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Prospective associations between childhood low-level lead exposure and adult mental health problems: The Port Pirie cohort study

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ABSTRACT

Low-level environmental lead exposure during childhood is associated with poorer emotional/behavioural functioning in later childhood and adolescence. Scarce research has examined whether these apparent effects persist into adulthood. This study is the first to examine prospective associations between lead exposure across early childhood and several common adult mental health problems.

Childhood data (including blood lead concentrations) and adult data (from mental health questionnaires and psychiatric interviews) were available for 210 participants (44% males, mean age = 26.3 years) from the Port Pirie cohort study (1979–1982 birth cohort).

Participants had a mean childhood (to 7 years) average blood lead concentration of 17.2 μg/dL. Among females, childhood blood lead showed small significant positive associations with lifetime diagnoses of drug and alcohol abuse and social phobia, and with anxiety, somatic and antisocial personality problems. For example: for a 10 μg/dL blood lead increase, females were 2.84 times (95% CI 1.10, 7.30) more likely to have an alcohol abuse diagnosis. However, adjustment for childhood covariates – particularly stimulation within the home environment – rendered these associations non-significant. No significant or sizeable unadjusted or adjusted associations were seen for males.

The associations between early lead exposure and emotional/behavioural functioning in children might persist into adulthood, at least for females. However, it is unclear whether such results arise from residual confounding, or other mechanisms. Interventions that focus on improving the childhood home environment may have a long-term positive impact on adult mental health outcomes. However, more prospective research using large and representative samples is needed to substantiate these results.

1. Introduction

Extensive research demonstrates that childhood low-level environmental lead exposure (i.e., below acute poisoning levels, <40 micrograms per decilitre (μg/dL)) shows small but significant prospective associations with emotional/behavioural problems in later childhood/adolescence. Childhood lead levels are associated with later externalising problems and aggressive behaviour, as well as internalising problems amongst girls, including somatic complaints, anxiety and depressed mood (Bellinger et al., 1994; Burns et al., 1999; Chen et al., 2007; Fergusson et al., 1993; Marcus et al., 2010; Naicker et al., 2012; Needleman, 1979; Needleman et al., 1996; Silva et al., 1988; Thomson et al., 1989; Wasserman, 1998). Similar associations with emotional/behavioural problems as well as diagnosed mental disorder (e.g., ADHD) have been demonstrated within cross-sectional research (e.g., Braun et al., 2006, 2008; Sciarillo et al., 1992). Although adjusting for standard covariates (like income and maternal intelligence) attenuates these effects, small though significant associations remain. Given this, ≥10 μg/dL was uniformly considered a blood lead level of 'concern' or 'action' until recently, but as there is no known 'safe' exposure level, some advisory groups have further decreased this reference level to 5 μg/dL, or distanced themselves from any reference entirely (Centers for Disease Control and Prevention, 2012 and National Health and Medical Research Council, 2012).

Recent assessments of prospective cohorts suggest that these associations persist into adulthood, documenting deficits in brain

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structure and functioning in regions including the frontal cortex and basal ganglia among adults (20–26 years) with higher childhood blood lead levels (Brubaker et al., 2010; Cecil et al., 2008, 2011). As these regions are implicated in behavioural regulation and mood, it is possible that childhood lead exposure may influence adult mental health.

However, relatively limited prospective evidence suggests that childhood lead exposure is associated with adult emotional/behavioural functioning: specifically, higher levels of psychopathic personality (Wright et al., 2009) and criminal behaviour (Fergusson et al., 2008; Wright et al., 2008), and an increased likelihood of a diagnosis of schizophrenia (Opler et al., 2004, 2008) have been demonstrated among adults with higher childhood lead levels. Several cross-sectional (Bouchard et al., 2009; Rhodes et al., 2003) and longitudinal (Rajan et al., 2007) studies of adults have also shown small associations between *adult* lead exposure and mental health symptomatology, including somatisation and phobic anxiety, and diagnoses of major depressive disorder and panic disorder, mostly in samples of older men.

