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Childhood lead exposure and sex-based neurobehavioral functioning in adolescence

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Abstract

It is well documented that childhood lead exposure is associated with long-term decreases in intelligence quotients (IQ). Lesser known is the relationship with neurobehavioral domains, especially in adolescence. This study sought to identify cross-sectional and longitudinal associations between lead exposure and adolescent executive and visual-motor functioning and examine sex-based differences. Participants were 681 children from Jintan, China who had their blood lead levels (BLLs) assessed at age 3–5 years and 12 years old and neurobehavioral functioning assessed through the University of Pennsylvania Computerized Neurocognitive Battery (PennCNB) platform http://www.med.upenn.edu/bbl at 12 years old. Mean BLLs were 6.41 mcg/dl at age 3–5 years and 3.10 mcg/dl at 12. BLLs at 3–5 years and 12 years were used as predictors for the individual neurobehavioral domains in general linear models while controlling for father and mother occupation and education, residence location, age, and adolescent IQ. Models were run separately for males and females. In adjusted models, males BLLs at 3–5 years were associated with increased time to correctly complete tasks in multiple domains including abstraction/flexibility (β = 19.90, 95% CI(4.26, 35.54) and spatial processing (β = 96.00, 95% CI 6.18, 185.82) at 12 years. For females in adjusted models, BLLs at 3–5 years were associated with increasing time to correctly complete tasks on the episodic memory domain task (β = 34.59, 95% CI 5.33, 63.84) at 12 years. Two adolescent cross-sectional relationships remained in the adjusted

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Competing interests

The authors have no competing interests to declare.

CRediT authorship Contribution statement

Olivia M. Halabicky: Conceptualization, Methodology, Formal Analysis, Writing – original draft, Writing – review & editing. **Xiaopeng Ji:** Conceptualization, Writing – review & editing. **Raquel E. Gur:** Writing – review & editing, Software, Resources. **Ruben C. Gur:** Writing – review & editing, Software, Resources. **Chonghuai Yan:** Investigation, Resources, Supervision. **Aimin Chen:** Writing – review & editing. **Jianghong Liu:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition.

models for males only, suggesting a positive association between BLLs and increasing time for correct responses on the attentional domain task (β = 15.08, 95% CI 0.65, 29.51) and decreasing time for correct responses on the episodic memory task (β = −73.49, 95% CI −138.91, −8.06) in males at 12 years. These associations remained with and without controlling for IQ. These results suggest that lead exposure is associated with overall deficits in male and female neurobehavioral functioning, though in different domains and different timing of exposure.

Keywords

Lead exposure; Child development; Neurobehavioral functioning; Executive functioning

1. Introduction

While global advances have removed many sources of lead exposure, children are still being exposed to low-levels of lead in their everyday lives. In fact, global estimates suggest 1 in 3 children, approximately 800 million, have blood lead levels at 5 mcg/dl or greater (UNICEF and Pure Earth, 2020). In high-income countries such as the United States, at least four million households with children are exposed to low levels of lead from lead-based paint, water pipes and contaminated air/soil (Centers for Disease Control and Prevention, 2018). Childhood lead exposure via air pollution, electronic waste, lead pipes, traditional medicines, and even baby food is also a public health burden in China (Ying et al., 2018). Lead exposure in children, even with a low-level exposure, is of particular concern due to its potential influence on the developing brain and negative associations with intelligence quotients (IQ) in childhood (Tatsuta et al., 2020).

While lead exposure has been consistently associated with decreased IQ and generalized neurocognition, fewer studies have examined associations with neurobehavioral functioning in a domain-specific fashion with the inclusion of executive and visual-motor functioning. Executive functioning includes several processes that mutually aid in goal-oriented problem solving through planning, monitoring, and achievement (Marcovitch and Zelazo, 2009). This higher order cognitive construct includes multiple domains such as abstraction/flexibility, working and episodic memory, and attention (Friedman and Miyake, 2017). Visual-motor functioning includes actions where visual information requires a response with a motor action (Sulik et al., 2018). Altogether, neurobehavioral functioning is critical to examine due to associations with health outcomes and behaviors later in life, such as links with obesity, substance abuse, and risky sexual behavior in adolescence (Gowey et al., 2018; Grenard et al., 2008; Khurana et al., 2015; Pentz et al., 2015).

