.g., low family income, stressful life events etc). For these children, Pb exposure can represent an "additional insult to children's development" (Weitzman et al. 2002, p. 402). Hence, it follows that:

1. Given the intersection of factors that influence childhood development, it is important to identify individual and community vulnerability so that supportive services can be applied. The use of tools that seek to obtain national snapshots of childhood

functioning are extremely useful for this purpose. One such measure has recently been launched in Australia, the Australian Early Development Index (AEDI; Brinkman, 2010; Brinkman, McDermott & Lynch, 2010)[34]. As measurement programs such as the AEDI are rolled out in the years to come more data will become available about the functionality and needs of Australian children. While tools such as the AEDI do not directly measure Pb exposure levels, the American National Health and Nutrition Examination Surveys measured PbB levels and there is scope to follow this model, especially for at-risk children.

One caveat relating to the association between Pb exposure and children's cognitive abilities is that cognitive challenges may not present until later in childhood due to the increasing and evolving demands of children's education, especially in light of suggestions from this study that speed of information processing and memory skills may be especially vulnerable to low-level Pb-exposure. Weitzman (2002) suggested that developmental monitoring should continue into middle childhood (and beyond if necessary). In particular Weitzman has noted that a focus on assessments conducted in early childhood may produce false negatives because children's abilities are still developing.

2. Enhancement and management of a child's environment, including educational experience, may help support children's development in the face of Pb exposure. If domains of a child's life, like those measured by the AEDI, are supported and improved then the effects of even minimal Pb exposure will be reduced; children from families facing socioeconomic challenges and stressors should be strongly encouraged to be enrolled in formal enrichment programs. Indeed, early intervention[35] is widely considered as the best preventative approach to ameliorate the development of

[34] The AEDI measures domains of early childhood development that are empirically and clinically linked to the predictors of good adult health, education and social outcomes. These domains are (1) Physical health and wellbeing; (2) Social competence; (3) Emotional maturity; (4) Language and cognitive skills (school-based) and (5) Communication skills and general knowledge (AEDI, 2009).

[35] As Vimpani et al. (2002) explain, early intervention can refer to intervention which occurs as close as possible to identification of a potentially detrimentral outcomes or pattern of behaviour and that this may or may not necessarily occur early in the life course.

pervasive long-term cognitive and behavioural challenges (Powell, Lochman & Boxmeyer, 2007; Shonkoff & Phillips, 2000; Vimpani, Patton & Hayes, 2002).

Dissemination of information about the impacts of low-level Pb exposure to health and allied health professionals and families.

Communicating the impacts of Pb-exposure is challenging because "these effects correspond to "altered structure or function" but not "clinical disease"" (Bellinger, 2004, p. 394) and because effects "would not necessarily be evident to the casual observer and would likely go undetected unless one were looking with the right assessment tools" (Bellinger, 2004, p.394).

As further evidence accumulates, knowledge gains regarding the effects of low-level Pb exposure should be disseminated to health and allied health professionals In doing so, low-level Pb-exposure could be framed as a psychological and developmental consideration for health and allied health professionals working with children and families (e.g., pediatricians, pediatric nurse practitioners, general practitioners and psychologists). Specific clinical practice recommendations relating to Pb exposure are summarised by Binns et al. (2007) and by Weitzman et al. (2002; in the context of pediatric tobacco exposure but some recommendations are applicable to Pb exposure) and are beyond the scope of this discussion but it is clear that there are opportunities to advocate for low-level Pb exposure as a clinical consideration in children's development.

It is envisaged that health and allied health professionals educated about low-level Pb exposure, could also play a significant role in educating children and families about Pb exposure risks, the potential functional impacts of Pb and strategies that can promote and support childhood development.

Ongoing implementation and development of strategies to manage lead hazards and lead contamination safely.

As discussions of Pb exposure move forward to consider low-level exposure, there is a need for ongoing programs and initiatives that address the remediation and management of Pb hazards, like leaded petrol and paint.

Leaded petrol remains as a major ongoing source of Pb exposure in many developing and low-income countries (e.g., Afghanistan, Algeria, Bosnia-Herzegovina, Iraq, Montenegro, Myanmar, North Korea, Sebia and Yemen; WHO, 2010) and for select populations such as rural communities. The global eradication of the use of Pb-petrol will represent the most significant step to reduce PbB levels of the global population; however, WHO (2010) estimated that approximately two hundred million people continue to be exposed to leaded petrol (a figure that does not include the short-term exposure of transient populations such as tourists).

The second most pervasive source of Pb exposure on a global scale is from Pb-paint. Although the production of Pb-paint has been abolished, Pb-paint continues to be an exposure route as it disintegrates, or is disturbed by home renovations; it can form paint chips and inhalable dust. Hence, the ongoing monitoring of residential conditions and education of residents is necessary to alert populations to the pervasive threat of Pb exposure through paint.

Implications of potential detriments to speed of information processing abilities and memory

Evidence that Pb may have a negative impact upon children's speed of information processing and memory capabilities has potential implications for the way that children learn, retain and engage material, their educational attainment and their career prospects. While, insult to any cognitive ability are of concern, insults to memory, as documented in this study, are alarming because memory underpins activities of daily living and educational attainment.

It is possible that individual and population-level deficits in the domains of speed of information processing and memory may require the educational system to reconsider the ways in which children learn and also the pace of learning.

11.4 Suggestions for future research

As highlighted through Chapters 2 and 3 of this thesis, this research follows from a substantial background of previous research which has responded to evolving questions about the effects of Pb on children's cognition; questions have evolved as critical knowledge and conceptual gains have been made and because population Pb levels have systematically decreased. Questions about the associations between Pb exposure and cognitive abilities continue to evolve and in the current climate, questions relating to the effects of low-level Pb exposure are of key importance. There are a number of avenues for further research that reflect the recent knowledge gains, to which this study contributes. In particular the areas of research described below are potential opportunities to advance the field.

Exposure markers

The reliability and accuracy of measures of Pb exposure underpin the value of setting Pb 'action levels' to guide intervention. There is a need to evaluate the specificity and reliability of Pb exposure indices measured at increasingly low-levels of exposure (≤ 10 µg/dL). Moving beyond PbB as the primary Pb exposure, tt would be wise to consider the utility of alternative measures of Pb exposure (such as K-X-Ray; Tong, 1995) at these lower levels of exposure. In particular epigenetic work conducted by Wright, Schwartz, Wright, Bollati, Tarantini, Park et al. (2010) has suggested that changes in DNA methylation have the potential to serve as a biomarker of previous Pb exposure and this opportunity requires further investigation.

Underlying mechanisms

Mudge (1996) recognised that it is unlikely that one sole mechanism can account for the range of functional deficits that have been attributed to Pb exposure. While gains have been made regarding how Pb may insult the structure of the human brain, there is scope to further build on this basis and in particular, to explore the epigenetic impacts of low-level Pb exposure, both across the life-course and trans-generationally; knowledge about the molecular mechanisms of Pb neurotoxicity could allow preventative treatments to be developed, improve interventions and inform models of human physiological toxic responses. The quest to understand the physiological mechanisms of Pb toxicity may be further aided through future advances in the technologies of medicine and chemistry.

Longitudinal impacts of low-level Pb exposure in dynamic and evolving workplaces

Saloman (1990) described computers (and associated technologies) as the defining technology of "our time" (p. 260) and envisaged that these technologies would shape human identity, output and cognitive function. Twenty-one years on from Saloman's (1990) statement, human lives and lifestyles are now inextricably intertwined with technology. It is timely to consider – what will the relationship be between low-level Pb exposure and the cognitive abilities of current and future generations who have been (and will continue to be) exposed to a proliferation of computers (and associated technologies)? It is hypothesised that due to technology use, human cognitive abilities may evolve to enhance some abilities (e.g., Gs, Gf, Gv) while neglecting the development of others (e.g., Gc).

Future research is especially pertinent in the context of this study, which has noted that speed of information processing abilities, in particular, may be vulnerable to the deleterious impact of Pb exposure. As Mudge (1996) considered the question, "will other adverse health effects become evident as children reach adulthood?" (p.228); similarly, this thesis raises questions about how detriments to childhood cognition may present in adulthood; for example, how will children who may have experienced insults to their speed of

information processing respond to work lives that are likely to be demanding, ever-evolving, and to require quick information processing capabilities? In addition, will the role of technology in our lives serve as a protective factor against insults to speed of information processing (long-term use of technologies may enhance Gs to the degree that Pb-induced detriments produce minimal insults), or will Pb-related insults to speed of information processing challenge some individual's ability to engage the technologies of the future ?

Further research efforts to advance understandings of the impacts of low-level Pb exposure on children's cognitive abilities

Further research efforts are required to advance understandings of the specific impacts of low-level Pb on childhood cognition. Based on this research, there is scope to further explore the effects of low-level Pb exposure on abilities such as memory and speed of information processing; in particular more thorough and targeted exploration of the constructs of working memory and short term memory may provide further insights into the effects of Pb upon cognition.

Evaluation and development of intervention programs for low-level Pb exposure

Opportunities exist to quantify the effectiveness of interventions undertaken at lower levels of Pb exposure. Evaluations of screening, monitoring and intervention programs will inform development of the best practice approaches to the management of low-level Pb exposure. Evaluations of these approaches will help devise successful and cost-effective policy responses to low-level Pb exposure.

11.5 Final summary and conclusions

This study was initiated in response to a "counterintuitive" (Canfield et al., 2003, p. 1523) question which emerged from the research field; are lower levels of Pb exposure more deleterious to children's cognitive abilities than higher levels? The most controversial

contemporary issue in our understanding of the health effects of Pb in children is around the interpretation of the shape of the curve relating neurodevelopmental outcomes to Pb exposure (as estimated by the PbB concentration). In line with previous research this study noted an inverse moderate unadjusted association between a Pb exposure and children's generalised cognitive abilities; the shape of this association was nonlinear. In adjusted multiple regression modelling it was noted that PbB concentration significantly explained variance in children's speed of information processing abilities and components of memory performances (working memory and long-term storage and retrieval).

This study was initiated and finalised during a period when international discussions about appropriate Pb 'action levels' gained momentum and conceptualisations of 'safe levels' of Pb exposure were reconsidered. The main contributions of this study lie with the weight that it adds to views that the 'action levels' for Pb exposure require reconsideration, as well as recognition that there is no threshold free from the deleterious effects of Pb exposure; relatively low-levels of Pb exposure can negatively impact children's cognitive performance, particular in the important domains of speed of information processing and memory.

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APPENDICES

List of Appendices

Appendix A: Efforts to reduce lead exposure in Port Pirie and Broken Hill

A number of initiatives have been undertaken in Port Pirie and Broken Hill to limit Pb exposure and contamination. Practically, changes to the mode of transportation of ore from Broken Hill to Port Pirie mean that Pb ore is now contained via rail cars (compared to open truck transport favoured in the past) which limit the dispersion of particulate materials.

In Port Pirie, initiatives run through the Environmental Health Centre seek to achieve a balance between the health of the community and the longevity and productivity of the Pb smelter and the city of Port Pirie. The South Australian Government's Port Pirie Lead Implementation Program had a primary target of reducing the Pb exposure levels of pregnant women and children under 5 years of age (specifically, the *Tenby10* program aimed for 95% of the children in Port Pirie to have a PbB level of less than 10 µg/dL by the end of 2010; targets were not fully realised). Activities undertaken as part of the *Tenby10* program included routine PbB monitoring of pregnant women and children under 5 years of age, counselling and education about Pb contamination in Port Pirie, home and environmental assessments, Pb abatement and renovation advice, removal of Pb contaminated material, loanage of vacuum cleaners (for removal of ceiling and carpet dust), subsidised washing machines for purchase and a school-based breakfast program (to ensure that children have a nutritious breakfast).

In Broken Hill, collaborative activities undertaken between the New South Wales Health Department and the New South Wales Environment Protection Authority, in consultation with Broken Hill Council, industry and the community, have made substantial in-roads in the reduction of community PbB levels. In 1994, the New South Wales Government established the Broken Hill Environmental Lead Centre; a multidisciplinary team (nurses, technicians, educators and scientists) which sought to implement a Pb reduction strategy (Balding & Reddan, 1997). The five key components of the strategy were growth in education and awareness-raising, clinical monitoring of PbB levels, environmental testing and remediation of children's home environments and contaminated public spaces. Under the

strategy, key projects included newborn PbB monitoring, school-based education, targeted programs that recognised Indigenous communities as an at-risk group and ‘greening’ programs (which involved planting trees, fencing problem areas and controlling stormwater flow; Balding & Reddan, 1997). In addition, within New South Wales, elevated PbB levels became a notifiable paediatric health condition so that health authorities could closely monitor these cases (Population Health Division, New South Wales Government, 2008).

Appendix B: Summary of relevant cross-sectional studies investigating the associations between Lead and children's cognitive abilities.

Table 1

Summary of cross-sectional studies exploring the impact of Pb on child cognitive abilities in the absence of clinical poisoning.

First Author (date) ***Location***	**N; mean age (years); Source Attribution**[a]	**Mean Exposure measure** [b c]	**Measure (s) of cognitive abilities**	**Confounders collected**	**Key findings**
De la Burdé (1975) *Virginia, USA.*	137; 7; Pica.	'high' PbD = 202.1; 'control' PbD = 111.6.	WISC.	Age, sex, race & SES.	High PbD participants had significantly ($p < 0.1$) lower FSIQ than controls (mean difference = 3.5 IQ points).
Winneke (1983) *Germany.*	115; 9.4; Pb Smelter.	Geometric mean PbD = 6.2.	WISC.	52 variables covering child, family, social environmental & medical history.	Significant negative correlation between WISC -VIQ and PbD ($r = - 0.5$, $p < 0.1$).
Hunter (1985) *Leeds, United Kingdom.*	302; 9.9; Pb works.	PbB =11. 9.	Reaction Time.	None reported.	Positive significant relationship ($p < 0.05$) between log Pb & age adjusted mean RT for all four trial blocks but accounted for only about 1 % of the total variance.