We report emotional/behavioural outcomes of adults from the Port Pirie cohort study (Burns et al., 1999; Baghurst et al., 1985, 1992; McMichael et al., 1988; Tong et al., 1996, 1998, 2000a,b), the largest prospective study of childhood lead exposure, with one of the longest follow-up periods. In this cohort, childhood blood lead levels showed small positive associations with externalising problems for boys, and both internalising and externalising problems for girls, at the 13-year assessment (Burns et al., 1999). This paper reports the most recent cohort follow-up since the 13-year assessment. Our main objective was to examine prospective associations between childhood lead exposure and several common adult mental health problems in this cohort. Ours is the first prospective study to examine such associations. Given previous early childhood results including those from this cohort, and results of recent adult follow-up studies, we hypothesised that lead may act as a non-specific risk factor for increasing adult psychopathology, with associations being potentially gender-specific in nature.

2. Materials and methods

2.1. Sample

This study assessed a subset of the Port Pirie study cohort: 723 singleton infants born in 1979–1982, within 30 km of the South Australian regional lead-smelting town. This original cohort represented 90% of all live births in the region at the time. Mothers were assessed prenatally, and children were assessed periodically from birth to 7 years. A subsample was also assessed at 11–13 years. Further details are reported elsewhere (Baghurst et al., 1985, 1992; Burns et al., 1999; McMichael et al., 1988; Tong et al., 1996, 1998, 2000a,b).

During 2008–2009, we attempted to recontact all 723 original cohort members (see Section 2.2). Four members had died, and eight were deemed ineligible for follow-up, as intellectual disability prevented them from providing fully informed consent and/or completing the protocol. Altogether, 402 participated (aged 25–29 years), with 340 completing both a questionnaire and an interview (47% retention). Of those eligible who did not participate, 37% actively declined for reasons including lack of time, sickness, lack of interest and the personal nature of study questions; 22% never replied to letters or voicemails; and contact details could not be obtained for 42%. A final criterion for inclusion in the current analyses (but which did not prevent participation in the adult assessment) was complete data for lead exposure and covariates at the 7-year assessment. Thus, due to missing data for these early childhood variables ($n = 130$), 210 participants (44% male, mean age = 26.3 years) had full data for the 7-year assessment, and formed the current analysis sample.

2.2. Procedure

Deceased cohort members were identified through the National Death Index. Remaining individuals' contact details were sourced from the Australian Electoral Commission and White Pages search engines, from their parents, or other Port Pirie residents. We contacted individuals initially by mail, then telephone (multiple call attempts and two voice messages). Information sheets, consent forms, and questionnaires were posted to consenting participants, and trained researchers, who were blind to participants' questionnaire responses, conducted telephone interviews. Approval was obtained from the University of Adelaide Research Ethics Committee.

2.3. Measures

More detail regarding the following childhood measures can be found elsewhere (Baghurst et al., 1985, 1992; Burns et al., 1999; McMichael et al., 1988; Tong et al., 1996, 1998, 2000a,b).

2.3.1. Childhood blood lead concentrations

Capillary blood lead samples were collected when children were 6, 15 and 24 months, and then annually until 7 years. Samples were collected, stored and prepared according to Australian Standards (Baghurst et al., 1985; McMichael et al., 1988). Estimations of blood lead concentrations were performed using electrothermal atomisation atomic absorption spectrometry, standardised to a packed cell volume of 35%.

Average blood lead concentration at each assessment age was estimated by constructing individual plots of blood lead concentration against age, and dividing the area under the curve by the specified age. Such exposure measures based on multiple assessments are often more strongly related to developmental outcomes than single time-point measures (Dietrich et al., 2001; Lanphear et al., 2005; McMichael et al., 1988).

2.3.2. Adult psychiatric disorder

Lifetime prevalence of DSM–IV disorder was assessed using the Composite International Diagnostic Interview (WMH-CIDI 3.0), which has good reliability and validity (Haro et al., 2006). Participants were coded as cases/non-cases for each disorder.

2.3.3. Adult emotional/behavioural problems

Participants completed the widely used and extensively validated Adult Self-Report (ASR), the adult version of the Child Behaviour Checklist (Achenbach and Rescorla, 2003). We used the seven DSM-IV-oriented subscales rather than the nine narrowband subscales, so that the symptomatology of these lower-level problems was more closely aligned with clinical disorder diagnoses (albeit at a different severity level) (Achenbach et al., 2005). Scores were kept continuous, in order to assess symptoms at all levels.