Prior research has focused predominantly on cross-sectional relationships between lead and domain specific neurobehavioral functioning (Arnold and Liu, 2020). For example, in 60 month old children, blood lead levels (BLLs) (mean 5.43 mcg/dl) were associated with deficits in selective attention/shifting (McCabe et al., 2010). In school children 3–7 years old, BLLs (mean 11.4 mcg/dl) have been inversely associated with visual-motor abilities (Palaniappan et al., 2011). In older children, BLLs at 7.5–10 years (mean 1.5–5.4 mcg/dl) were cross-sectionally associated with decreased working memory, cognitive

flexibility, attention, inhibition, and visual-motor integration (Chiodo et al., 2007, 2004; Kim et al., 2010). In adolescence, when neurobehavioral functioning outcomes begin to mature (Boelema et al., 2014), negative associations are reported between BLLs (mean ~2–3 mcg/dl) and unitary executive functioning in 11–13 year olds (Kim et al., 2012; Min et al., 2007).

Fewer studies examining longitudinal associations between early lead exposure and later neurobehavioral functioning exist and, further, report mixed results. Negative associations have been suggested between BLLs in early childhood and later outcomes including working memory and cognitive flexibility at 5.5 years (Canfield et al., 2004) and 10 years (Stiles and Bellinger, 1993), suggesting the long-term impact on cognitive functioning. However, one longitudinal examination of attentional outcomes reported no significant relationships between 30 month old BLLs (mean 4.22 mcg/dl) and 8 year old outcomes, which could be due to subjective teacher reports of attention (Chandramouli et al., 2009). From a developmental perspective, elucidating the longitudinal associations between lead and objective measures of neurocognitive function will provide a better understanding of how early-life neurotoxicant exposures link to neurobehavioral perturbations from childhood to adolescence.

Associations between lead exposure and neurobehavioral function outcomes appear to have sex-based differences. For example, researchers noted that deficits in inhibition and attention in 8–10-year-old children were significant only for male participants with mean BLLs of 1.5 mcg/dl (Kim et al., 2010). However, unitary executive functioning domains were only significantly associated with lead in females in cross-sectional studies of 6 year old children (mean 4.2 mcg/dl) (Barg et al., 2018) and 12–13 year old children (mean 2.76 mcg/dl) (Kim et al., 2012). Differences in associations for males versus females may suggest the need for variability in risk assessment and intervention strategies based on neurobehavioral domains and further research is needed to clarify these relationships.

Examining the influence of childhood and adolescent lead exposure on objective and domain specific neurobehavioral functioning is crucial as both time points are critical periods of robust neural plasticity when environmental exposures can impair neurodevelopment (Funahashi and Andreau, 2013). Furthermore, additional research is needed to elucidate sex-based differences in neurobehavioral functioning domains related to early and concurrent lead exposure. The aims of this study were thus twofold: (1) To examine how lead exposure at preschool age and early adolescence are associated with early adolescent executive and visual-motor functioning outcomes, respectively; and (2) To identify whether there were sex differences within these relationships.

2. Methods

2.1. Design

This study is part of an ongoing, longitudinal project, the China Jintan Child Cohort Study. There are two waves of data collection used in this study. Wave 1 began between the Fall of 2004 and Spring 2005 when children were between 3 and 5 years old. Recruitment of parents and children occurred within four preschools in Jintan city, Jiangsu province, China.

Preschools were chosen to represent the city's geographic, social, and economic profiles (Liu et al., 2010). Wave 2 data collection occurred between 2011 and 2013 when children were in the last month of 6th grade and approximately 12 years of age. Data was collected both in the schools during the morning before school started (i.e., blood collection) and also in a laboratory setting (i.e., neurobehavioral testing). More detailed information on recruitment and enrollment procedures is reported in a cohort profile update (Liu et al., 2015, 2011).

2.2. Participants

For these analyses, we included a subsample of children (Fig. 1, n = 681) from the 1100 who participated in Wave 2 of data collection and had complete data on the University of Pennsylvania Computerized Neurocognitive Battery (PennCNB) platform outcomes, and all covariates (age at blood lead testing in Wave 1, sex, parental education and occupation, residence location, and adolescent IQ). Written informed consent was obtained from parents at both Waves 1 and 2. Institutional review board approval was obtained from the University of Pennsylvania and the Ethical Committee for Research at Jintan Hospital in China.