Note. Studies are presented in order of year of publication. FSIQ: Full Scale IQ; *N*: Sample size; Pb: lead; PbB: blood lead; PbD: dentine lead; SES: socioeconomic status; VIQ: Verbal IQ; WISC: Wechsler Intelligence Scale for Children.

[a] 'Source attribution' refers to the main Pb exposure (e.g., mine).

[b] PbB units = microgram per deciliter (µg/dL); PbD units = microgram per gram (µg/g).

[c] Arithmetic mean reported, unless otherwise stated.

Table 1

Continued.

First Author (date) ***Location***	**N; age (years); Source Attribution**[a]	**Mean Exposure measure** [b c]	**Measure of cognitive abilities**	**Confounders collected**	**Key findings**
Fulton (1987) *Edinburgh Scotland.*	501; 6 - 9; Plumbo-solvent water supply.	PbB = 10.4.	British Ability Scales.	33 confounders including maternal IQ, school, SES, experiences, household, family environment, occupation, parent mental health, pre-natal & postnatal factors.	Strong negative adjusted correlation between PbB and performance upon the BAS combined score (mean = 112, *SD* = 13.4; β = -3.79, *SE* = 1.37, *p* = 0.003), number skills (β = 1.47, *SE* = 0.83, *p* = 0.04), word reading (β = -3.16, *SE* = 1.05, *p* = 0.001).
Pocock (1987) *London, UK.*	402; 6; General exposure.	PbD: low: 2.5, medium: 5.0, high: 8.0.	WISC-R.	Child gender, social class, family size, birth order, gestation, birth weight, length of hospital stay after birth, mother's IQ, quality of marital relationship, mothers' mental health, family characteristics, social background, parental education, attitude & interest.	Optimally criterion process capability (Cp) reached its minimum when 11 variables were entered, and the standardised regression coefficient for log PbD in this optimal model was not statistically significant (β = - 0.77, *p* = 0.22).
Rabinowitz (1991) *Taiwan.*	515; Grade 1-3; General exposure & Pb smelter.	PbD: Taipei City = 4.3; Near Pb smelter = 6.3.	CPM.	Parental education, parental age, employment, family composition, areas lived, language usage, pregnancy events, delivery, maternal &child health	Scores on the CPM were negatively correlated with Pb levels (*r* = - 0.19, *p* = 0.0001). Association was stronger for female children (*r* = - 0.26, *p* = 0.0001) & for children of parent's with lower educational attainment (*r* = - 0.15) versus those whose father's were college graduates (*r* = 0.004).

Note. Studies are presented in order of year of publication. BAS: British Ability Skills; Cp: Optimally criterion process capability; CPM: Raven's Coloured progressive matrices; *N*: Sample size; Pb: lead; PbB: blood lead; PbD: dentine lead; *SE*: standard error; SES: socioeconomic status; WISC-R: Wechsler Intelligence Scale for Children – Revised.

[a] 'Source attribution' refers to the main Pb exposure (e.g. mine).

[b] PbB units = microgram per deciliter (µg/dL); PbD units = microgram per gram (µg/g).

[c] Arithmetic mean reported, unless otherwise stated.

Table 1

Continued.

First Author (date) *Location*	N; age range (years); Source Attribution[a]	Mean Exposure measure [b c]	Measure (s) of cognitive abilities	Confounders collected	Key findings
Minder (1994) *Amsterdam, Netherlands.*	43; Mean age = 10.2. General exposure.	PbH = 1.26 µg/g.	11 measures including RT, Trail making task.	27 variables covering child, social and environmental.	After correction for confounders, significant ($p < 0.05$) correlations between Pb hair, RT and speed of Trail Making Test B.
Sovcikova (1997) *Bratislava, Republic of Slovakia.*	395; 9 - 10; Mining & smelting.	PbB = 3.65.	WISC Comprehension & Digit Span, RPM, Bender Gestalt Test, Benton Test, Vienna Determination Test, SRT.	Child gender, child illness, maternal education, parental assistance with homework, parental smoking, car ownership, proximity to petrochemical plant.	With confounder control, a moderate, statistically significant inverse association between PbB levels ($0.01 < p \leq 0.05$) and RPM and Benton Test ($0.01 < p \leq 0.05$) scores.
Lanphear (2000) *USA (NHANES III).*	4853; 6-16; General exposure.	Geometric mean PbB = 1.9.	WISC-R (Digit Span, & Block design) WRAT-R (maths & reading)	Adjustment for gender, ethnicity, poverty, country region, parent education, parent marital status, serum ferritin level, & serum cotinine level.	Inverse relationship between PbB & scores digit span (coefficient = - 0.05, $SE = 0.02$, $p = 0.04$), block design (coefficient = -0.10, SE = 0.04, $p = 0.01$), arithmetic (coefficient = - 0.70, $SE = 0.17$, $p < 0.001$) & reading (coefficient = - 0.99, $SE = 0.19$, $p < 0.001$).
Calderón (2001) *Sau Luis Potosi, México.*	80; 6 - 9; Pb smelter.	Morales: geometric mean PbB = 8.98; Martinez: geometric mean PbB = 9.73.	WISC-RM	SES, clinical history, neurological examination, nutritional status & iron levels	PbB significantly negatively ($r = - 0.30$, $p = 0.01$) associated with a 'sequential' factor (arithmetic, digit span & coding).

Note. Studies are presented in order of year of publication. *N*: Sample size; NHANES – III: The third National Health and Nutrition Examination Survey; Pb: lead; PbB : blood lead; PbH: lead in hair; RPM: Raven's Progressive Matrices; RT: Reaction Time; *SE*: standard error; SES: socioeconomc status; SRT: Simple Reaction Time, WISC: Wechsler Intelligence Scale for Children; WISC-R: Wechsler Intelligence Scale for Children – Revised; WISC-RM: Wechsler Intelligence Scale for Children – Revised, version for Mexico; WRAT-R: Wide Range Achievement Test-Revised.

[a] 'Source attribution' refers to the main Pb exposure (e.g., mine).

[b] PbB units = microgram per deciliter (µg/dL); PbH units = microgram per gram (µg/g).

[c] Arithmetic mean reported, unless otherwise stated.

Table 1

Continued.

First Author (date) *Location*	N; mean age (years); Source Attribution[a]	Mean Exposure measure [b c]	Measure (s) of cognitive abilities	Confounders collected	Key findings
Rahman (2002) *Karashi, Pakistan.*	138; 8.4; Industrial & general exposure.	PbD = 5.68; PbB = 16.08.	RPM	Height-for-age & haemglobin levels.	After adjustment for confounders, association between PbB & Raven's performance remained significant (β = - 0.63, p = 0.02, R^2 = 0.23).
Wang (2002) *Kaohsiung City, Taiwan.*	934 ; 8.9; General exposure.	PbB = 5.50.	Class ranking used to infer learning achievement	Control for Father's SES & maternal education.	PbB significantly correlated with class ranking for Chinese (β = 0.37, *SE* = 0.15, p <0.05, R^2 = 0.14), mathematics (β = 0.38, *SE* = 0.16, p < 0.05, R^2 = 0.10), history (β = 0.43, *SE* = 0.15, p < 0.05, R^2 = 0.04) & science (β = 0.32, SE = 0.16, p < 0.05, R^2 = 0.07).
Chiodo (2004) *USA.*	246 ; 5.5; General exposure.	PbB = 5.4.	WISC-III**,** measures of executive function, information processing & attention.	Maternal alcohol prior to & after conception. Controlled for SES, maternal education, children in the family, HOME, maternal IQ, child's gender, parity & Family Environment Scale	A significant inverse association existed between PbB and: • FSIQ (r = - 0.32, $p \leq$ 0.001; β = - 0.20), $p \leq$ 0.01), • VIQ (r = - 0.28, $p \leq$ 0.001; β = - 0.20, $p \leq$ 0.05), • PIQ (r = - 0.30, $p \leq$ 0.001; β = - 0.14, p ≤ 0.001), • VC (r = - 0.29, $p \leq$ 0.001; β = -0.15, $p \leq$ 0.01) & • PO (r = - 0.30, $p \leq$ 0.001; β = -0.21, $p \leq$ 0.01).

Note. Studies are presented in order of year of publication. FSIQ: Full Scale IQ; HOME: Home Observation for Measurement of the Environment Inventory; *N*: Sample size; PbB: blood lead; PbD: dentine lead; PIQ: Performance IQ; PO: Perceptual Organization; RPM: Raven's Progressive Matrices; *SE*: standard error; SES: socioeconomc status; VC: Verbal Comprehension; VIQ: Verbal IQ: WISC-III: Wechsler Intelligence Scale for Children – Third Edition.

[a] 'Source attribution' refers to the main Pb exposure (e.g., mine).

[b] PbB units = microgram per deciliter (µg/dL); PbD units = microgram per gram (µg/g).

[c] Arithmetic mean reported, unless otherwise stated.

Table 1

Continued.

First Author (date) *Location*	**N; mean age (years); Source Attribution[a]**	**Mean Exposure measure [b c]**	**Measure (s) of cognitive abilities**	**Confounders collected**	**Key findings**
Després (2005) *Quebec, Canada.*	110; 6; General exposure.	Mean geometric PbB = 4.1.	Gross motor, RT, fine motor skills, preclinical alterations, neuromotor functioning.	SES, parental education, number siblings, maternal distress, maternal RPM, intra-family violence, HOME, reproductive history, pre-natal terotagenic exposure, child nutrition.	In adjusted analyses Pb significantly positively associated with fine motor skills, longer RT ($r = 0.21$, $p \leq 0.05$, F = 8.89, $p \leq 0.001$) & neuromotor functioning ($r = 0.32$, $p \leq 0.001$) & sway oscillations.
Hu (2006) *Mexico City*	146 pregnant women.	1st trimester PbB = 7.0; 2nd trimester PbB = 6.0; 3rd trimester PbB = 6.8; delivery PbB = 7.3; cord PbB = 6.2; 12 month PbB = 5.2 & 24 month PbB = 4.8.	24 month BSID.	Demographic, socioeconomic, and other factors. Maternal IQ assessed using subtests of the WAIS.	Significant relationships identified between MDI & 1st trimester PbB ($\beta = -4.13$; $p = 0.03$) & whole PbB ($\beta = -3.77$; $p = 0.04$).
Kim (2009) *Korean Cities*	267; 9.1; General exposure	PbB = 1.74.	KEDI-WISC.	Age, gender, parental education, yearly income, maternal smoking during pregnancy, indirect smoking after birth, birth weight & mother's age at birth.	Significant linear relationship between PbB & FSIQ ($\beta = -0.17$, $p = 0.01$) & VIQ ($\beta = -0.19$, $p = 0.003$), but not PIQ.
Cho (2010) *Korean Cities*	267; 9.1; General exposure	PbB = 1.74.	Inhibitive control, sustained attention, sequencing & cognitive flexibility & processing speed	KEDI-WISC IQ, age, gender, educational level of the father, maternal IQ, residential area & birth weight.	Significant inverse association between PbB & Commission errors of the CPT ($\beta = 0.09$, $p = 0.04$; lower CPT scores indicate better attention and response inhibition ability).

Note. Studies are presented in order of year of publication. BSID: Bayley Scales of Infant Development; CPT: Continuous performance test; FSIQ: Full Scale IQ; HOME: Home Observation for Measurement of the Environment Inventory; KEDI-WISC: Korean Educational Development Institute–Wechsler Intelligence Scales for Children; MDI: Mental Development Index; *N*: Sample size; PbB: blood lead; PIQ: Performance IQ; RPM: Raven's Progressive Matrices; RT: Reaction Time; SES: socioeconomc status; VIQ: Verbal IQ; WAIS-III: Wechsler Adult Intelligence Scale – Third Edition.

[a] 'Source attribution' refers to the main Pb exposure (e.g., mine).

[b] PbB units = microgram per deciliter (µg/dL);

[c] Arithmetic mean reported, unless otherwise stated.

Appendix C: Information letters sent to families in Port Pirie and Broken Hill and study consent forms

Government of South Australia
Children, Youth and Women's Health Service
Women's & Children's Hospital

THE UNIVERSITY OF ADELAIDE AUSTRALIA

Broken Hill
Department of Rural Health

Health Effects of Lead in Children

Dear Parents,

Please find enclosed an invitation for your family to take part in the research project *Health Effects of Lead in Children* whose aim is to find out whether the current levels of exposure to lead of children living in Port Pirie and Broken Hill to lead can be considered safe.

If you and your child would like to take part in this important work, please sign the attached consent form and either return it to your child's class teacher – or put it in the reply-paid envelope and drop it in the post. You will then be contacted by one of our Research Assistants, Ms Trudi Manfield (8638 4100) if you live in Port Pirie, or by Ms Lisa Baker (8080 1260) if you live in Broken Hill.

Thank you for considering our request.

Yours sincerely,

Assoc Prof Peter Baghurst

Head, Public Health Research Unit

Women's and Children's

Hospital

Children Youth and Women's Health Service

Dr Nicholas R Burns

Deputy Head, School of Psychology

The University of Adelaide

Professor Ted Nettelbeck

School of Psychology

The University of Adelaide

The Health Effects of Lead in Children

An Information Sheet for Parents

This is an invitation to you and your 7 – 8 year-old child to take part in important work to determine whether exposure to lead in Port Pirie and Broken Hill is now sufficiently low that we can be confident that the intelligence and socialisation of children living in these cities will develop to their full potential. The possibility that lead may affect children's development has been in the news for decades. However, the clean-up which has happened over the past twenty five years means exposures are now very much lower than they have ever been. It's now time to make sure they are low enough.