2.3.4. Covariates

2.3.4.1. Child emotional/behavioural problems. Mothers completed the Child Behaviour Checklist (Achenbach, 1991) at the 5-year assessment. Additionally, mothers and teachers completed the Conners' Rating Scales (Conners, 1989) at the 7-year assessment.

2.3.4.2. Child intelligence. Children completed all 10 subscales of the revised version of the Wechsler Intelligence Scale (WISC-R: Wechsler, 1974) at the 7-year assessment. The same research psychologist evaluated all children.

2.3.4.3. Potential confounding factors. The confounding potential of several childhood factors was assessed as in previous studies (Lanphear et al., 2005). Individually, confounding variables were those that (1) were significantly related to lead and/or mental health outcomes (i.e., the 'significance testing' criterion, Tong and Lu, 2001) and (2) changed lead coefficients by >10% when included in regressions predicting mental health outcomes (the 'change in estimate' criterion, Tong and Lu, 2001). These included parental education (years of secondary school completed) and smoking status (yes/no) at the prenatal assessment, paternal occupational prestige level (using the Daniel Occupational Prestige scale (Daniel, 1984)), maternal age at delivery and intelligence levels (using the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981)); whether the parents were living together (yes/no); breastfeeding duration (in months); and the level of stimulation and support in the home environment (using the Home Observation for Measurement of the Environment, i.e., HOME (Bradley and Caldwell, 1984)). These variables were subsequently entered into regressions in a stepwise fashion, and were retained if their addition/removal changed the lead coefficient by >10%.

2.4. Statistical analysis

We kept lead concentration variables untransformed (and report arithmetic means) as they were reasonably normally distributed. Additionally, we used linear lead terms as they best represented the associations between lead and mental health outcomes. As the childhood average lead variables at each age were highly collinear (average $r = .87$), they were separately tested as independent variables in a series of regressions. As the examined age span increased, so did the lead coefficient, and average childhood blood lead at 7 years produced the best-fitting model (i.e., highest R^2), so we subsequently used it in the final models. This pattern is consistent with the findings of other lead studies (Lanphear et al., 2005; McMichael et al., 1988; Tong et al., 1996).

Associations between childhood blood lead and adult mental health problems were tested using PASW (version 18.0.2). First, we conducted a series of unadjusted linear regressions between average childhood blood lead and CIDI disorders (using logistic regression) and ASR DSM-IV-oriented symptom levels (using continuous linear regression). We also split ASR subscales scores at the median and performed logistic regressions, given the skewed nature of the distributions. However, as this did not appreciably change results, we only show the linear ASR subscale regressions. Second, we adjusted for (1) earlier levels of emotional/behavioural problems, (2) early childhood IQ, and (3) potential confounders. However, as adjusting for earlier emotional/behavioural problems or IQ had no appreciable effect on the lead coefficient or the model R^2, these variables were not retained. All regressions were stratified by gender, given the gender-specific associations found previously in this cohort (Burns et al., 1999). While we also conducted subsidiary regression analyses on the combined (i.e., both genders) sample that incorporated gender x lead interaction terms, we were also mindful that these moderated regressions might not have sufficient power to detect interaction effects (with a combined sample of $n = 210$).

3. Results

3.1. Sample characteristics

At the adult assessment, 75% of participants had completed high school, 74% were working full-time, and only 10% were unemployed (50% of these due to childcare/health reasons). Additionally, 62% of participants were married/in de facto relationships, and 1% were of Aboriginal/Torres Strait Islander descent. An average of 16.6 years ($SD = 2.3$) had elapsed since this sample had last participated during childhood.

The participants differed significantly (i.e., $p < .05$) from other cohort members on several childhood variables (Table 1): they had a larger birth weight and gestational age, their mothers were older at their birth and had lived in Port Pirie for longer, their parents were less likely to be smokers, and they had higher 3-year-old HOME scores. All differences were of a small effect size (i.e., Cohen's $d \sim 0.3$).

3.2. Initial analyses

Descriptive statistics are presented in Table 2. Females showed significantly higher levels of anxiety and somatic problems, and a higher lifetime incidence of panic attacks, specific phobia and PTSD, and males showed a significantly higher incidence of alcohol abuse. There were no significant or sizeable gender differences in lead levels.