2.3. Measures

2.3.1. BLLs at 3–5 years and 12 years—BLLs were collected twice for the participants. The first collection was when children were 3, 4, or 5 years of age, between November 2004 and March 2005, and again when children were approximately 12 years old. Fasting blood samples (0.5 ml venous blood) were collected in the morning at each child's school in the health clinic by a trained pediatric nurse utilizing a standardized research protocol to avoid lead contamination (World Health Organization, 2011). Samples from both waves were frozen and sent to the Research Center for Environmental Medicine of Children in Shanghai Jiaotong University for analysis. Specimens were analyzed twice via graphite furnace atomic absorption spectrophotometer using a replication procedure with the final measure being the mean of repeated measurements (World Health Organization, 2011). Kaulson Laboratories provided quality control reference materials. The limit of detection was 1.8 mcg/dl for Wave 1 and 1.0 mcg/dl for Wave 2. Those values below the LOD were considered as half of the LOD (N = 3). Further details on sample collection have been previously published (Liu et al., 2013, 2021).

2.3.2. Computerized Neurocognitive Battery (PennCNB)—The **PennCNB**, a validated tool of neurobehavioral functioning (Moore et al., 2015), was completed during Wave 2 when children were around 12 years old. Tests were administered by trained research assistants in a controlled lab environment (Jintan Cohort Research Lab in Jintan Hospital) and lasted approximately one hour. The battery included 4 domains, detailed below, which were scored for accuracy and response time: abstraction /flexibility, attention, spatial processing, and episodic memory. Two additional domains were scored only for speed: sensorimotor, and motor speed (Gur et al., 2010). All tests included in the **PennCNB** were computerized and used clickable icons that appeared in a fixed order (Gur et al., 2010). Children were first acclimated to the testing instrument by performing an un-speeded version of the Mouse Practice test. The detailed procedure and application of this instrument in our sample has been published elsewhere (Ji et al., 2017).

2.3.3. Abstraction/flexibility—Two tests assessed abstraction/flexibility. The Penn Conditional Exclusion Test (SPCET) required subjects to decide which of 4 objects did not belong in a group, based on one of three sorting principles (e.g. shape, size, line thickness) (Gur et al., 2010). These principles changed after 10 successive correct responses. Accuracy scores were calculated by multiplying the number of correct responses by the number of categories attained, out of the 3 possible. The mean time to respond correctly was also assessed. The Penn Matrix Reasoning Test (PMAT) examined nonverbal reasoning via (Raven's-like) Matrices. Subjects are asked to determine a missing piece of a matrices based on patterns presented in the existing matrices. Accuracy was determined by the number of correct responses and mean time to answer for correct responses was also measured.

2.3.4. Attention—The Penn Continuous Performance Test (PCPTN) assessed attention by using the traditional continuous performance test paradigm. Participants responded to a set of 7-segment displays presented at 1/sec., whenever they form a digit or letter. The accuracy score was the amount of true positive responses and the mean response time for correct responses was also measured (Gur et al., 2010).

2.3.5. Spatial processing—The Penn Line Orientation Test (VSPLOT) used a computerized version of Benton's test. Subjects are presented with two lines at an angle and are asked to identify corresponding lines on a simultaneously presented array. The number of correct responses was the accuracy score and the mean response time for accurate responses was the time measure.

2.3.6. Episodic memory—The Visual Object Learning Test (SVOLT) used 10 Euclidean shapes as stimuli. Subjects were asked to identify these both immediately after stimuli were presented and again at a 20-minutes delay. During the immediate recall participants were shown 20 Euclidean shapes, 10 for recall and 10 for novel, and asked to identify if they've seen the shape before by clicking one of four buttons, definitely yes, probably yes, probably no, definitely no. This process was repeated at the 20-minutes delay. The participant's accuracy score was the number of correctly recognized shapes and correctly rejected novel shapes. Time was recorded as the median response time for correct responses.

2.3.7. Sensorimotor—The Mouse Practice Test (MPRACT) required subjects to click on a green square as quickly as possible as it appears on the screen in various locations and disappears after the click. The square became increasingly smaller as the task continued. The median response time is used as the accuracy measure.

2.3.8. Motor speed—The Computerized Finger Tapping Test (SCTAP) measured how quickly the subject could press the spacebar using only their index finger. Subjects were first given a practice trial with each hand, then proceeded for 5 trials with the dominant and nondominant hand each. The subject was then asked to tap the spacebar repeatedly for 10 s when the green "GO" screen was shown. The computer recorded the number of taps, reflective of the accuracy measure.