Background information – a very brief history

In 1979 a group of researchers from the CSIRO, the SA Department of Health, the Women's and Children's Hospital, and Child and Youth Health began a study of the effects of lead on children's development in Port Pirie. One of the important aims of the research was to find out whether lead can interfere with the development of intelligence and behaviour of children as they grow up. The results of this Port Pirie Cohort Study were reported back to the participating families and presented at scientific meetings around the world. Children with the highest exposures to lead scored a few IQ points less than the children with the lowest exposure. However, the interpretation of these findings has been controversial. The effects were small – and critics have argued that these effects would have been even smaller (or non-existent) if we had measured more carefully other things that shape a child's IQ. Others have argued that whatever the doubts, our findings were enough to demand action. In Port Pirie, the SA Department of Health (through the Environmental Health Centre); the Port Pirie Council; the smelter operators; and of course the residents, have made Port Pirie a much cleaner place to live – and the greatly reduced levels of lead detectable in our children's blood today are a tribute to that cooperation. In Broken Hill, the Environmental Lead Centre was

established as apart of the *New South Wales Lead Management Action Plan*. Its activities included blood lead monitoring, assisting industry to reduce emissions, removal of lead contaminated soil and house dust, and community education. There has been a steady decline in blood lead levels among preschool children living in Broken Hill over recent years, and the percentage of children in Broken Hill with blood lead levels in the recommended range has increased from 14% in 1991 to 69% in 2003.

So are our children safe now?

Although we have made enormous progress over the past 25 years, there is still some unfinished business. Around the world, it has been assumed that a blood lead concentration below 10 units[†] requires no action, which implies this is a safe level. It may surprise you that this 'safe exposure' level was not chosen just on scientific grounds – but also because it was realistically achievable. (Twenty five years ago, even in communities where there was no lead industry, few people had blood lead levels below 10 units!). Following the phasing out of leaded petrol, many communities in Australia and elsewhere now have average blood levels below 10 units. Indeed some have average levels as low as 3 – 5 units. But two studies, both conducted in the USA, have suggested that there may still be undesirable effects of lead on children's IQ at blood levels ***below*** 10 units.

Should we be concerned about this?

The provision of a safe and secure environment, which enables our children to develop to their full potential, is so important that we cannot ignore these findings. The validity of the studies from North America continues to be questioned by some research scientists. In particular, questions have been asked about how well the other things which shape a child's IQ (besides lead) were measured. With the lessons learned from the earlier lead studies, and with recent advances in our understanding of 'intelligence' (and how to measure it) we need a new study.

What will happen in this new study?

We shall be relating the lead concentration in a small drop of blood (obtained by a very skilled nurse pricking your child's finger), to his or her performance on some intelligence tests, which involve pencil and paper – and some fun computer "games". Please be aware that your child may be away from the classroom for up to two hours while testing occurs. We would also like to measure the performance of both biological parents on similar tests (some of them very much shorter!) at a time, which suits you both best. These tests will be performed by a research assistant who has been specially trained in the University of Adelaide's School of Psychology. The assistant will ask to be allowed to come and meet you and your child at home (at whatever time suits you) and to leave a questionnaire for you to fill out about your child' birth (whether it was preterm or not); your child's feelings and behaviour; the environment where your child spends most time out of school hours; any major life events that have happened to you or your family recently; how satisfied you are, and a brief general health questionnaire. Some of the information sought is fairly personal in nature. We would like you to try and answer all questions – but if any question should make you feel uncomfortable, you can simply ignore it. We'll also seek your permission to ask your child's teacher about how your child behaves at school.

Do we have to take part?

No, there is no compulsion whatsoever for you or your child to take part in this research.

Do parents have to donate blood as well as our child?

No, we will not be measuring blood lead concentrations in parents. And if your child currently participates in a lead monitoring program (such as the program run by Environmental Health Centre in Port Pirie, or the ELC in Broken Hill) we may be able to use the result from that blood sample in our study.

Will we be paid for taking part?

Each participating parent is entitled to claim up to $25 to cover the costs (travel etc), and inconvenience of taking part in the research. This claim will be paid by cheque, posted to you from the Women's and Children's Hospital, when your family's interviews are completed.

My child's biological father/mother no longer lives with us. Can we still take part?

Yes, if you can let us know how we can contact that person, we will send them this same invitation.

Who gets to see our results?

Your privacy is extremely important to us – so we will not be sharing your results with anybody, - not even your partner. If you wish to know your results, or your child's, we shall arrange for a psychologist to talk with you, personally, about them. Please ring (08) 8161 6935 to arrange an appointment. Your identity will not be released to anyone, and the results of the research will be published in such a way that it will be impossible for anyone to identify you or anyone in your family.

Could this research threaten the livelihoods of people living in Port Pirie and Broken Hill?

The main aim of this research is to determine whether current exposure levels to lead in Port Pirie and Broken Hill are safe for the children, or if more clean-up work is needed. We have no desire to threaten the lead industry, which is aware of our work, - and is still investing in programs to make both cities cleaner.

Thank you for considering this invitation. If you would like to ask for any more information on what is involved, please feel free to contact us.

Assoc. Prof. Peter Baghurst	Dr Nick Burns	Professor David Lyle
Or	or	
Professor Michael Sawyer	Professor Ted Nettelbeck	Department of Rural Health
Women's and Children's Hospital,	School of Psychology	University of Sydney
CYWHS	University of Adelaide	Corrindah Court
72 King William Road	North Terrace	Broken Hill
North Adelaide SA 5006	Adelaide SA 5005	New South Wales 2880
Phone: (08) 8161-6935	Phone: (08) 83035738	Phone: (08) 8080 1236

This research proposal has been approved by the Human Research Ethics Committee of the Women's and Children's Hospital, Children Youth and Women's Health Service, in Adelaide. Should you have any concerns about the ethical conduct of this work please feel free to contact the Committee through the Secretary, Ms Brenda Penny, Women's and Children's Hospital, 72 King William Rd, North Adelaide SA 5006; Phone (08) 8161 6521.

Health effects of lead in children – Parent Consent Form

I _____(please print your name)

hereby consent to my and my child's involvement in the research project entitled

"**Health effects of lead in children"**

1. I have read and understood the nature and purpose of the research project as described on the attached Information Sheet. I understand it, and agree to myself and my child taking part.
2. I have had the opportunity to contact the researchers using the contact details provided on the Information Sheet if I have required any additional information or explanation relating to my/my child's involvement in this study.
3. I understand that I or my child may not directly benefit by taking part in this study.
4. I acknowledge that I have had the opportunity to seek further clarification from the researchers about any possible discomforts and inconveniences, as outlined in the information sheet and these have been explained to me.
5. I understand that while information gained in the study may be published, I and my child will not be identified and information will be confidential.
6. I understand that I can withdraw my child and myself from the study at any stage and that this will not affect any future care or services (e.g., health, education or community) that I or my child may access.
7. I understand that there will be no payment to me or my child for taking part in this study other than the $25 to cover any inconvenience – as specified in the Information Sheet.
8. I have had the opportunity to discuss taking part in this research project with a family member or friend.
9. I am aware that I should retain a copy of the consent form, when completed, and the Information Sheet.
10. I consent to the researchers of this study accessing information relating to my child's birth weight and gestational age at birth from the hospital at which my child was born, if I am unable to provide them with this information.
11. I give consent for my child's teacher to be contacted in order to complete a questionnaire on my child's behaviour at school.

Full name of Child: …….

Biological mother[1]

Signed:……Dated:…….

Biological Mother's Contact Details:

Name:……

Address:……..

……

Telephone number:……..(h) ……(wk) ……(mob)

Biological father[1]

Signed:……Dated:…….

Biological Father's Contact Details:

Name:……

Address:……..

……

(insert "as above" if appropriate)

Telephone number:……..(h) ……(wk) ……(mob)

[1] Important

If one of the child's biological parents is not part of this household and you would prefer for us (the researchers) to contact them, please provide their contact details in the space provided above, and write "PLEASE CONTACT" by their name.

For the researcher to complete at interview:

I certify that I have explained the study to the parent(s) and consider that he/she understands what is involved.

Signed: …….Title:……..

Dated:……

This research proposal has been approved by the Human Research Ethics Committee of the Women's and Children's Hospital, Children Youth and Women's Health Service, in Adelaide. Should you have any concerns about the ethical conduct of this work please feel free to contact the Committee through the Secretary, Ms Brenda Penny, Women's and Children's Hospital, 72 King Will

Appendix D: Questionnaire completed by mothers and fathers.

Government of South Australia
Children, Youth and Women's Health Service

Women's & Children's Hospital

THE UNIVERSITY OF ADELAIDE AUSTRALIA

Making sure they are now safe…

A study funded by the National Health and Medical Research Council on

The Health Effects of Lead in Children

Parent questionnaire

The University of Sydney
Faculty of Medicine

Broken Hill
Department of Rural Health

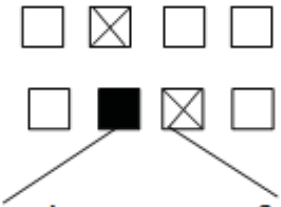
HOW TO FILL OUT THIS QUESTIONNAIRE

- Apart from the questions about your background, there are **NO right or wrong** answers. We are interested in your views and opinions.
- We would like you to answer all the questions as accurately and as honestly as you can—and since it is normal for mothers and fathers to have different opinions about their children's health and behaviour **we would like you to answer these questions without consulting your partner.**
- Please be assured that your responses to the questions in this booklet will be kept completely confidential.
- The pages in this booklet are double sided. Please make sure you answer the questions on both sides of the page.
- Please give **one** answer for each question, unless stated otherwise.
- If you find certain questions too intrusive, please leave those items blank and continue with the rest of the survey.
- If you find there is no answer exactly fitting your situation, please answer with the response **that fits best**, and if you like, place a comment in the margin.
- In most places we shall simply be asking you to put a cross in a box.

Please follow the instructions below carefully:

USING BLACK OR BLUE PEN, PLACE A CLEAR 'X' INSIDE THE BOX.

IF YOU MAKE A MISTAKE, FILL IN THE ENTIRE BOX,
AND PLACE A CLEAR 'X' IN THE CORRECT BOX AS SHOWN IN THE EXAMPLE TO THE RIGHT.



- In a some places we shall also be asking you to put a number in a box. If there is room for a two digit number like "23" but your answer is a single digit number like "9", please enter a zero in the unused box, i.e., write "09", as indicated here.... | 0 | 9 |
- In just a few places you may also be asked to simply write in a box. It would be helpful if you could stay within the borders of that box.

THANK YOU

Child's Name.....

First-name of person filling out this questionnaire.....

Relationship to child.....

We value your privacy!

As soon as you have completed this questionnaire, please put it In the envelope provided, and seal it. It will then be forwarded to Adelaide without being opened. The Research Officer will not see any of your answers and this corner will be cut off after its arrival in Adelaide.

Your child's medical history

Does your child have any on-going medical conditions requiring any special medication or equipment?

No ☐

Yes ☐

If yes, please describe briefly in the box below

Has your child ever had any accidents or illnesses that have kept him or her away from school for more than 3 weeks?

No ☐

Yes ☐

If yes, please describe briefly in the box below

Would you describe your child as healthy?

No ☐

Yes ☐

If no, please describe briefly any of your concerns in the box below

Have you ever had any concerns about either the growth or the development of your child?

No ☐

Yes ☐

If yes, please describe briefly any concerns in the box below

How many days has your child been absent from school in the last 4 weeks because of ill health or any other unplanned reason?

____ days

If your child missed more than 1 day's schooling, please indicate the major reason(s) in the box below

A little bit about your living arrangements

How many nights does your child sleep at your house each week? ☐ nights

Which of the following situations best describes your current living arrangements?

I am the only adult in my household ☐

I live with my child's other natural parent ☐

I live with a partner who is not my child's other natural parent ☐

Other (please describe in the box below) ☐

☐

How many *other* children under the age of 18 years live at your house?

☐ other children

Please list the ages (in years) of any other children that live at your house (on the following line separated by commas)

☐ years

Do you currently smoke?

No ☐

Yes ☐

If you do smoke, please indicate how many cigarettes you would smoke each day

☐ cigarettes per day

How many people in *your* household currently smoke 1 cigarette or more per day? (Please indicate with a '0' if nobody smokes in your household)

☐ smokers

Family lifestyle

About how many books does your child have?	none	1 or 2	3 to 9	10 or more
	☐	☐	☐	☐

About how often do your read aloud to your child	Never	Several times a year	Several times a month	About once a week	At least 3 times a week	Every day
	☐	☐	☐	☐	☐	☐

How often is your child expected to do each of the following?	Almost never	Less than half the time	Half the time	More than half the time	Almost always
Make his/her own bed	☐	☐	☐	☐	☐
Clean his/her own room	☐	☐	☐	☐	☐
Clean up after spills	☐	☐	☐	☐	☐
Bathe himself/herself	☐	☐	☐	☐	☐

Is there a musical instrument (for example, piano, drum, guitar etc,) that your child can use here at home?	Yes	No
	☐	☐

Does your family get a daily newspaper?	Yes	No
	☐	☐

About how often does your child read for enjoyment?	Never	Several times a year	Several times a month	Several times a week	Every day
	☐	☐	☐	☐	☐

Does your family encourage your child to start and keep doing hobbies?	Yes	No
	☐	☐

Does your child get special lessons or belong to an organisation that encourages activities such as sports, music, art, dance, drama, etc.?	Yes	No
	☐	☐

How often has a family member taken or arranged to take your child to any type of museum (children's, scientific, art, historical, etc) within the past year?

Never	Once or twice	Several times	About once a month	About once a week or more often
☐	☐	☐	☐	☐

Family lifestyle (page 2 of 2)

About how often does your family get together with relatives or friends?	Once a year or less	A few times a year	About once a month	Two or three times a month	About once a week or more
	☐	☐	☐	☐	☐

About how often does your child spend time with your partner?