3.3. Associations with DSM-IV mental disorder

For females, childhood lead showed small but significant associations with three of the eight lifetime disorders analysed (Table 3): for a hypothetical 10 μg/dL increase (as modelled in many reports (Lanphear et al., 2005; Tong et al., 1996)), females were more likely to have a lifetime diagnosis of drug abuse (OR 6.19, 95% CI 1.79–23.29), alcohol abuse (OR 2.84, 95% CI 1.10–7.30), and social phobia (OR 3.11, 95% CI 1.10–8.59). However, lead was neither sizeably nor significantly associated with disorder among males.

After adjusting for potential confounders, lead coefficients were greatly attenuated and rendered non-significant, with only results for specific phobia approaching significance (Table 3). Consistent with childhood Port Pirie results (Tong and Lu, 2001), The HOME

Table 1
Early childhood socio-demographic characteristics of Port Pirie cohort members, according to adult participation status.

Variable	Port Pirie cohort members		
	Study sample ($n = 210$)	Remainder of the birth cohort ($n = 513$)	p-Value[‡]
Gender – male (%)	39%	47%	>0.10
Length of mother's residence in Port Pirie (years)	14.0 ± 11.1	11.9 ± 10.8	0.02
Father smoked during pregnancy (%)	42.1	55.5	0.001
Mother smoked during pregnancy (%)	20.2	33.5	0.001
Father's occupation status (Daniel score)[†]	39.6 (19.7)	38.1 (21.4)	>0.10
Mother's education (years of high school)	3.6 (1.0)	3.5 (1.0)	>0.10
Father's education (years of high school)	3.5 (1.1)	3.5 (1.1)	>0.10
Mother's age at child's birth (years)	26.4 ± 4.4	25.6 ± 4.8	0.03
Gestational age (weeks)	40.0 ± 1.7	39.7 ± 1.9	0.03
Birth weight (g)	3480.9 ± 482.8	3333.5 ± 541.1	0.001

[†] Higher Daniel scores indicate lower socio-economic status.
[‡] Differences in means analysed using two-tailed t-tests, differences in proportions tested using chi square tests for independence.

Table 2
Sample values for independent and dependent variables.

Variable	Total $n=210$	Males $n=83$	Females $n=127$	Sex difference p-Value[a]
Childhood average (to 7 years) blood lead levels	17.2 ± 5.2	17.9 ± 5.4	16.7 ± 5.0	>0.10
Incidence (%) of CIDI DSM-IV diagnosed disorders (lifetime)				
Alcohol abuse	26.7	38.6	18.9	0.003
Panic attacks	22.9	13.3	29.1	0.01
Drug abuse	13.3	16.9	11.0	>0.10
Major depressive disorder	10.5	4.8	14.2	0.053
Specific phobia	8.6	2.4	12.6	0.02
Social phobia	11	6.0	14.2	>0.10
Post-traumatic stress disorder	9.5	0	15.7	<0.001
Alcohol dependence	6.2	8.4	4.7	>0.10
Mean levels of ASR DSM-IV oriented emotional/behavioural problems				
Anxiety problems	4.2 ± 2.8	3.5 ± 2.6	4.7 ± 2.9	0.002
Somatic problems	2.0 ± 2.3	1.2 ± 1.8	2.5 ± 2.5	<0.001
Depressive problems	4.7 ± 3.8	3.9 ± 3.5	5.2 ± 4.0	0.02
AD/H problems - hyperactivity	2.4 ± 1.9	2.5 ± 2.1	2.3 ± 1.8	>0.10
AD/H problems - inattention	3.0 ± 2.4	3.1 ± 2.4	2.86 ± 2.4	>0.10
Antisocial personality problems	3.2 ± 3.4	3.6 ± 3.9	3.0 ± 3.0	>0.10
Avoidant personality problems	2.8 ± 2.3	2.5 ± 2.3	3.0 ± 2.4	>0.10

[a] Analysed using two-tailed t-tests.

Table 3
Associations between childhood average blood lead and lifetime psychiatric disorder.