2.3.9. Covariates—Covariates included sociodemographic characteristics including age at Wave 1 collection period, residence location (city, town, or rural), and mother and father occupation (unemployed, skilled/unskilled, and professional) and education and models were additionally stratified by sex. These data points were assessed via a parental questionnaire during Wave 1 data collection. These covariates were chosen based on previous research which suggests such sociodemographic characteristics as predictors of neurocognitive performance (Zysset et al., 2018) and study in this cohort suggesting these sociodemographic variables as predictors of BLLs (Liu et al., 2012). We included age at Wave 1 as a covariate because the study protocol allowed for variability in enrollment age including children from ages 3–5 years, which corresponds to when their initial BLLs were drawn. All participants were followed up during Wave 2 in their last month of grade 6 where the average age was 12 years. Adolescent IQ was additionally included in the models to control for known associations between IQ and executive functioning abilities in children (Arffa, 2007). Full-scale IQ was assessed using the Chinese version of the Wechsler Intelligence Scale for Children-Revised (WISC-R), which is standardized in China and has demonstrated good reliability in Chinese children (Yue, ES, 1987). Research assistants who administered the WISC-R were blind to the blood lead concentrations, as previously described elsewhere (Dang et al., 2012).

2.4. Statistical analysis

Sample characteristics were summarized by descriptive statistics such as means, medians, standard deviation (SD), and frequencies. Data were examined for outliers and overall normality. The differences between the included and exclude groups, as well as between male and female subjects, were compared using t tests and chi-squared tests. We examined the distributions of the BLL and PennCNB variables and found some domains to be right skewed. As a sensitivity analysis, we log transformed all PennCNB variables and reran the below models to confirm the findings. General linear models were used to examine associations between BLL measures simultaneously and the PennCNB measures in models adjusted for father and mother occupation and education, residence location, age at Wave 1, and adolescent IQ. These models were run separately for males and females. In our preliminary analysis, we did not find significant interactions between BLLs and sex and, therefore, utilized a sex-stratified analysis because of potential sex-based differences. Additionally, we ran the models without controlling for adolescent IQ in recognition that IQ may serve as a mediator in the relationship between BLLs and the neurocognitive outcomes. All analyses were conducted with StataCORP 15 statistical package.

3. Results

3.1. Descriptive analysis

After examination of the data, eight outliers within the PennCNB data were removed (>10 SD above the mean; 2 observations MPRACT, 4 observations SCTAP, and 2 observations VSPLOT). The outlier observations were from different cohort participants and were a mix of males and females. We believe these outliers to be potentially due to child distraction. The sample consisted of 377 males and 304 females (Table 1). BLLs between Waves 1 and 2 were significantly, positively correlated ($r = 0.113$, $p = 0.003$). There was a significant

difference in the mean BLLs at 3–5 years old between sexes, 6.76 mcg/dl and 5.99 mcg/dl for males and females, respectively (p = 0.0001). Most mothers and fathers worked as unskilled or skilled laborers (Fathers: 59.06%; Mothers: 46.33%) and a majority of children lived in cities (66.57%) compared to towns (18.91%) and countryside (14.52%). Males had significantly higher IQ scores than females, 106.99 and 102.28, respectively (p = 0.0002). There were significant differences in multiple PennCNB measures between males and females. There were no significant differences between those with and without follow up data, except for excluded children having a higher proportion with BLLs collected in Wave 1 at 5 years of age and having fewer items correct on the PCPTN compared to included children (Table 1).

3.2. General linear models of BLLs and executive function

In the adjusted models (Table 2), there were significant relationships for both longitudinal and cross-sectional associations. Considering males, there was a significant positive relationship where a 1 mcg/dl increase in BLLs at 3–5 years was associated with an increase in 19.9 ms to correct responses with abstraction/flexibility testing (SPCET; p = 0.013) and an increase in 96.0 ms in correct response time for the spatial memory task (VSPLOT; p = 0.036). Cross-sectionally, there was a positive association between a 1 mcg/dl increase in BLLs and 15.08 ms increased time to correct responses for the attention task (PCPTN; p = 0.041) and a decrease of 73.49 ms in time to correct responses for the episodic memory task (SVOLT; p = 0.028). For females, there was a significant positive association between a 1 mcg/dl increase in BLLs at 3–5 years and 34.59 ms increase in time to correct responses for the episodic memory task (SVOLT; p = 0.021). In both the log transformed models and the models which did not control for adolescent IQ, the results were unchanged. As a sensitivity analysis, we ran the models while including the PennCNB outliers in the models. We found the results were mostly unchanged, except for a significant association for females between Wave 1 BLLs and sensorimotor timing. Because the outlier value of sensorimotor time was well above the mean (Observation: 2800 ms; Mean: 583 ms) the inclusion of this value may greatly skew the data and results.