Don't know	No partner, step-parent or par-ent-figure	Never	A few times a year or less	About once a month	About once a week	At least 4 times a week	Once a day or more often
☐	☐	☐	☐	☐	☐	☐	☐

About how often does your child spend time with his/her father, stepfather, or father-figure in ***outdoor activities***?

Don't know	No father, step-father or father-figure	Never	A few times a year or less	About once a month	About once a week	At least 4 times a week	Once a day or more often
☐	☐	☐	☐	☐	☐	☐	☐

How often does your child eat a meal with both you and your partner?

Don't know	No father, step-father or father-figure	Never	A few times a year or less	About once a month	About once a week	At least 4 times a week	More than once a day
☐	☐	☐	☐	☐	☐	☐	☐

When your family watches TV together, do you or your partner discuss TV programs with him/her?	Don't have a TV	Yes	No
	☐	☐	☐

How many times in the last week have you ...

had to ground your child?		(times)
had to smack your child?		(times)
had to take away TV or other privileges?		(times)
praised your child for doing something worthwhile?		(times)
taken away or reduced his/her pocket-money?		(times)
shown your child physical affection (a kiss, hug, stroke of the hair, etc)?		(times)
sent your child to his or her room?		(times)
told another adult (partner, friend, co-worker, visitor, relative) something good about your child?		(times)

Pregnancy and child-birth
(Mothers only—Fathers please turn to next page)

How many times had you been pregnant before you became pregnant with this child?

[ ] pregnancies

How many live babies were born to you *before* you became pregnant with this child?

[ ] babies

At which hospital was this child born? [ ] Hospital

Did you give birth to this child by (please cross one box)

Vaginal delivery? [ ]

Caesarean section? [ ]

Was this child born early or pre-term?

No [ ]

Yes [ ]

Please indicate the weeks of gestation when your child was born. [ ] weeks

What did your baby weigh at birth? (If you cannot remember we can find out for you)

[ ] grams

or

[ ] pounds [ ] ounces

Please describe any problems or complications with the birth of this child

[ ]

Did your baby spend more than a few hours in Special- or Intensive-Care ?

No [ ]

Yes [ ]

How many cigarettes were you smoking each day when you found out you were pregnant with this child?

[ ] cigarettes per day

How many cigarettes were you smoking each day when your child was born?

[ ] cigarettes per day

As best as you can recall, how many 'drinks' of beer, wine and spirits were you consuming around the time you found out you were pregnant?

[ ] drinks per day/ per week (please cross out one)

How many 'drinks' of beer, wine and spirits were you consuming at the time your child was born?

[ ] drinks per day/ per week (please cross out one)

For how many months did you breast-feed this child? [ ] months

ID

(Office use only)

A little bit about you…

How old are you? ____ years

How many years have you lived in Port Pirie or Broken Hill ____ years

What is your highest level of education?

- Primary school ☐
- Some years of high school ☐
- Year 12, matriculation, or equivalent ☐
- Technical, trade or TAFE certificate ☐
- A university degree ☐

Are you currently employed?

- No ☐
- Yes ☐

If you are currently employed what is your position title and name of your employer? If you undertake home duties or are a student please record this information here.

If you are currently unemployed, what is your *usual* occupation?

Please estimate the *combined* annual income of everyone living in your household (Please include any benefits or pensions you may receive)

- Less than $20,000 or under $400/week ☐
- Less than $50,000, or under $1000/week ☐
- Less than $80,000, or under $1600/week ☐
- More than $80,000 (or over $1600/week) ☐

Recent events in your life (just the past year)

Listed below are a number of events. Please read each item carefully and then indicate whether or not each event has happened to you ***in the past year***.

Please put a cross in the YES box if the event has occurred.
Please cross the 'Still affects me' box if the event is still having an effect on your life.

EVENT	YES	Still affects me
Have you had a serious illness or been seriously injured?	☐	☐
Has one of your immediate family * been seriously ill or injured?	☐	☐
Have any of your close friends or other close relatives been seriously ill or injured?	☐	☐
Have any of your immediate family died?	☐	☐
Have any of your other close relatives or close friends died?	☐	☐
Have you separated from your partner (not including death)?	☐	☐
Have you had any serious problem with a close friend, neighbour or relative?	☐	☐
Have you or an immediate family member been subject to serious racial abuse, attack or threats?	☐	☐
Have you, or an immediate family member been subject to any abuse, attack, threat – perhaps due to you or someone close to you having a disability of any kind (i.e. a mental health problem, a learning disability or a physical problem)?	☐	☐
Have you, or an immediate family member been subject to any other form of serious abuse, attack or threat?	☐	☐
Have you or your partner been unemployed or seeking work for more than one month?	☐	☐
Have you or your partner been sacked from your job or made redundant?	☐	☐
Have you had any major financial difficulties (e.g. debts, difficulty paying bills)?	☐	☐
Have you, or an immediate family member had any Police contact or been in a court appearance?	☐	☐
Have you, or an immediate member of your family been burgled or mugged?	☐	☐
Have you or another individual who lives with you given birth?	☐	☐
Have you or another individual who lives with you suffered from a miscarriage or had a still-birth?	☐	☐
Have you moved house (through choice)?	☐	☐
Have you moved house (not through choice)?	☐	☐
Have you had any housing difficulties?	☐	☐
Have you had any other significant event (Please specify in the box below)	☐	☐

** immediate family includes: mother, father, sister, brother, partner, child*

Your thoughts and feelings

This section consists of 20 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the past **two weeks, including today.** Put a cross in the box beside the statement you have picked. If several statements in the group seem to apply equally as well, put a cross in the box by the highest number for the group. Be sure that you do not choose more than one statement for any group, including *Changes in Sleeping Pattern* and *Changes in Appetite*.

Sadness

0 I do not feel sad. ☐
1 I feel sad much of the time. ☐
2 I am sad all the time. ☐
3 I am so sad or unhappy that I can't stand it. ☐

Pessimism

0 I am not discouraged about my future. ☐
1 I feel more discouraged about my future than I used to be. ☐
2 I do not expect things to work out for me. ☐
3 I feel my future is hopeless and will only get worse. ☐

Past Failure

0 I do not feel like a failure. ☐
1 I have failed more than I should have. ☐
2 As I look back, I see a lot of failure. ☐
3 I feel I am a total failure as a person. ☐

Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy. ☐
1 I don't enjoy things as much as I used to. ☐
2 I get very little pleasure from the things I used to enjoy. ☐
3 I can't get any pleasure from the things I used to enjoy. ☐

Guilty Feelings

0 I don't feel particularly guilty. ☐
1 I feel guilty over many things I have done or should have done. ☐
2 I feel quite guilty most of the time. ☐
3 I feel guilty all of the time. ☐

Your thoughts and feelings (page 2 of 4)

Punishment Feelings

0 I don't feel I am being punished. ☐
1 I feel I may be punished. ☐
2 I expect to be punished. ☐
3 I feel I am being punished. ☐

Self-Dislike

0 I feel the same about myself as ever. ☐
1 I have lost confidence in myself. ☐
2 I am disappointed in myself. ☐
3 I dislike myself. ☐

Self-Criticalness

0 I don't criticise or blame myself more than usual. ☐
1 I am more critical of myself than I used to be. ☐
2 I criticise myself for all of my faults. ☐
3 I blame myself for everything bad that happens. ☐

Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself. ☐
1 I have thoughts of killing myself, but I would not carry them out. ☐
2 I would like to kill myself. ☐
3 I would kill myself if I had the chance. ☐

Crying

0 I don't cry anymore than I used to. ☐
1 I cry more than I used to. ☐
2 I cry over every little thing. ☐
3 I feel like crying, but I can't. ☐

Agitation.

0 I am no more restless or wound up than usual. ☐
1 I feel more restless or wound up than usual. ☐
2 I am so restless or agitated that it's hard to stay still. ☐
3 I am so restless or agitated that I have to keep moving or doing something. ☐

Your thoughts and feelings (page 3 of 4)

Loss of Interest

0 I have not lost interest in other people or activities. ☐
1 I am less interested in other people or things than before. ☐
2 I have lost most of my interest in other people or things. ☐
3 It's hard to get interested in anything. ☐

Indecisiveness

0 I make decisions about as well as ever. ☐
1 I find it more difficult to make decisions than usual. ☐
2 I have much greater difficulty in making decisions than I used to. ☐
3 I have trouble making decisions. ☐

Worthlessness

0 I do not feel I am worthless. ☐
1 I don't consider myself as worthwhile and useful as I used to. ☐
2 I feel more worthless as compared to other people. ☐
3 I feel utterly worthless. ☐

Loss of Energy

0 I have as much energy as ever. ☐
1 I have less energy than I used to have. ☐
2 I don't have enough energy to do very much. ☐
3 I don't have enough energy to do anything. ☐

Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern. ☐
1a I sleep somewhat more than usual. ☐
1b I sleep somewhat less than usual. ☐
2a I sleep a lot more than usual. ☐
2b I sleep a lot less than usual. ☐
3a I sleep most of the day. ☐
3b I wake up 1-2 hours early and can't get back to sleep. ☐

Your thoughts and feelings (page 4 of 4)

Irritability

0	I am no more irritable than usual.	☐
1	I am more irritable than usual.	☐
2	I am much more irritable than usual.	☐
3	I am irritable all the time.	☐

Changes to Appetite

0	I have not experienced any changes in my appetite.	☐
1a	My appetite is somewhat less than usual.	☐
1b	My appetite is somewhat greater than usual.	☐
2a	My appetite is much less than before.	☐
2b	My appetite is much greater than usual.	☐
3a	I have no appetite at all.	☐
3b	I crave food all the time.	☐

Concentration Difficulty

0	I can concentrate as well as ever.	☐
1	I can't concentrate as well as usual.	☐
2	It's hard to keep my mind on anything for very long.	☐
3	I find I can't concentrate on anything.	☐

Tiredness or Fatigue

0	I am no more tired or fatigued than usual.	☐
1	I get more tired or fatigued more easily than usual.	☐
2	I am too tired or fatigued to do a lot of the things I used to do.	☐
3	I am too tired or fatigued to do most of the things I used to do.	☐

Partner Relationships

If you are living with a partner, (regardless of whether that partner is the other parent of the child in this study) please answer this section: otherwise, please move to the next section.

Most persons have disagreements in their relationships. Please indicate below, with a cross in the box, the approximate extent of agreement or disagreement between you and your partner for each item on the following list.

The questions in this section are rather personal in nature. We only ask them because partner relationships may affect a child's behaviour. Please remember that this information will be treated strictly confidentially—and will not be divulged by us to anyone, including your partner. Also, make sure that your questionnaire is sealed up in the enveloped provided. It will then be forwarded to Adelaide, for optical scanning, without being opened by our Research Officers in either Port Pirie or Broken Hill.

	Always Agree	Almost Always Agree	Occasionally Disagree	Frequently Disagree	Almost Always Disagree	Always Disagree
Handling family finances	☐	☐	☐	☐	☐	☐
Matters of recreation	☐	☐	☐	☐	☐	☐
Religious matters	☐	☐	☐	☐	☐	☐
Demonstrations of affection	☐	☐	☐	☐	☐	☐
Friends	☐	☐	☐	☐	☐	☐
Sex relations	☐	☐	☐	☐	☐	☐
Conventionality (correct or proper behaviour)	☐	☐	☐	☐	☐	☐
Philosophy of life	☐	☐	☐	☐	☐	☐
Ways of dealing with parents or in-laws	☐	☐	☐	☐	☐	☐
Aims, goals and things believed important	☐	☐	☐	☐	☐	☐
Amount of time spent together	☐	☐	☐	☐	☐	☐
Making major decisions	☐	☐	☐	☐	☐	☐
Household tasks	☐	☐	☐	☐	☐	☐
Leisure time interests and activities	☐	☐	☐	☐	☐	☐
Career decisions	☐	☐	☐	☐	☐	☐

Partner relationships (page 2 of 3)

	All the time	Most of the time	More often than not	Occasionally	Rarely	Never
How often do you discuss or have considered divorce, separation, or terminating your relationship?	☐	☐	☐	☐	☐	☐
How often do you or your partner leave the house after a fight?	☐	☐	☐	☐	☐	☐
In general, how often do you think that things between you and your partner are going well?	☐	☐	☐	☐	☐	☐
Do you confide in your partner?	☐	☐	☐	☐	☐	☐
Do you ever regret that you married? (or lived together)	☐	☐	☐	☐	☐	☐
How often do you and your partner quarrel?	☐	☐	☐	☐	☐	☐
How often do you and your partner "get on each other's nerves"?	☐	☐	☐	☐	☐	☐

	Every day	Almost every day	Occasionally	Rarely	Never
Do you kiss your partner?	☐	☐	☐	☐	☐

	All of them	Most of them	Some of them	Very few of them	None of them
Do you and your partner engage in outside interests together?	☐	☐	☐	☐	☐

How often would you say the following events occur between you and your partner?

	Never	Less than once a month	Once or twice a month	Once or twice a week	Once a day	More often
Have a stimulating exchange of ideas	☐	☐	☐	☐	☐	☐
Laugh together	☐	☐	☐	☐	☐	☐
Calmly discuss something	☐	☐	☐	☐	☐	☐
Work together on a project	☐	☐	☐	☐	☐	☐

Partner relationships (page 3 of 3)

The boxes on the following line represent different degrees of happiness in your relationship. Please cross the box which best describes the degree of happiness, all things considered, of your relationship with your partner.

☐	☐	☐	☐	☐	☐	☐
Extremely unhappy	Fairly un-happy	A little unhappy	Happy	Very happy	Extremely happy	Perfect

Which of the following statements best describes howyou feel about the future of your relationship?