DSM-IV lifetime disorder	Females ($n=127$)[b]				Males ($n=83$)[c]			
	OR[a] (95% CI)	p-Value	AOR[a] (95% CI)	p-Value	OR[a] (95% CI)	p-Value	AOR[a] (95% CI)	p-Value
Drug abuse	6.19 (1.79, 23.29)	0.004	2.84 (0.60, 13.79)	>0.10	1.22 (0.39, 3.39)	>0.10	0.54 (0.11, 2.84)	>0.10
Alcohol abuse	2.84 (1.10, 7.30)	0.04	1.79 (0.60, 5.69)	>0.10	1.48 (0.66, 3.71)	>0.10	1.79 (0.74, 4.41)	>0.10
Social phobia	3.11 (1.10, 8.59)	0.04	1.63 (0.48, 5.69)	>0.10	1.48 (0.28, 6.73)	>0.10	0.66 (0.11, 4.05)	>0.10
Specific phobia	2.84 (0.90, 8.59)	0.056	3.39 (0.90, 11.81)	0.061	2.59 (0.09, 70.29)	>0.10	1.22 (0.03, 47.12)	>0.10
Post-traumatic stress disorder	2.59 (0.90, 6.73)	0.08	0.60 (0.20, 2.16)	>0.10	n/a	–	n/a	–
Alcohol dependence	2.84 (0.43, 17.31)	>0.10	1.10 (0.07, 14.88)	>0.10	0.39 (0.06, 2.37)	>0.10	0.35 (0.06, 2.16)	>0.10
Panic attack	1.79 (0.82, 4.05)	>0.10	0.82 (0.31, 2.37)	>0.10	1.97 (0.60, 6.19)	>0.10	1.22 (0.17, 7.93)	>0.10
Major depressive disorder	1.10 (0.35, 2.84)	>0.10	0.31 (0.07, 1.22)	>0.10	0.48 (0.06, 3.71)	>0.10	0.31 (0.02, 4.05)	>0.10

[a] OR/AOR = odds ratio/adjusted odds ratio, reflecting the likelihood of a disorder diagnosis for a 10 μg/dL increase in childhood average blood lead.
[b] Regressions for females adjusted for: HOME and maternal education (drug abuse); HOME and paternal occupation (alcohol abuse); paternal occupation and maternal education (specific phobia); HOME and mothers' age at birth (social phobia); HOME, maternal education, paternal occupation, and breastfeeding (PTSD); HOME, breastfeeding, single parent family status, and mothers' age at birth (alcohol dependence); HOME, paternal occupation, and mothers' age at birth (major depressive disorder); HOME, paternal occupation, and breastfeeding (panic attacks).
[c] Regressions for males adjusted for paternal and maternal education, mothers' age at birth (drug abuse); paternal education, single parent family status (alcohol abuse); HOME, paternal occupation, breastfeeding, single parent family status (specific phobia); paternal education, mothers' age at birth (social phobia); paternal education (alcohol dependence); paternal and maternal education, mothers' age at birth (major depressive disorder); paternal and maternal education, paternal occupation, single parent family status, breastfeeding, mothers' age at birth (panic attacks).

(measuring stimulation within the home) had the largest effect on the lead coefficient (i.e., the 'change in estimate' criterion) – adjusting for this alone rendered lead coefficients non-significant, although it rarely showed a significant unique association with disorder, suggesting the total variance explained by these two predictors was essentially shared (and the bivariate correlation between childhood average blood lead and HOME scores was 0.55). In subsidiary analyses that included the whole sample, no significant lead × gender interactions were found within moderated regressions.

3.4. Associations with emotional/behavioural problems

For females, average blood lead showed small but significant associations with three of the seven ASR subscales (Table 4): for a 10 μg/dL increase, females showed increases in anxiety problems (1.9 scale points, 95% CI 0.92–2.86), somatic problems (1.1 points, 95% CI 0.25–1.99) and antisocial personality problems (1.1 points, 95% CI 0.10–2.14). Lead showed non-significant and near-zero associations with all ASR subscales in males.

These associations reduced considerably following confounder adjustment, with lead no longer significantly associated with any ASR subscale, and only results for anxiety problems approaching significance (Table 4). Once again, the HOME had the largest effect on the lead coefficient (i.e., by the 'change in estimate' criterion), with its inclusion enough to render the association non-significant in most instances. Again, all lead main effects and lead x gender interactions within subsidiary moderated regressions were small and non-significant.