4. Discussion

In this longitudinal cohort of Chinese children with early childhood and early adolescent lead exposure, we found associations between lead exposure and neurobehavioral functioning outcomes which differed by sex. Specifically, BLLs at 3–5 year old were positively associated with measures of abstraction/mental flexibility (SPECT) and spatial processing (VSPLOT) in males and episodic memory (SVOLT) in females. Considering cross-sectional relationships, only associations with males remained significant, suggesting a relationship between BLLs and increasing time to correct responses for attention (PCPTN) and a decreasing time to correct responses for episodic memory (SVOLT).

The association between early childhood lead exposure and impaired early adolescent neurobehavioral outcomes are consistent with previous studies and suggest early toxicant exposures may induce a developmental cascade of neurobehavioral deficits (Bellinger et al., 2016). Similar longitudinal associations have been reported for measures of cognitive

flexibility, where 6 month old BLLs (7.2 mcg/dl) were significantly negatively associated with 5.5 year old outcomes (Canfield et al., 2004). As our study examined outcomes in 11 year old children, we present additional findings of longitudinal relationships. Stiles and colleagues have reported significant relationships between childhood lead exposure (<8 mcg/dl) and 10 year old executive functioning outcomes (Stiles and Bellinger, 1993). As exposure in their sample was greater than the current study, our results add further evidence for associations with an even lower level of lead exposure. However, findings are still mixed in the literature as others have reported null longitudinal associations between early BLLs and later neurobehavioral outcomes (Chandramouli et al., 2009). This may be due to differences in sustained lead exposure, and further studies utilizing repeated measures of lead exposure would help to elucidate relationships. Importantly, results reported here were consistent in models with and without controlling for adolescent IQ. As IQ has been suggested as a predictor of some, but not all, executive and motor function outcomes, future research may test whether IQ is a mediator between lead and neurobehavioral outcomes (Ardila et al., 2000; Kopp et al., 2019).

Cross-sectional relationships between BLLs and neurobehavioral measures were only seen for males in the attentional and episodic memory domains in the adjusted models. These results add to conflicting previous findings between adolescent lead exposure and attention. Some report significant associations in 8–11 year olds (Hong et al., 2015) and others null findings in 9–10 year olds (Prpíc-Majíc et al., 2000). These studies could not account for lead exposure in early childhood, a critical period of development where environmental insults are incredibly detrimental to the highly plastic brain, which potentially contributed to variable results (Knudsen, 2004). Our results suggest that as BLLs increased, time to correct responses in the episodic memory test decreased, an unexpected finding. Importantly, in females, we report opposing results, where as BLLs increased so did the time to correct responses. It should be noted that males' accuracy in the episodic memory task decreased as BLLs increased, though the results were non-significant. These results may be due to effect modification by unrepresented social factors and warrant further investigation in future research.

Differences in male and female associations between lead exposure and neurocognitive outcomes has been reported in previous literature (Singh et al., 2018). Indeed, development of the prefrontal cortex, the area of the brain responsible for higher order cognition, has been suggested to differ between males and females (Wierenga et al., 2019). Previous lead exposure research has reported males and females differ in their neurobehavioral responses, where males seem to be more impacted in the inhibition and attentional domains (Kim et al., 2010) and females more for unitary executive functioning measures (Barg et al., 2018; Kim et al., 2012). The differences in neurobehavioral outcomes in our study could, therefore, be due to sex-based developmental differences. Hormonal and epigenetic mechanisms may be in part responsible for sex-based differences. Estradiol and progesterone, both sex hormones, have been suggested as neuroprotective for females, potentially accounting for the significance of effects in males (Schwarz et al., 2010; Seiger et al., 2016). Estrogens may also modify epigenetic mechanisms which regulate systems associated with neurodevelopment, which may result in sex-specific changes in neurobehavioral function (Nugent and McCarthy, 2011). In this sample, differences could also be due to varying levels

of lead exposure, where males saw significantly greater BLLs at 3–5 years old compared to females (6.76 and 5.99 mcg/dl, respectively).