- ☐ I want desperately for my relationship to succeed and *would go to almost any length* to see that it does.
- ☐ I want very much for my relationship to succeed, and *will do all that I can* to see that it does.
- ☐ I want very much for my relationship to succeed, and *will do my fair share* to see that it does.
- ☐ It would be nice if my relationship succeeded, but *I can't do much more that I am doing now* to help it succeed.
- ☐ It would be nice if it succeeded, but *I refuse to do any more than I am doing now* to keep the relationship going.
- ☐ My relationship can never succeed, and *there is no more that I can do* to keep the relationship going.

Thank you!

We are especially grateful that you agreed to participate in this research.

Appendix E: Summary of WISC-IV: Wechsler Intelligence Scale for Children-Fourth Edition subtests

Each WISC-IV subset will be summarised in their order of administration:

Block Design

Block design requires the observation of a 2-dimensional shape the re-creation of the design using three-dimensional coloured blocks. A specific time limit is set for the completion of each design. The Block design task loads upon PRI.

Similarities

Two words are read to the participant and viewed in the stimulus book. The participant is required to describe how the items are conceptually similar. For example: “In what way are an apple and a banana alike?” The optimal response is that they are both fruit. SI measures verbal reasoning, comprehension and problem solving (Zhu & Weiss, 2005) and loads on VCI.

Digit Span

Digit Span has two components; Digit Span Forward and Digit Span Backward. In Digit Span Forward, the examiner reads a string of numbers to the participant and the participants repeats them verbatim. In Digit Span Backward the participant repeats the string of numbers in the reverse order to which they heard them. Digit Span taps Working Memory and the ability to hold information in consciousness whilst actively manipulating the information.

Picture Concepts

In Picture Concepts three rows of pictures are presented in the stimulus book and the participant identified the particular item from each row that forms groups with common characteristics.

Coding

Using a key where numbers (1 to 9) are paired with a shape, participants were required to fill an empty grid so that each number has its corresponding shape. Participants have 120 seconds to complete as much of the grid, in order, as they can. The Coding task is orientated to capture the PSI.

Vocabulary

To begin pictures were viewed in the stimulus book and they require naming. Beyond these items, participants define words that are read aloud by the examiner and viewed in the stimulus book. Vocabulary measures Gc, acquired knowledge and concept formation (Zhu & Weiss, 2005). Vocabulary loads on VCI.

Letter-Number Sequencing

A series of letters and numbers are read to the participant and the string was reorganised and recited so that the numbers are grouped first, in ascending order and the letters are grouped second alphabetically. Letter-Number Sequencing taps WMI and the ability to hold information in consciousness whilst actively manipulating the information.

Matrix Reasoning

The participant considered an incomplete matrix and to identified which of six options would be the missing component. Matrix Reasoning is designed to capture Gf and loads upon the Perceptual organisational/PRI.

Comprehension

The Comprehension involves answering questions based upon social rules and appropriate behaviour. According to Zhu and Weiss (2005) the task is designed to measure "verbal reasoning and conceptualization, verbal comprehension and expression, the ability to evaluate and use past experience, verbal problem solving, and the ability to demonstrate practical information" (p.302). The subtest loads upon the VCI.

Symbol Search

A symbol was identified as a 'target' and the participant scans an array of symbols circling the symbol. Instructions ask the participant to work as quickly as possible for 120 seconds.

Appendix F: Wechsler Intelligence Scale for Children-Fourth Edition psychometric information

Using an Australian sample, WISC-IV Australian internal consistency coefficients were calculated in terms of individual subtest scores and composite scores. Subtest coefficients ranged from 0.75 for Comprehension, to 0.89 for Matrix Reasoning. Reliability coefficients for the composite scores ranged from 0.88 for PSI to 0.95 for FSIQ (Wechsler, 2003). To investigate test-retest reliability, a sample of 40 children and adolescents were readministered the WISC-IV Australian 14 to 50 days after initial administration. Corrected stability coefficients ranged from 0.71 for Word Reasoning to 0.90 for Vocabulary. Likewise, the composite scores ranged from 0.80 for WMI to 0.95 for FSIQ (Wechsler, 2003).

Using principal factors for factor extraction and oblique rotation for factor correlations, Exploratory Factor Analysis on the Australian data confirmed the predicted four factor model for the core subtests. Confirmatory Factor Analysis reinforced the fit of the four factor model for the Australian Sample (Wechsler, 2003).

Appendix G: Summary of potential covariates measured in previous research

Table 1

Summary of covariates measured in previous research

Covariate	Measured in previous studies First author (date)		
Demographic information			
Gender of the child	Cross-sectional studies De la burde (1975) Pocock (1987) Sovcikova (1997) Lanphear (2000) Chiodo (2004) Kim (2009) Cho (2010)	Prospective studies Dietrich (1987) Ernhart (1987) Ernhart (1988) Hansen (1989) Bellinger (1991) Wasserman (1992) Tong (1998) Fergusson (1993) Canfield (2003) Schnaas (2006)	
Familial variables			
Parental cognitive abilities	*Maternal cognitive abilities* Cross-sectional studies Fulton (1987) Pocock (1987) Chiodo (2004) Després (2005) Hu (2006) Kordas (2006) Surkan (2007) – primary caregiver's IQ	Prospective studies Ernhart (1987) Ernhart (1988) Cooney (1989) Dietrich (1991) Bellinger (1991) Wasserman (1992) Mc Michael (1992) Bellinger (1994) Canfield (2003) Schnaas (2006)	*Paternal cognitive abilities* Cooney (1989) – PPVT
	Parental education Cross-sectional studies Pocock (1987) Rabinowitz (1991) Lanphear (2000) Calderón (2001) Wang (2002) Després (2005) Kim (2009) Cho (2010)	Prospective studies Ernhart (1988) Port Pirie cohort Cooney (1989) Ernhart (1989) Schnaas (2006) – head of household	*Maternal education* Hansen (1989) Wasserman (1992) Fergussoon (1993) Bellinger (1994) Sovcikova (1997) Canfield (2003) Chiodo (2004)

Table 1

Continued.

Covariate	Measured in previous studies First author (date)		
Psycho-social & environmental factors			
Markers of SES	*Combined annual family income* Canfield (2003) Schnaas (2006) Kim (2009) *Number of children in family* Hansen (1989) Dietrich (1991) McMichael (1992) Fergusson (1993) Minder (1994) Chiodo (2004) Després (2005) *Social background/class* Pocock (1987) – determined by father's occupation (manual vs. Non-manual) and classification on the Registrar General's classifications. Moore (1982) Bellinger (1991)	*Parental Occupation* De la Burde (1975) – mother working fulltime Fulton (1987) Raboinowitz (1991) Cooney (1989) Boston Cohort – maternal occupation Chiodo (2004), Dietrich (1987),Wang (2002) - Hollingshead's Index of Social Position (based on occupation) Mcmichael (1992) - Daniel's Scale of Occupational prestige (Daniel,1984) Schnaas (2006) – head of household *Ethnicity/race* Rabinowitz (1991) - Language(s) spoken Lanphear (2000) Surkan (2007)	*Pb exposure pathways and SES* Fulton (1987) – School location; Bellinger (1991) – number of residential changes; Wasserman (1992) - apartment living; Fergusson (1993) - Type of home (materials), living near busy road; Sovcikova (1997) - car ownership, proximity to plant; Rabinowitz (1991), Cho (2010)- Area of residence; Kordas (2006) - Home ownership, number of family members per room, family possessions (car, computer, VCR, TV set, stove, refrigerator, radio, and electricity). Calderón (2001) - Bronffman index of SES(comprising crowding, housing conditions, potable water availability, drainage and fathers education).
Care-giving environment	Studies using the *Home Observation for Measurement of the Environment Inventory (*HOME)		*Other measures of environment*
	Cross-sectional studies Chiodo (2004; & Family Environment scale) Després (2005)	Prospective studies Moore (1982) Dietrich (1987) Cooney (1989) Bellinger (1991) Wasserman (1992) McMichael (1992) Fergusson (1993) Canfield (2003)	Rabinowitz (1991), Bellinger (1992) - Parent age Bellinger (1991) - hours per week in childcare Rabinowitz (1991) - Family composition; Bellinger (1991) - Number of adults in household. Minder (1994) - Environmental noise

Table 1

Continued.

Covariate	Measured in previous studies First author (date)
Psycho-social & environmental factors continued.	
Family cohesion /Stress	Boston Cohort - Family Stress Index, Family Adaptability and Cohesion Evaluation Scales, Social Readjustment Rating Scales, Parenting Stress Index, Children's Life Events Inventory, Social Support Network, Child Stress Index. Pocock (1987) - Parent attitude, interests Ernhart (1989) – authoritarian family ideology scale Fergusson (1993) - Maternal emotional responsiveness and avoidance of punishment Sovcikova (1997) - Parent assistance with h/w Després (2005) - Intra family violence
Parent's mental health	Fulton (1987) Pocock (1987) – Mother's mental health Després (2005) - Maternal distress
Quality of Dyadic Relationship	Pocock (1987) Fergusson (1997) – Parental conflict
Parent's current smoking behaviour	McMichael (1992) Minder (1994) Sovicoka (1997)
Pre- and post-natal factors	
Child health	*Child health* Rabinowitz (1991) and maternal health Sovcikova (1997) *Factors impacting blood lead level* Moore (1982), Hansen (1989) - Incidence of pica Port Pirie Cohort – mouthing activity at 15 months, season and rain water use. Laphear (2000) - Serum ferritin and cotinuine level Rahman (2002) Haemoglobin level *Specific endpoints* Bellinger (1991) - Recent medication use Dietrich (1992) - Hearing screen Minder (1994) - Allergies Calderón (2001) - Neurological exam *Nutrition and growth* Cooney (1989), Wasserman (1992) – Height, weight, head circumference Calderón (2001) - Nutritional status, Iron levels Rahman (2002) - Height Canfield (2003) - Child iron status Després (2005) - Child nutrition
Childbehaviour/ educational factors	Cooney (1989) -Bayley Infant Behaviour & Toddler Temperament Questionnaire. Bellinger (1991) - Preschool attendance. Stiles (1993) - educational history. Minder (1994) - Television viewing habits, sleeping habits, emotional functioning, restless behaviour . Kordas (2006) - forgetting to do homework

Table 1

Continued.

Covariate	Measured in previous studies First author (date)		
Pre- and post-natal factors			
Maternal factors	*Maternal age at child's birth* Dietrich (1987) Ernhart (1988) Cooney (1989) Hansen (1989); adjusted for parity) Bellinger (1994) Wasserman (1998) Tong (1998) Kim (2009) *Gravidit/Parityy of mother (Reproductive history)* Després (2005) Dietrich (1991; plus parity) Ernhart (1988; plus parity) Chiodo (2004) – parity *Postnatal complications* Dietrich (1987) – Postnatal Complications Scores Hansen (1989) Fulton 1987 Cooney (1989)	*Prenatal exposure to teratogenic agents* Ernhart (1987) - alcohol, smoking and other drugs Erhhart (1988) Cooney (1989) Dietrich (1991) - maternal alcohol, cigarette and marijuana use during pregnancy Canfield (2003) - smoking Chiodo (2004) - Maternal alcohol use prior to and after conception Després (2005) Kim (2009) Port Pirie cohort *Health information* Port Pirie Cohort – Body Mass Index, maternal nutritional practices.	
Delivery factors	*Mode of delivery* Rabinowitz (1991)	*Hospital stay post birth* Pocock (1987), Hansen (1989)	
Neonatal factors	*Birth weight* Moore (1982) Pocock (1987) Dietrich (1987) Ernhart (1987) Ernhart (1988) Cooney(1989) Bellinger (1991) Wasserman (1992) McMichael (1992) Fergusson (1993) Canfield (2003) Schnaas (2006) Surkan (2007) Cho (2010) *Jaundice* Port Pirie Cohort Hansen (1989) plus phototherapy	*Birth order* Ernhart (1987) Pocock (1987) Bellinger (1991) Dietrich (1991) Erhhart (1988) Mexico city cohort Minder (1994) Tong (1998) *Fetal growth* Dietrich (1987) - Head circumference Port Pirie Cohort – Size for gestational age *Intervention* Port Pirie Cohort – Oxygen at birth	*Gestational age* Pocock (1987) Dietrich (1987) Cooney (1989) *Incidence and duration of breast-feeding* McMichael (1992) Fergusson (1997) *5-minute Apgar* Dietrich (1991) Port Pirie Cohort Mexico City Cohort

Appendix H: Items from the Middle Child Home Observation for Measurement of the Environment Inventory (MC HOME)

Items from the MC HOME (adapted from Bradley et al., 1988, p. 63)

I. Emotional and Verbal Responsivity

1. Family has fairly regular and predictable daily schedule for child (meals, bedtime. TV, homework etc.)
2. Parent sometimes yields to child's fears or rituals (allows nightlight, accompanies child on a new experience, etc.)
3. Child has been praised at least twice during past week for doing something
4. Child is encouraged to read on their own
5. Parent encourages child to contribute to conversation during the visit
6. Parent shows some positive emotional response to praise of child by visitor
7. Parent responds to child's questions during interview
8. Parent used complete sentence structure and some long words in conversing
9. When speaking of or to child, parent's voice conveys positive feelings
10. Parent initiates verbal interchanges with visitor, asks questions, makes spontaneous comments

II. Encouragement of maturity

11. Family requires child to carry out certain self-care routines (e.g., makes bed, cleans room, cleans up after spills, bathes self). (A 'yes' requires 3 out of 4.)
12. Family requires child to keep living and play area reasonably clean and straight
13. Child puts their outdoor clothing, dirty clothes, night clothes in special place
14. Parents sets limits for child and generally enforces them (curfew, homework before TV, or other regulations that fit family pattern)

15. Parent introduces interviewer to child
16. Parent is consistent in establishing and or applying family rules
17. Parent does not violate rules of common courtesy