4. Discussion

This study is the first to examine prospective associations between childhood lead exposure and several common adult mental health problems. Unadjusted results suggested that early lead exposure is associated with emotional and behavioural functioning, at least in females. Specifically, females with higher childhood blood lead levels showed higher odds of lifetime diagnosis of social phobia and drug/alcohol abuse, and higher levels of anxiety, somatic and antisocial personality problems. However, these associations disappeared after adjustment for HOME scores and other confounding factors.

Associations with these particular types of psychiatric problems show a similar pattern to that in early childhood cross-sectional and prospective studies, including previous Port Pirie analyses, that found small associations between lead levels and

Table 4
Linear regression between childhood average blood lead and ASR subscales.

ASR DSM-IV oriented subscale	Females ($n=127$)[b]				Males ($n=83$)[c]			
	B[a] (SE)	p-Value	Adjusted B[a] (SE)	p-Value	B[a] (SE)	p-Value	Adjusted B[a] (SE)	p-Value
Anxiety problems	1.9 (0.5)	<0.001	1.2 (0.6)	0.059	0.2 (0.6)	>0.10	−0.2 (0.6)	>0.10
Somatic problems	1.1 (0.4)	0.012	0.3 (0.5)	>0.10	0.3 (0.5)	>0.10	0.4 (0.5)	>0.10
Depressive problems	0.7 (0.7)	>0.10	−0.1 (0.9)	>0.10	−0.5 (0.7)	>0.10	−0.9 (0.8)	>0.10
AD/H problems - hyperactivity	0.4 (0.3)	>0.10	0.1 (0.4)	>0.10	−0.1 (0.5)	>0.10	−0.1 (0.6)	>0.10
AD/H problems - inattention	0.4 (0.4)	>0.10	−0.1 (0.6)	>0.10	−0.5 (0.5)	>0.10	−0.7 (0.5)	> .10
Antisocial personality problems	1.1 (0.5)	0.032	0.1 (0.6)	>0.10	−0.5 (0.8)	>0.10	−0.9 (0.9)	>0.10
Avoidant personality problems	0.8 (0.4)	0.06	0.4 (0.5)	>0.10	0.1 (0.5)	>0.10	0.2 (0.5)	>0.10

[a] Values represent the change in ASR subscale scores accompanying a 10 μg/dL increase in childhood average blood lead.
[b] Regressions for females adjusted for HOME scores, along with the following outcome-specific variations: breastfeeding duration for anxiety problems; maternal education, paternal occupation, and mothers' age at birth for somatic problems and antisocial personality problems; breastfeeding for antisocial personality problems; mothers' age at birth and breastfeeding for avoidant personality problems; paternal occupation, maternal education, and breastfeeding for inattention; and mothers' age at birth and breastfeeding for depressive problems and hyperactivity.
[c] Regressions for males adjusted for HOME scores, paternal education, maternal education and single parent family status for anxiety problems; HOME scores, paternal education and maternal education for depressive problems; maternal occupation, maternal education, breastfeeding duration and single parent family status for somatic problems; HOME scores and paternal education for antisocial personality problems; maternal education for inattention; paternal education, maternal education, paternal occupation and breastfeeding duration for hyperactivity; and breastfeeding duration and single parent family status for avoidant personality problems.

anxiety, somatic problems, withdrawn behaviour, and phobia in girls (Burns et al., 1999; Sciarillo et al., 1992). Lead levels have also been associated with adult somatisation and phobic anxiety, but only for adult lead levels in middle-aged men (Rajan et al., 2007; Rhodes et al., 2003). Additionally, the Cincinnati study (Dietrich et al., 2001) found small significant associations between childhood lead and adolescent alcohol/marijuana consumption. Furthermore, lead-exposed rats have shown increased appetite for substances including alcohol and cocaine: this was speculated to result from their observed anxiety-reducing effects, which was not seen in the control rats (Virgolini et al., 1999). This mechanism may potentially explain our finding that females' alcohol and drug abuse was predicted by childhood lead. Biological (e.g., release of lead from bone following female hormonal changes) and social (e.g., peer group influences) sexual dimorphism might partly explain these gender-specific effects (Vahter et al., 2007), assuming they are real.