Deficits in neurobehavioral functioning abilities represent health consequences for children exposed to lead. Overall, reduced neurobehavioral functioning, including executive and visual-motor abilities, has been associated with negative health outcomes later in life, such as links with obesity, coronary heart disease, and diabetes (Gowey et al., 2018; Murdock et al., 2016; Rostamian et al., 2015). These associations are similar to that of lead exposure, which has also been linked with detrimental health outcomes such as cardiovascular disease and renal function (Navas-Acien et al., 2007; Tsaih et al., 2004). This data presents an interesting avenue for future research which may suggest impaired higher cognitive abilities as a partial mediator between lead exposure and health outcomes, as similar relationships have been suggested for associations between lead exposure and behavioral outcomes (Nigg et al., 2008). Further, diminished executive functioning abilities have also been associated with detrimental health behaviors such as substance abuse, unhealthy eating, and risky sexual activity (Grenard et al., 2008; Jasinska et al., 2012; Khurana et al., 2015). In fact, researchers have suggested that executive functioning abilities and health behaviors exist in a bi-directional, positive feedback loop, where improved executive functioning abilities increase positive health behaviors and reduce risky health behaviors, which may in turn increase executive functioning behaviors (Allan et al., 2016). Given the potential long-term impact of lead exposure, community health practitioners should pay attention to both recent and early-life lead exposure that may initiate health and developmental cascades. In particular, practitioners should be aware of potential sex-based differences associated with lead exposure, as no one child may present similarly. Our study highlights the importance of detection and management of low-level lead exposure as a target for neurobehavioral development throughout the childhood and adolescence. Specifically, continuous monitoring of BLLs and downstream signs and symptoms, as well as individualized preventions and interventions are needed for those who have early life exposure to neurotoxicants such as lead.

4.1. Strengths and Limitations

The major strength of this study is the large community-based sample with robust, laboratory-controlled psychophysiological testing of neurobehavioral functioning via a computerized battery and evaluation of blood lead. In addition, the study employed a longitudinal design with two waves of blood lead measurement across six years from early childhood to early adolescence and outcome measures assessed in adolescence, allowing for temporal examination.

However, there are limitations that should be considered. First, as this study examined observational data, we cannot confirm causality. Second, lead levels were measured at two points in time and, therefore, cannot account for sustained exposure across childhood development. Research with additional repeated lead exposure assessment is needed to confirm our findings. Finally, these data represent a sample of Chinese children and a specific cultural setting. Previous studies have reported differences in neurobehavioral, in particular executive function, outcomes in Chinese children versus western children (Schmitt

et al., 2018). It is possible our results are culturally specific and should be replicated in other samples.

5. Conclusion

Childhood lead exposure remains a persistent public health concern globally. Here we report that lead exposure in early childhood is associated with decreased neurobehavioral functioning abilities in both males and females, though the domain effected differed by sex. Specifically, BLLs at 3–5 years were longitudinally associated with abstraction/cognitive flexibility and spatial processing in males and episodic memory in females. Cross-sectionally, BLLs at 12 years were only associated with male outcomes including attention and episodic memory. These associations were found even while controlling for a number of sociodemographic variables and adolescent IQ.

These findings hold public health significance, as impaired neurobehavioral functioning has detrimental health consequences, including poor health decision making behavior and increased risk for cardiovascular and renal diseases. These detrimental outcomes are similarly associated with lead exposure and may suggest neurobehavioral functioning as a neurocognitive pathway between lead exposure and negative health outcomes, a potential area of future study. Examining how lead exposure influences neurocognition and further health decision making behaviors is a critical area of future study and may help develop interventions to reduce the negative health outcomes associated with lead exposure.