III. Emotional climate

18. Parent has not lost temper with child more than once during previous week
19. Mother reports no more than one instance of physical punishment occurred during past month
20. Child can express negative feelings toward parent without harsh reprisals
21. Parent has not cried or been visibly upset in child's presence during last week
22. Child has special place in which to keep their possessions
23. Parent talks to child during visit (beyond correction and introduction)
24. Parent uses some term of endearment or some diminutive for child's name when talking about child at least twice during visit
25. Parent does not express overt annoyance with or hostility toward child (e.g., complains, describes child as 'bad,' says child won't mind)

IV. Growth-Fostering Materials and Experiences

26. Child has free access to record player or radio
27. Child has free access to musical instruments (piano, drum, ukulele, guitar, etc.)
28. Child has free access to at least ten appropriate books
29. Parent buys and reads newspaper daily
30. Child has free access to desk or other suitable place for reading or studying
31. Family has a dictionary and encourages child to use it.
32. Child has visited a friend by self in the past week
33. House has at least two pictures or other type of art work on the walls

V. Provision for Active Stimulation

34. Family has a television, and it is used judiciously, not left continuously (No TV required an automatic ‘no,’ any scheduling scores ‘yes’)
35. Family encourages child to develop or sustain hobbies
36. Child is regularly included in family’s recreational hobby
37. Family provides lessons or organisational memberships to support child’s talents (YMCA, YWCA, gymnastic lessons, music lessons, art lessons, membership to art centre)
38. Child is ready access to at least two pieces of playground equipment in the immediate vicinity
39. Child has access to library card and family arranges for child to go to library once a month
40. Family member has taken child, or arranged for child to go to scientific, historical, or art museum within the past year
41. Family member has taken child, arranged for to take a trip on a plan, train or bus within the past year

VI. Family Participation in Developmentally Stimulating Experiences

42. Family visits or receives visits from relatives or friends at least once every other week
43. Child has accompanied parent on a family business venture 3-4 times within the past year (e.g., garage, clothing shop, appliance repair shop)
44. Family member has child, or arranged for child to attend some type of live musical or theatre performance
45. Family member has taken child or arranged for child to go on a trip of more than 50 miles from their home (50 miles radial distance, not total distance)
46. Parents discuss television programs with child

47. Parent helps child to achieve motor skills (e.g., ride a 2-wheel bicycle, roller skate, ice skate, play ball)

VII. Paternal involvement

48. Father (or father substitute)
49. Child sees and spends some time with father or father figure 4 days a week
50. Child eats at least one meal per day, on most days, with mother and father (or mother and father figures). (One parent families receive an automatic 'no')
51. Child has remained with this primary family group for all their life aside from 2-3 week vacations, illnesses, or parent visits from grandparents, etc. (A 'yes' requires no changes in mother's, father's, grandparent's presence in the home since birth).

VIII. Aspects of the Physical Environment

52. Child's room has a picture or wall decoration appealing to children
53. The interior of the house or apartment is not dark or perpetually monotonous
54. In terms of available floor space, the rooms are not overcrowded with furniture
55. All visible rooms of the house are reasonably clean and minimally cluttered
56. There is at least 100 square feet of living space per person in the house
57. House is not overly noisy (e.g., TV, shouts of children, radio, nearby roads or thoroughfares)
58. Building has no potentially dangerous structural or health defects (e.g., plaster coming down, stairway with boards missing, paint peeling, rodents)
59. Child's outside play environment appears safe and free of hazards.(No outside play area requires automatic 'no')

Appendix I: Example of study newsletter

Making sure they are now safe

A study of the Health Effects of Lead in Children,
funded by
the National Health and Medical Research Council

NEWSLETTER—October 2009

Over the past 25 years, increasing awareness of the possible problems of being exposed to lead, especially in children, has resulted in dramatic reductions in the amount of lead in the air and dust in Port Pirie and Broken Hill. '*Making sure they are now safe*' is a research project which commenced in Port Pirie and Broken Hill in 2007, to establish whether the levels of lead to which the children of both cities are *currently* exposed, are safe.

What stage are we at now?
Around 120 families have agreed to take part – but we still need more for this research to succeed. Those families who have already joined, have found the study easy and rewarding.

When will we know the results of the study?
Recruitment of families will continue to the end of this year—and into the earlier part of next year. The results will be analysed as soon as recruitment finishes. If any parent wishes to know the results for his or her child before the end of the study we will try and provide whatever information is possible at the time of the request.

Meet the Project Officers

Trudi Manfield (Port Pirie) has lived in Port Pirie for most of her life, and before she started working on the Lead Study she was a Speech Pathology Assistant. Married to local real-estate agent Sean, she has 3 beautiful daughters Danica (14), Cassidy (10) and Edyn (5); and the things she likes doing most in life are playing hockey, holidaying near the sea, and spending time with

Lyn Campigli (Broken Hill) is actively involved in several Community Service Projects, including Rescue and Rehabilitation of Australian Native Animals (RRANA); Joeys (South Australia Lone Cub Scouts) which involves Satellite meetings through the School of the Air, and monthly correspondence with children from outback properties of Western NSW. Together with husband Peter, she hosts American Field Service students and community service participants from overseas. She has two married daughters and six grandchildren, and her hobbies include gardening, patchwork,

Who is involved in this study?
The study involves seven and eight-year-old children and their families. The children need to be of this age in order to undertake the computer 'games' and 'tests' that are used to assess their abilities. Families need to be involved as well – because many things beside lead are important in determining the abilities and well-being of children.

More about the Study: What makes it different from previous studies?
Earlier studies were often undertaken to convince the world, - and especially local health authorities, - that exposure to lead was harmful – and that action was needed to reduce the amount of lead escaping into the environment from mining and refining activities. A large effort by industry, councils and state governments over the past 30 years has resulted in lower blood lead levels in Broken Hill and Port Pirie than have ever been observed in the past. However a few medical researchers are still not convinced that enough has been done. This latest study is trying to answer the question– Are current exposures to lead now safe?

COULD YOUR FAMILY HELP WITH THIS IMPORTANT WORK?

Please ring:-
Trudi Manfield, on 8638 4100 if you live in or around Port Pirie;
Lyn Campigli on 8080 1259 if you live in or around Broken Hill.

Will I get paid if my family takes part?

It is considered unethical to offer financial incentives to people to take part in medical research. However Mums and Dads are welcome to claim $25 *each* to cover costs of travel and time spent in the study.

Appendix J: Distribution of WISC-IV: Wechsler Intelligence Scale for Children-Fourth Edition FSIQ and subscale scores