The neurological mechanisms by which lead may be related to adult emotional/behavioural functioning remain unclear. However, lead levels are associated with impaired dopaminergic, glutaminergic and gabaergic system dysfunction and subsequent HPA axis dysfunction, mechanisms which are known to be abnormal in psychiatric disorders (Virgolini et al., 1999).

Overall, our results suggest that Port Pirie cohort females have remained more vulnerable to lead-associated emotional problems, compared with males. Port Pirie females have previously appeared more vulnerable to various lead-associated developmental deficits including emotional/behavioural problems, IQ, and neuropsychological development (Baghurst et al., 1992; Burns et al., 1999; McMichael et al., 1988; Tong et al., 1996). On balance of the evidence, there are more studies that suggest a male vulnerability to lead (e.g., Bellinger et al., 1985; Cecil et al., 2011; Dietrich et al., 1987), though some studies report greater susceptibility among females (e.g., Rabinowitz et al., 1991), or no difference at all (Bouchard et al., 2009), and others do not consider gender-specific associations (e.g., Fergusson et al., 1993). Given this disparity, conclusions regarding gender susceptibility to lead should be made with caution. Our findings might reflect circumstances specific to the Port Pirie sample (see also Tong et al., 2000a,b).

However, these lead associations disappeared after adjusting for several socio-demographic covariates, although the associations with both social phobia and anxiety problems remained of borderline statistical significance. This pattern shows similarities with much of the lead literature: most lead associations become smaller after adjustment, with only some retaining/approaching significance. Specifically, in the early-adolescent Port Pirie study, of eight lead associations with CBCL subscales in early-adolescent females, five remained significant following adjustment (Burns et al., 1999). There are several possible explanations for these findings.

It is possible that biased attrition may have influenced results. Our sample represented about one-third of the birth cohort (210 out of 723), and came from more socially advantaged backgrounds (as highlighted by the attrition analyses in Results). Given that children from lower-SES backgrounds appear more susceptible to the negative effects of lead, our sample's 'higher functioning' may have effectively attenuated such effects (Silva et al., 1988; Tong et al., 1996). In fact, when we replicated early-adolescent analyses of the Port Pirie cohort (Burns et al., 1999) using our smaller follow-up sample (67% of the original sample), most associations were smaller, and fewer were significant (results available on request). Thus, it is possible that *stronger* early adulthood associations may be present in the entire birth cohort. Furthermore, the size of the small and non-significant adjusted associations we found for social phobia and anxiety problems were similar to the significant associations found in early adolescence (Burns et al., 1999). It is notable that such effects have persisted over approximately 15 years. It is possible that attrition of original cohort members, resulting in a total sample of 210, has resulted in insufficient statistical power to detect small yet 'real' lead effects. As our retention percentages were reasonably similar to other prospective lead studies with adult follow-ups (Brubaker et al., 2010; Cecil et al., 2011; Mazumdar et al., 2011, 2012; Wright et al., 2009, 2008), a key issue plaguing such long-term studies is retaining enough participants (and power) to find small 'real' effects significant. While these issues may impact generalisability, this study is able to advance knowledge given its many strengths: it is one of the few prospective lead studies to follow a birth cohort over two decades (Cecil et al., 2011; Fergusson et al., 2008; Mazumdar et al., 2011, 2012), and is the only study to examine mental health symptoms and psychiatric diagnoses in young adulthood. Furthermore, its detailed prospective design has enabled us to adjust for many other aspects of the early childhood environment.

This paper strongly demonstrates the importance of considering the role that a child's broader environmental circumstances might play in the lead – psychiatric outcome association (see also Weiss and Bellinger, 2006). Of all the early childhood factors included, the HOME showed the strongest effect on the lead coefficient, consistent with earlier Port Pirie analyses (Tong and Lu, 2001). Additionally, many (though see Schnaas et al., 2006 for a notable exception) other prospective lead studies have found the

HOME to be one of the most significant confounders, along with SES, birth weight and maternal IQ (e.g., Bellinger et al., 1985; Dietrich et al., 1992; Lanphear et al., 2005). While Port Pirie participants' lead levels and HOME scores both showed significant bivariate associations with adult outcomes, their unique associations were mostly small and non-significant due to their large overlap. While this overlap was consistent with earlier Port Pirie results (Tong and Lu, 2001), it was somewhat larger than that seen in other cohort studies (e.g., see Ernhart et al., 1989), and may relate to sample-dependent variability within the HOME scores and other demographic characteristics. Thus, it is apparent that lead exposure and the broader environment may not be independent of one another, and need to be considered together when examining their associations with adult mental health outcomes (Weiss and Bellinger, 2006).