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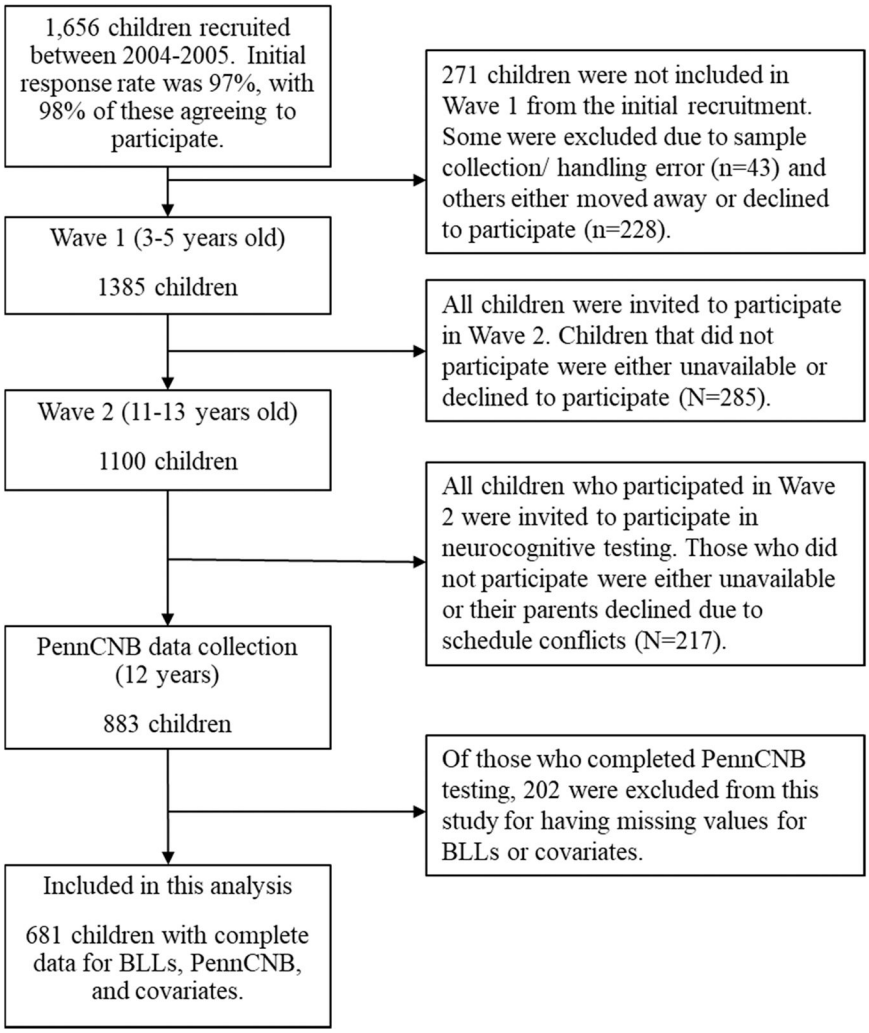

Fig. 1.

Jintan China Child Cohort recruitment and follow up flow chart.

Table 1

Participant Characteristics of Included versus Excluded Participants and Males and Females.

	Mean ± SD (or number and %) in parenthesis					
	Included (N = 681)	**Excluded**	**p-value***	**Males (N = 377)**	**Females (N = 304)**	**p-value***
Blood lead 3–5 years (mcg/dl)	6.41 ± 2.70	6.44 ± 2.58	0.881	6.76 ± 2.95	5.99 ± 2.30	0.0001
Blood lead 12 years (mcg/dl)	3.10 ± 1.14	3.17 ± 1.23	0.306	3.16 ± 1.11	3.02 ± 1.18	0.123
Father years education	11.54 ± 2.98	11.42 ± 3.03	0.452	11.50 ± 2.91	11.61 ± 3.07	0.615
Mother years education	10.82 ± 3.08	10.80 ± 3.00	0.905	10.82 ± 3.18	10.83 ± 2.96	0.971
Father's occupation			0.501			0.413
Unemployed	25 (3.67%)	27 (4.65%)		13 (3.45%)	12 (3.95%)	
Unskilled/skilled labor	396 (59.06%)	322 (55.42%)		212 (56.23%)	184 (60.53%)	
Professional	261 (38.27%)	232 (39.93%)		152 (40.32%)	108 (35.53%)	
Mother's occupation			0.105			0.079
Unemployed	176 (25.81%)	162 (27.46%)		96 (25.46%)	80 (26.32%)	
Unskilled/skilled labor	316 (46.33%)	239 (40.51%)		163 (43.24%)	152 (50.00%)	
Professional	190 (27.86%)	189 (32.03%)		118 (31.30%)	72 (23.68%)	
Age at the first blood lead test			0.000			0.874
3 years	194 (28.45%)	138 (19.80%)		105 (27.85%)	89 (29.28%)	
4 years	237 (34.75%)	195 (27.98)		131 (34.75%)	106 (34.87%)	
5 years	251 (36.80%)	364 (52.22)		141 (37.40%)	109 (35.86%)	
Residence			0.114			0.674
City	454 (66.57%)	405 (64.59)		257 (68.17%)	197 (64.80%)	
Town	129 (18.91%)	105 (16.75%)		68 (18.04%)	60 (19.74%)	
Countryside	99 (14.52%)	117 (18.66)		52 (13.79%)	47 (15.46%)	
Adolescent Intelligence Quotient (IQ)	104.39 ± 13.18	103.97 ± 15.59	0.592	106.09 ± 12.83	102.28 ± 13.34	0.0002
Abstraction/flexibility SPCET (#correct)	25.87 ± 6.94	25.27 ± 6.87	0.569	25.62 ± 6.73	26.19 ± 7.20	0.285
Abstraction/flexibility SPCET (time ms)	1693.47 ± 448.92	1676 ± 486.05	0.624	1642.01 ± 434.16	1757.29 ± 459.35	0.001
Abstraction/flexibility PMAT (#correct)	11.87 ± 4.59	11.48 ± 4.37	0.264	11.72 ± 4.72	12.06 ± 4.42	0.328
Abstraction/flexibility PMAT (time ms)	7911.18 ± 5727.82	7565.67 ± 5400.37	0.431	7764.45 ± 5697.69	8093.15 ± 5769.19	0.457
Attention (#correct)	83.90 ± 36.67	76 ± 38.66	0.006	79.96 ± 37.09	88.80 ± 35.61	0.002
Attention (time ms)	518.56 ± 131.32	514.96 ± 126.74	0.721	532.70 ± 155.79	501.01 ± 89.60	0.002