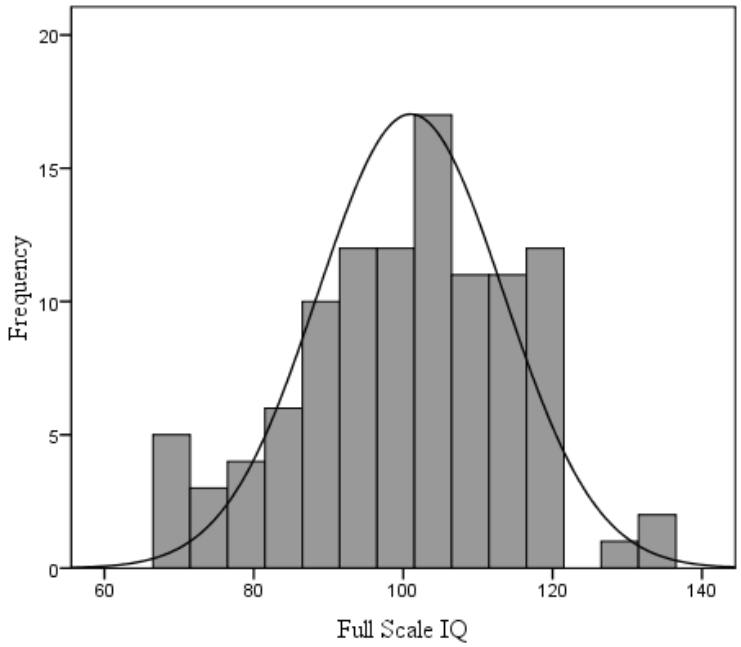


Figure 1

Distribution of Full Scale IQ scores

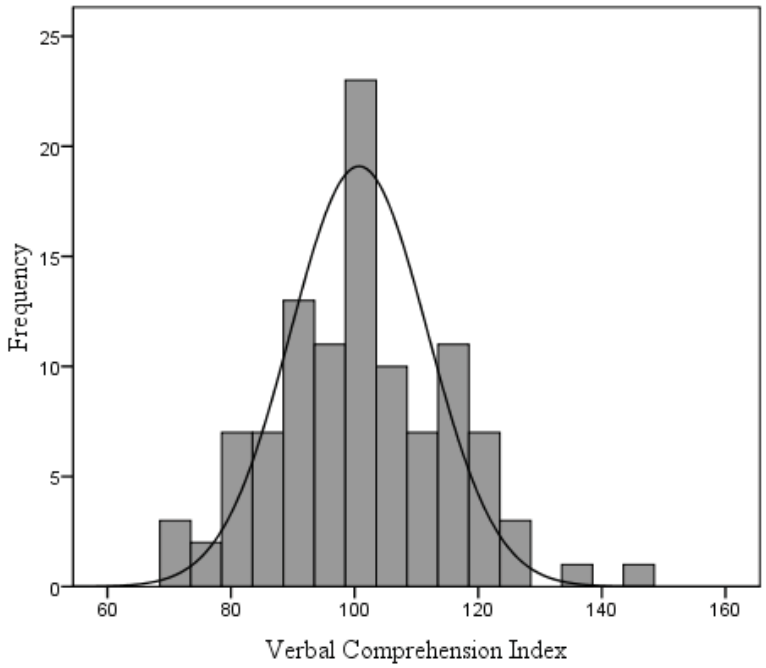


Figure 2

Distribution of Verbal Comprehension Index scores

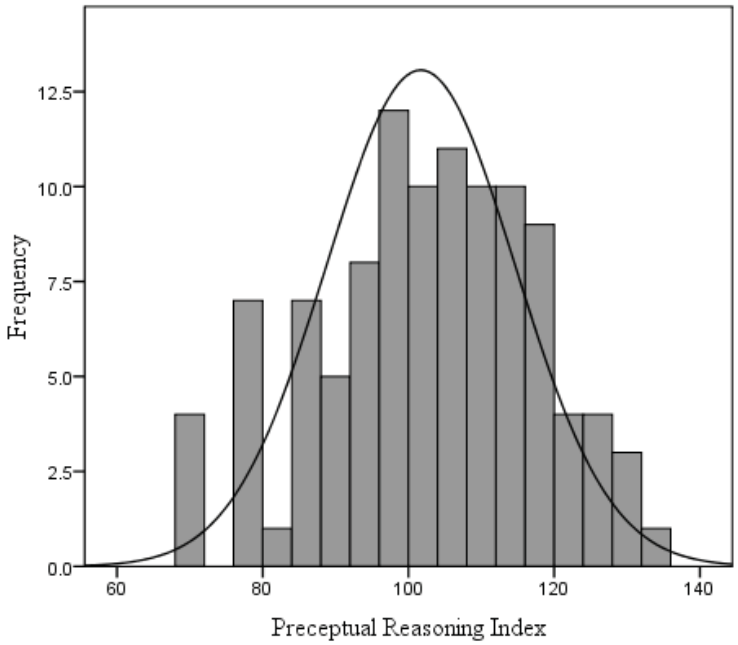


Figure 3

Distribution of Percepual Reading Index scores

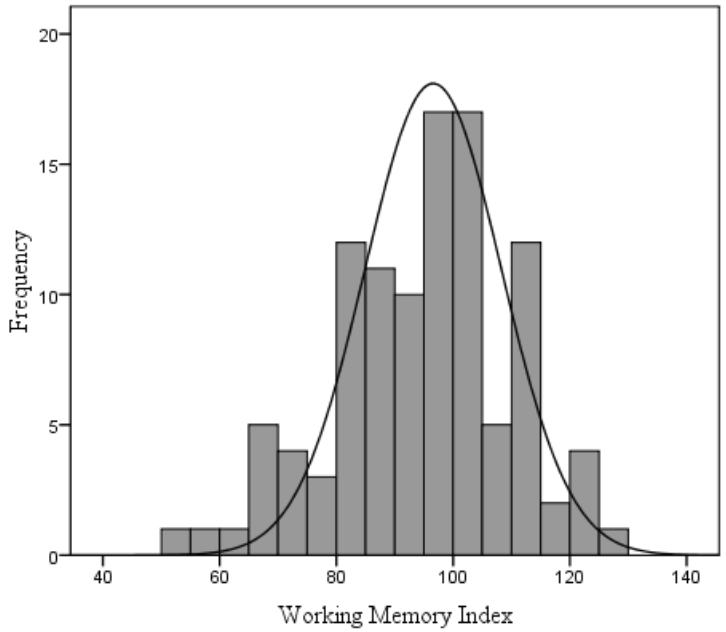


Figure 4

Distribution of Working Memory Index scores

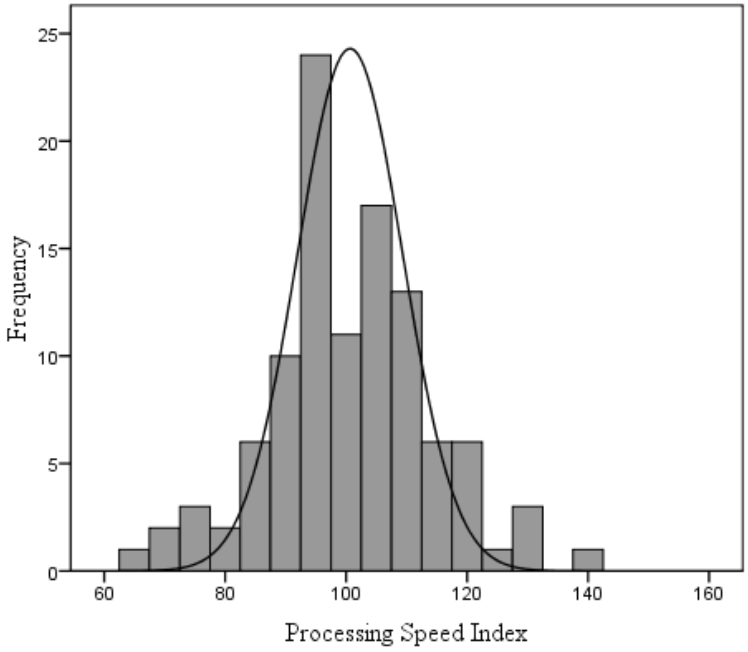


Figure 5

Distribution of Processing Speed Index scores

Appendix K: Distribution of WAIS-III FSIQ and subscale scores

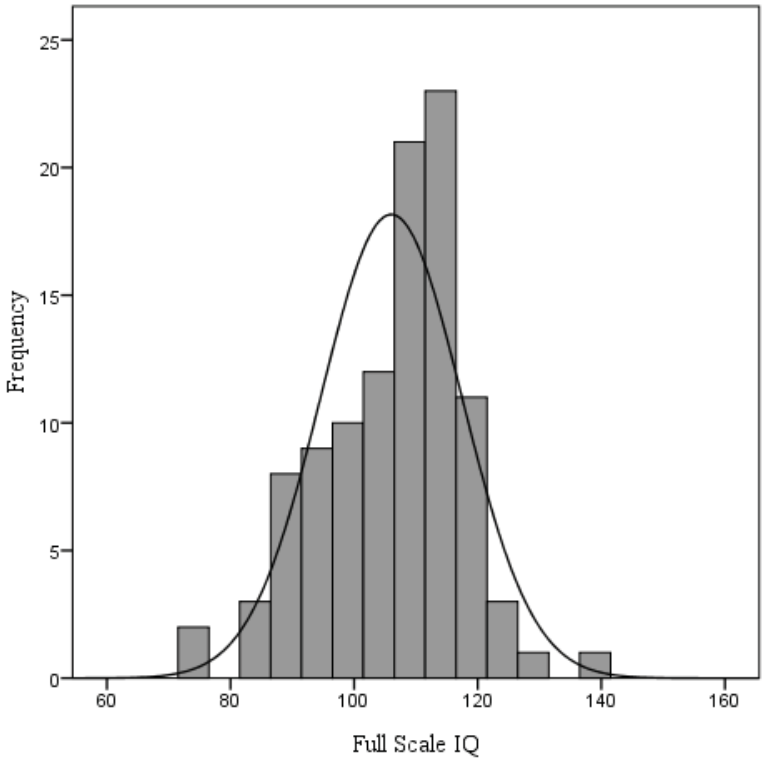


Figure 1

Distribution of Full Scale IQ scores

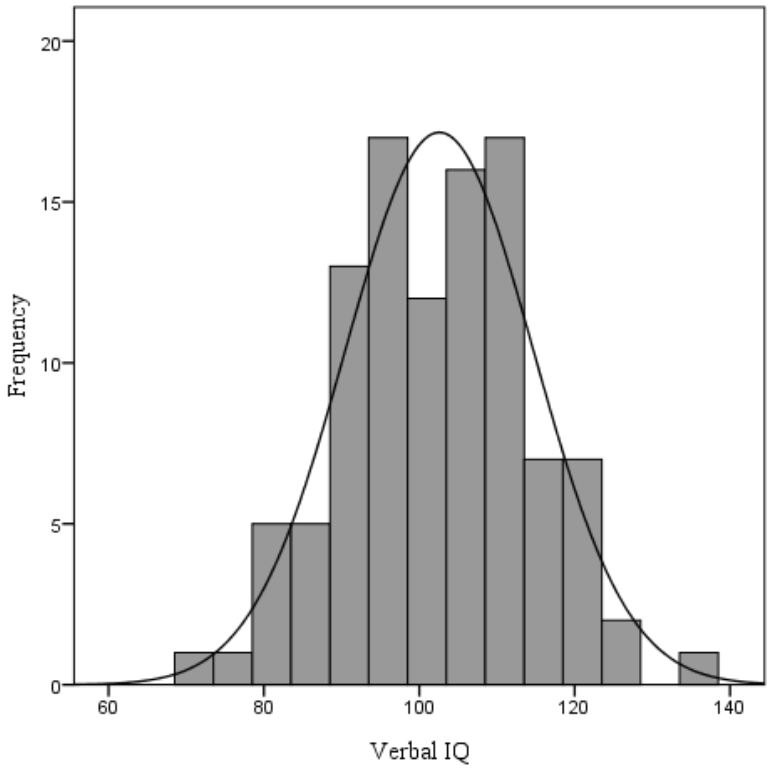


Figure 2

Distribution of Verbal IQ scores

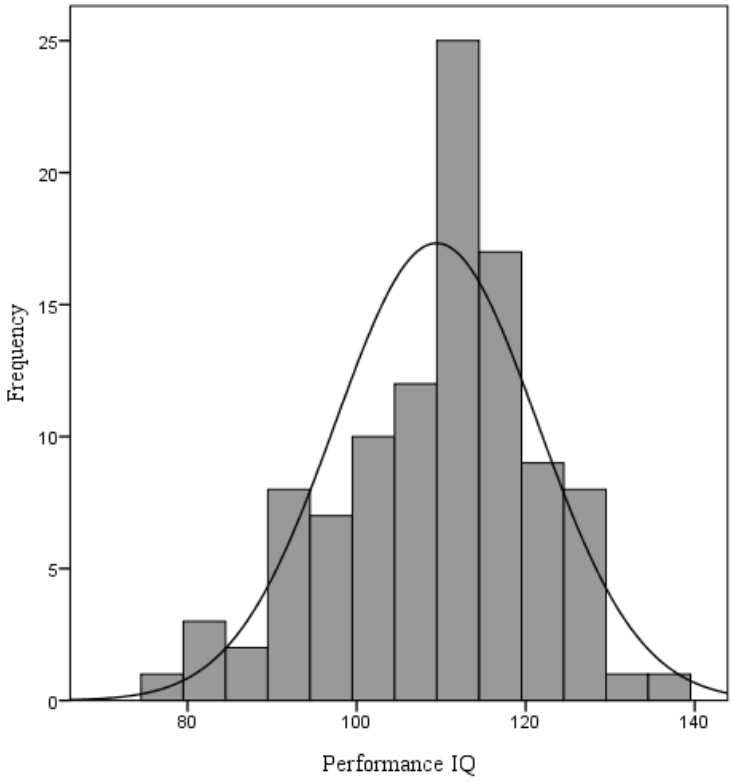


Figure 3

Distribution of Performance IQ scores

Appendix L: Unadjusted Spearman inter-correlations between potential covariates

Table 1

Unadjusted Spearman inter-correlations between potential covariates.

Potential covariates	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.
1. WAIS-III FSIQ	1.00	- 0.18	0.21*	- 0.03	0.39**	- 0.14	- 0.21*	- 0.12	0.16	0.01	- 0.04	0.10	0.05
2. Maternal IT	- 0.18	1.00	0.22*	0.08	- 0.06	0.11	- 0.05	- 0.02	- 0.10	0.00	0.09	0.14	- 0.15
3. SPM	0.21*	0.22 *	1.00	- 0.20	0.11	0.02	- 0.12	- 0.05	0.05	0.01	0.06	0.18	0.10
4. Paternal IT	- 0.04	0.08	- 0.20	1.00	0.03	- 0.05	0.02	0.17	- 0.01	0.17	- 0.20	0.10	0.15
5. MC HOME total	0.39**	- 0.06	0.11	0.02	1.00	- 0.17	- 0.12	- 0.15	- 0.16	0.33**	0.24*	- 0.02	0.16
6. Total stressful life events	- 0.14	0.11	0.02	- 0.05	- 0.17	1.00	0.48**	0.18	0.09	- 0.03	- 0.01	- 0.13	- 0.05
7. Stressful life events still affecting	- 0.21*	- 0.05	- 0.12	0.02	- 0.12	0.48**	1.00	0.18	- 0.07	0.03	0.08	- 0.35**	0.09
8. Maternal BDI-II	- 0.12	- 0.02	- 0.05	0.17	- 0.15	0.18	0.18	1.00	0.27*	- 0.47**	- 0.20	- 0.07	- 0.06
9. Paternal BDI-II	0.16	- 0.10	0.05	- 0.01	- 0.16	0.09	- 0.07	0.27*	1.00	- 0.27*	- 0.14	0.07	0.04
10. Dyadic Adjustment	0.01	0.00	0.01	0.17	0.33**	- 0.03	0.03	- 0.47**	- 0.27*	1.000	0.21	- 0.03	- 0.09
11. Parents' years residence in centre	- 0.04	0.09	0.06	- 0.20	0.24*	- 0.01	0.08	- 0.20	- 0.14	0.21	1.00	- 0.14	- 0.05
12. Mother's age at birth	0.10	0.14	0.18	0.10	- 0.02	- 0.13	- 0.35**	- 0.07	0.07	- 0.03	- 0.14	1.00	- 0.02
13. Birth weight	0.05	- 0.15	0.10	0.15	0.16	- 0.05	0.09	- 0.06	0.04	- 0.09	- 0.05	- 0.02	1.00

Note: BDI-II: Beck Depression Inventory – Second Edition; FSIQ: Full scale IQ; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; SPM: Standard Progressive Matrices; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition.

* Correlation is significant at the 0.05 level

** Correlation is significant at the 0.01 level

Appendix M: Historical, community and economic factors impacting study recruitment

It is hypothesised that historical, community, political and economic factors may have influenced the recruitment of participants into the current study. These factors will be discussed in turn in order to provide some context for the recruitment challenges faced in Port Pirie and Broken Hill.

Historical factors

As outlined in Chapter 1, the negative impacts of childhood Pb exposure were first formally recognised as an Australian phenomenon by Gibson et al. (1882) and later generalised to other populations. Hence, ties to Australian populations have been a part of contemporary discussions about Pb neurotoxicity from the outset. Following the eradication of leaded paint and petrol in Australia, late 20th and early 21st century discussions about the negative effects of population Pb exposure in Australia have revolved around a number of small rural communities (including Port Pirie and Broken Hill) exposed to Pb through the mining and smelting industries. Hence, these communities have been differentiated from the general population due to their associations with Pb.

As international discussions about the nature of Pb deficits gained momentum in the late 1970's and early 1980's, high Pb exposure and subsequently, often disadvantaged, communities were identified as locations for the establishment of prospective studies to advance knowledge about the effects of Pb on children. Indeed, the most significant Australian work in the field was the Port Pirie Cohort Study (e.g. Baghurst et al., 1992) which had a long-term profile within Port Pirie as it recruited children post-natally and followed them into their teens.

The presence of a long-term study such as the Port Pirie Cohort Study and the resultant media attention, can be hypothesised to have diminished tolerance for research

investigating Pb exposure and shaped their views about the effects of Pb upon their community. Adding to this, published research which has commented on the cognitive function of the population and even more sensitively, that of the communities' children, has no doubt shaped population numbers, inhabitant's sense of identity and self esteem and the emerging stereotypes and stigma associated with these communities. These points are not intended to diminish the objective value of research that seeks to delineate threats to human health and well-being, rather it is important to note that research agendas (regardless of their outcome) leave lasting impressions on individual participants and entire communities.

Community factors

Population attraction and retention in rural and remote communities in Australia is challenged by limited (Australia Futures Task Force, 2007):

- *Employment opportunities:* While the mining and smelting industries generate job opportunities, there can be limits to the diversity of employment beyond these industries (e.g. employment in the Arts may be limited).
- *Housing and infrastructure:* There can be limitations to the availability and affordability of appropriate housing as well as access to and maintenance of transportation, telecommunications, energy and water supplies.
- *Lifestyle and Community:* The social infrastructure of a region is built by the interplay of community amenities, projects, services (e.g. education, health, housing, culture, urban design, social assistance and welfare) and spaces which foster quality of life and well-being.
- *Healthcare:* Rural and remote communities have found it notoriously difficult to attract and retain specialised health professionals and this can affect the health of the community and exacerbate the challenges of distance and transportation.

- *Education and Training:* Rural communities may be challenged by a lack of education and training opportunities such that young people, the future skilled employees, must leave the community to be educated, thus reducing their community ties and investment.

When these challenges are coupled with industry which produces "poisoned landscapes" (Bailey, Sargent, Goodman, Feeman, Brown, 1994) of persistent environmental contamination and threatens population health, communities can struggle to attract and retain populations even further and can suffer from transient populations and reduced investment in infrastructure, community, health care and education. This threat to population retention has only grown momentum over the last century as more evidence is accumulated about the detrimental effects of Pb exposure on humans .

While the communities of Port Pirie and Broken Hill have been educated and engaged by public health initiatives aiming to reduce and manage Pb exposure levels of the population, there is limited published information available about how Port Pirie and Broken Hill residents conceptualise and view the possible detriments related to Pb exposure – for example, whether the risk of Pb exposure is viewed as valid or real, and how community members negotiate health risk, with decisions to live and work in these cities. Small insights are offered by Mudge (1996) who conducted her doctoral thesis on data from the the Port Pirie Cohort Study; Mudge (1996) noted that teachers, an educated group with investments in child wellbeing, present varied and defensive attitudes towards Pb exposure. Likewise, Mudge (1996) referenced the work of Bullock (1988) who conducted interviews with Port Pirie residents while researching the material for *Port Pirie, the friendly city: The undaunted years*. Bullock (1988) reported that through hundreds of interviews he gleaned that the general opinion of the community was that "outside reports [of the effects of Pb exposure] were a load of rubbish and there were countless people who had lived in Pirie to ripe old ages, without any apparent ill-effects from lead" (p.270).