As with most prospective studies, we cannot determine the specific role that each factor plays in subsequent adult mental health outcomes. It is possible that lead is confounded with early childhood stimulation (as measured by the HOME), or acts as a proxy for social disadvantage, which may explain the association with developmental outcomes. Alternatively, the shared variance may be a proxy of lead exposure: children who are supervised/stimulated less may have greater interaction with objects contaminated by dirt- or dust-borne lead, and thus may inhale/ingest higher quantities of lead (Tong and Lu, 2001). If this were true, then the lead association may be real, and the HOME association confounded. However, a more accurate explanation may lie somewhere in-between: as the shared variance is not a discrete entity, some may be attributed to lead, and some to the home environment.

And then again, while of theoretical interest, solely considering the discrete role of each factor may be less relevant from an intervention perspective: unique effects that are determined through statistical adjustment do not translate to real-life circumstances, where factors co-occur (to varying degrees) in a child's life, and so are inextricably entwined (Weiss and Bellinger, 2006). It is possible that it is the *combination* of lead exposure and environmental enrichment (which the HOME measures) that is related to adult outcomes, such that environmental enrichment may mitigate the adverse effects of lead (Guilarte et al., 2003; Tong et al., 1996). Thus, the HOME may modify rather than confound the association, and lead may exhibit stronger effects for children with low HOME scores. Low statistical power precluded us from properly testing this possibility.

Of course, we cannot assume that associations found here are causal given our observational design. However, this possibility is given credence when considering animal experiments demonstrating lead's neurotoxic effects (Guilarte et al., 2003; Virgolini et al., 1999), as well as the fact that early childhood functioning did not predict later lead levels in earlier Port Pirie analyses (Tong et al., 1996).

As few participants showed lead levels below 10 μg/dL, we could not test the possibility that stronger associations existed at these low levels, as found in recent studies examining cognitive outcomes (Lanphear et al., 2005). In fact, lead levels of children in developed nations have reduced substantially due to improved occupational and environmental practices (e.g., lead-free petrol and paint). Thus, our results may hold particular import for children exposed prior to these reforms, and for children in developing countries where lead exposure is poorly regulated (Tong et al., 2000a,b). Port Pirie cohort members have only reached early adulthood, and it is possible that consequences of their lead exposure may persist for some time. This possibility needs further investigation in other long-term prospective studies.

Finally, it is important to emphasise that lead's adjusted effect explained, at most, 4% variance in adult mental health outcomes, and adjusting for childhood covariates still only resulted in a small amount of variance explained (e.g., highest R^2 in continuous regressions was 0.15). It is possible that various childhood developmental outcomes (e.g., executive functioning) may act as indirect mechanisms by which early childhood lead exposure and adult mental health outcomes are linked (although we did not find such an association for early childhood IQ). Given the almost 20-year time period separating exposure and outcome measures, such 'distal mediation' effects may be as important as direct effects. It is true that small direct lead associations have important public health implications at the population level, assuming they can be generalised. However, focussing on improving multiple factors that have a unique influence on mental health (with parenting practices as a potential candidate) may ultimately best counteract the relatively smaller detrimental contribution of lead.

5. Conclusions

Our data suggest that early childhood lead exposure may show small associations with adult emotional and behavioural functioning in females. However, as associations disappeared following adjustment, it is unclear whether lead exposure or early childhood confounders were driving these associations. Thus, focussing more broadly on improving other aspects of the childhood home environment may have a long-term positive impact on adult mental health outcomes.

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Conflict of interest

All authors state that there are no competing interests.

Ethical approval

This study was approved by the University of Adelaide Research Ethics Committee (approval ID # H-173-2006). All participants gave written informed consent prior to participation.

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