Bullock (1998) highlights an important limitation to community understandings of the effects of low-level Pb exposure; low-level exposure is not accompanied by distinct and obvious symptoms, but rather Pb can produce a subtle range of changes to the nuances of cognitive functioning. Indeed, the findings of research investigating the effects of Pb on childhood cognitive abilities has harboured highly complex statistical models and used 'IQ point loss' as the primary explanatory dialogue; these concepts hold little explanatory power for the general population. In addition, despite knowledge gains about the effects of Pb there remains a lack of consensus about the safest level of exposure. This lack of consensus has stalled the review of the Pb exposure guidelines. Communities may have been left frustrate and confused by the way that research about Pb exposure has remained on the political agenda, but how no major political or knowledge-based advances have been made for several decades.

Indeed the challenges and intricacies associated with understandings of Pb exposure are documented by Ferguson and Lieu (1997) who investigated American paediatrician's (N = 155) practice and attitudes towards PbB testing as primary care physicians. This research found that despite CDC recommendations for universal PbB testing, 73% of paediatricians did not adhere to this guideline and only 46% of paediatricians fully understood the reasons for the recommendation. Paediatricians that agreed with the statements "Lead testing is not necessary for my patients" and "The venipuncture necessary for a lead test is not worth the trauma to the child or the inconvenience to parents" were significantly ($p < 0.05$) less likely to undertake the universal screening that had been recommended. Hence, this research illustrated that even a specialist group, trained in child health, can exhibit a lack of understanding of the need for screening of Pb levels and about the effects of Pb exposure for children.

From a health promotion perspective, the concept of "issue fatigue" (Maibach, Nisbet, Baldwin, Akerlof & Diao, 2010, p. 9) may also hold some explanatory power in discussions about challenges to recruitment. "Issue fatigue" has previously been observed in population

level responses to the threats of climate change; Maibach et al. (2010) found that widespread concern about global warming distinctly and markedly declined as education and media campaigns increased and there was an emergence of individuals and groups driven by the conviction that climate change was a fallacy. Hence, an increase in discussion about a topic was linked to diminished community concern and the emergence of extremist oppositional movements. It can be hypothesised that communities (and individuals) become overloaded with information and adaptively become desensitised to the threats of an issue, a literal 'switching off' of attention and interest; through public health campaigns, families in Port Pirie and Broken Hill are consistently reminded that they have additional responsibilities, over and above, those imposed on other families and that they need to implement a large set of mitigation strategies to minimise the neurological impact of Pb exposure on their children.

Economic factors

The communities of Port Pirie and Broken Hill grew in rural Australia due to the geological and geographic characteristics of the land – their link to industry is inherent and at the cornerstone of community identity. The Pb indistry delivers economic benefits to the community, skills the workforce, funds community programs and supports local businesses and indeed, many families on the mining or Pb smelting industry for their livelihoods.

Industry links may have influenced some community member's decisions to consent for their family to be involved in this study. For example, while the occupational spread of families in the sample aligned with the ABS 2006 Australian census data (ABS, 2007, 2007a) for these regions (and included families employed by the mining and smelting industries), it is possible that some families felt discouraged to participate or threatened by the study agenda due to their occupational ties in each region. Research of this kind can challenge people's decisions to be involved in the mining and smelting industry and highlight tensions between employment choices and decisions relating to the health and wellbeing of one's family.

Historically, mining companies have been characterised as taking a "devil my care" (Jenkins, 2004, p. 24) view of the repercussions of their activities upon the land where they operate, but more recently companies have become more savvy in creating dialogue (through public media and informal channels) that positions industry as an important *part of* the community. As Jenkins (2004) writes "[t]he companies frame themselves as central components of the communities in which they operate, as neighbours and as key instigators of economic development and improved standards of living. The rationale behind the existence of a mine [or smelter] in a community is that the community will be better off in both the short and long term"' (p. 29). For example, in Port Pirie the smelter operators, Nystar, have been actively involved in community outreach and education; The Port Pirie *Tenby10* program was an initiative chaired by Nystar and partnered by the South Australian Department of Health, the Port Pirie Regional Council, and the Environmental Protection Agency. Under the *Tenby10* program, Nystar ran smelter bus tours, planted vegetation around the smelter to reduce dust movement, installed 'wind roses' to aid understanding of emission distribution patterns, installed dust monitors, established policies for employee and contractor personal hygiene (shower before leaving work, not allowing children access to work vehicles), monitoring employee and contractor blood lead levels and introducing a number of site cleanliness policies.The *Tenby10* program expired at the end of 2010 and in September 2010, Nystar launched the *Ten for Them* initiative which is set to be a community outreach and education program, but it is yet to state targets or timelines for community PbB level reduction.

To complicate the situation, the impacts of community Pb exposure have the propensity to negatively impact the sustainability of Port Pirie and Broken Hill as regional centres. In a number of western countries Pb smelters have been closed due to an inability to sufficiently reduce emissions to meet community exposure standards. The emissions released by the Nystar smelter in Port Pirie already account for the fact that for the full year 2010,

27.7% of children under the age of 5 years had PbB levels exceeding 10 µg/dL, the NHMRC recommendation.

If the recommended PbB level guidelines are revised and lowered, which is highly anticipated, this will further complicate and challenge the acceptability of mining and smelting emissions in Port Pirie and Broken Hill. Industry closure would negatively impact the employment rate and opportunities within the communities of Port Pirie and Broken Hill and may result in diminished population numbers.

Appendix N: Multiple regression modelling with 'breastfeeding' substituted by potential covariates to the breastfeeding – cognitive abilities association

Table 1

Multiple regression model with FSIQ as the dependent variable (n = 73) and breastfeeding substituted for maternal age at child's birth.

Model		Unstandardised Coefficient β (Std. Error)	*P*-level
Step 1[a]	(Constant)	40.93 (24.11)	0.10
	WAIS-III FSIQ	0.03 (0.16)	0.85
	Current maternal smoking	5.15 (5.26)	0.33
	Birth weight	0.00 (0.00)	0.18
	MC HOME total	1.27 (1.01)	0.21
	Total stressful life events	- 0.77 (0.80)	0.34
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	-12.73 (5.60)	0.03
	Low income	0.00	
	Middle Income	5.20 (3.82)	0.18
	High Income	7.92 (4.40)	0.08
	Maternal age at child's birth	0.96 (0.34)	0.01
Step 2[b c]	(Constant)	53.25 (24.22)	0.03
	WAIS-III FSIQ	0.03 (0.15)	0.86
	Current maternal smoking	5.80 (5.22)	0.27
	Birth weight	0.00 (0.00)	0.11
	MC HOME total	1.01 (0.01)	0.32
	Total stressful life event	-0.68 (0.83)	0.42
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 12.75 (5.47)	0.02
	Low income	0.00	
	Middle Income	5.03 (3.77)	0.19
	High Income	6.11 (4.36)	0.17
	Maternal age at child's birth	0.87 (0.34)	0.01
	PbB	- 2.66 (1.22)	0.03
	PbB^2	0.13 (0.07)	0.07

Note. Blood lead terms are **bold**. FSIQ: Full scale IQ; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; *n*: subsample size; PbB: blood lead; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition.

[a] $R^2 = 0.43$, Adjusted $R^2 = 0.35$.

[b] $R^2 = 0.48$, Adjusted $R^2 = 0.38$, $\Delta R^2 = 0.05$. $\Delta F\ (2, 61) = 2.60$, $p = 0.08$.

[c] $F\ (11, 61) = 5.02$, $p < 0.001$.

Table 2

Multiple regression model with FSIQ as the dependent variable (n = 74) and breastfeeding substituted for highest level of parental education

Model		Unstandardised Coefficient β (Std. Error)	*P*-level
Step 1[a]	(Constant)	69.49 (22.91)	< 0.001
	WAIS-III FSIQ	0.12 (0.16)	0.48
	Current maternal smoking	- 2.41 (4.81)	0.62
	Birth weight	0.00 (0.00)	0.31
	MC HOME total	0.38 (1.02)	0.71
	Total stressful life events	- 0.83 (0.86)	0.34
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 6.56 (5.47)	0.24
	Low income	0.00	
	Middle Income	6.18 (4.14)	0.14
	High Income	10.36 (4.58)	0.03
	Low parental education	0.00	
	Middle parental education	0.66 (3.62)	0.86
	High parental education	2.46 (3.99)	0.54
Step 2[b c]	(Constant)	72.94 (22.56)	< 0.001
	WAIS-III FSIQ	0.16 (0.16)	0.33
	Current maternal smoking	- 0.60 (4.88)	0.90
	Birth weight	0.00 (0.00)	0.15
	MC HOME total	0.28 (1.03)	0.79
	Total stressful life event	- 0.80 (0.90)	0.38
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 6.85 (5.37)	0.21
	Low income	0.00	
	Middle Income	5.66 (4.12)	0.17
	High Income	8.08 (4.60)	0.08
	Low parental education	0.00	
	Middle parental education	- 0.50 (3.64)	0.87
	High parental education	- 0.79 (4.26)	0.85
	PbB	- 2.89 (1.33)	0.03
	PbB^2	0.15 (0.08)	0.06

Note. Blood lead terms are **bold**. FSIQ: Full scale IQ; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; *n*: subsample size; PbB: blood lead; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition.

[a] $R^2 = 0.38$, Adjusted $R^2 = 0.28$.

[b] $R^2 = 0.42$, Adjusted $R^2 = 0.31$, $\Delta R^2 = 0.05$. ΔF (2, 61) = 2.41, $p = 0.10$.

[c] F (12, 61) = 3.73, $p < 0.001$.

Table 3

Multiple regression model with FSIQ as the dependent variable (n = 74) and breastfeeding substituted for gestation

Model		Unstandardised Coefficient β (Std. Error)	*P*-level
Step 1[a]	(Constant)	68.90 (23.02)	< 0.001
	WAIS-III FSIQ	0.13 (0.16)	0.41
	Current maternal smoking	-2.73 (4.83)	0.57
	Birth weight	0.00 (0.00)	0.39
	MC HOME total	0.46 (1.02)	0.66
	Total stressful life events	- 0.79 (0.88)	0.37
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	-5.81 (5.70)	0.31
	Low income	0.00	
	Middle Income	6.23 (4.02)	0.13
	High Income	10.63 (4.58)	0.02
	Less than 37 weeks gestation	0.00	
	37 to 40 weeks gestation	- 0.30 (3.15)	0.93
	More than 40 weeks gestation	4.38 (6.06)	0.47
Step 2[b c]	(Constant)	76.15 (22.82)	< 0.001
	WAIS-III FSIQ	0.14 (0.16)	0.38
	Current maternal smoking	- 1.12 (4.89)	0.82
	Birth weight	0.00 (0.00)	0.24
	MC HOME total	0.31 (1.030	0.76
	Total stressful life event	- 0.75 (0.92)	0.41
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 6.37 (5.56)	0.26
	Low income	0.00	
	Middle Income	5.71 (3.96)	0.16
	High Income	8.42 (4.57)	0.07
	Less than 37 weeks gestation	0.00	
	37 to 40 weeks gestation	- 0.15 (3.07)	0.96
	More than 40 weeks gestation	4.50 (5.92)	0.45
	PbB	- 2.80 (1.26)	0.03
	PbB^2	0.14 (0.08)	0.07

Note. Blood lead terms are **bold**. FSIQ: Full scale IQ; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; *n*: subsample size; PbB: blood lead; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition.

[a] $R^2 = 0.38$, Adjusted $R^2 = 0.28$.

[b] $R^2 = 0.43$, Adjusted $R^2 = 0.32$, $\Delta R^2 = 0.05$. ΔF (2, 61) = 2.64, $p = 0.08$.

[c] F (12, 61) = 3.82, $p < 0.001$.

Table 4

Multiple regression model with FSIQ as the dependent variable (n = 74) and breastfeeding substituted for birth order

Model		Unstandardised Coefficient β (Std. Error)	*P*-level
Step 1[a]	(Constant)	66.39 (22.67)	0.01
	WAIS-III FSIQ	0.14 (0.16)	0.38
	Current maternal smoking	- 2.24 (4.86)	0.65
	Birth weight	0.00 (0.00)	0.26
	MC HOME total	0.41 (1.01)	0.69
	Total stressful life events	- 0.86 (0.86)	0.32
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 6.56 (5.64)	0.25
	Low income	0.00	
	Middle Income	6.11 (4.16)	0.15
	High Income	10.27 (4.64)	0.03
	First born child in family	0.00	
	Second born child in family	0.55 (3.35)	0.87
	Third or later born child in family	0.11 (3.89)	0.98
Step 2[b c]	(Constant)	72.50 (22.34)	< 0.001
	WAIS-III FSIQ	0.16 (0.16)	0.30
	Current maternal smoking	- 0.39 (4.90)	0.94
	Birth weight	0.00 (0.00)	0.15
	MC HOME total	0.24 (1.03)	0.82
	Total stressful life event	- 0.83 (0.89)	0.35
	No smoking during pregnancy	0.00	
	Smoked during pregnancy	- 7.55 (5.51)	0.18
	Low income	0.00	
	Middle Income	5.16 (4.09)	0.21
	High Income	7.64 (4.66)	0.11
	First born child in family	0.00	
	Second born child in family	1.24 (3.31)	0.71
	Third or later born child in family	1.80 (3.91)	0.65
	PbB	- 2.90 (1.27)	0.03
	PbB^2	0.14 (0.08)	0.06

Note. Blood lead terms are **bold**. FSIQ: Full scale IQ; MC HOME: Middle Child Home Observation for Measurement of the Environment Inventory; *n*: subsample size; PbB: blood lead; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition.

[a] $R^2 = 0.37$, Adjusted $R^2 = 0.27$.

[b] $R^2 = 0.43$, Adjusted $R^2 = 0.31$, $\Delta R^2 = 0.05$. ΔF (2, 61) = 2.74, $p = 0.07$.

[c] F (12, 61) = 3.76, $p < 0.001$.