	Mean ± SD (or number and %) in parenthesis					
	Included (N = 681)	**Excluded**	**p-value***	**Males (N = 377)**	**Females (N = 304)**	**p-value***
Spatial processing (#correct)	9.69 ± 3.93	9.77 ± 4.03	0.794	9.72 ± 4.03	9.64 ± 3.82	0.777
Spatial processing (time ms)	8067.66 ± 2678.42	8314.36 ± 2625.52	0.249	7370.98 ± 2461.73	8559.60 ± 2853.27	0.000
Episodic memory (#correct)	15.18 ± 3.03	14.75 ± 318	0.068	15.14 ± 2.99	15.24 ± 3.07	0.664
Episodic memory (time ms)	1599.32 ± 637.34	1618.12 ± 718.04	0.712	1585.95 ± 698.75	1615.90 ± 552.48	0.543
Sensorimotor (time ms)	574.56 ± 98.11	590.78 ± 139.80	0.057	571.36 ± 104.24	578.52 ± 89.96	0.345
Motor speed (time ms)	111.47 ± 24.23	112.39 ± 24.57	0.813	112.90 ± 18.51	109.69 ± 29.78	0.085

*Student t-test or χ^2 test was used for significant difference test.

Table 2

BLLs influence on neurobehavioral outcomes for males and females.

Neurobehavioral outcome[a]	Males (N = 377)				Females (N = 304)			
	BLLs 3–5 years β (SE)	p-value	BLLs 12 years β (SE)	p-value	BLLs 3–5 years β (SE)	p-value	BLLs 12 years β (SE)	p-value
Abstraction/flexibility SPCET (#correct)	0.11 (0.13)	0.389	−0.03 (0.32)	0.918	−0.12 (0.19)	0.516	0.62 (0.35)	0.078
Abstraction/flexibility SPCET (time ms)	19.90 (7.95)	**0.013**	8.44 (20.14)	0.675	4.13 (12.10)	0.733	34.38 (22.32)	0.125
Abstraction/flexibility PMAT (#correct)	−0.01 (0.08)	0.933	−0.23 (0.21)	0.269	0.10 (0.11)	0.369	0.15 (0.20)	0.454
Abstraction/flexibility PMAT (time ms)	−19.03 (105.05)	0.856	−229.59 (265.94)	0.389	134.71 (150.59)	0.372	191.34 (278.25)	0.492
Attention (#correct)	−0.24 (0.68)	0.721	−2.30 (1.71)	0.081	−0.87 (0.92)	0.347	−2.99 (1.70)	0.080
Attention (time ms)	−2.35 (2.90)	0.419	15.08 (7.34)	**0.041**	3.98 (2.35)	0.092	0.07 (4.35)	0.986
Spatial processing (#correct)	0.03 (0.07)	0.690	−0.16 (0.19)	0.386	−0.07 (0.10)	0.495	0.21 (0.18)	0.237
Spatial processing (time ms)	96.00 (45.67)	0.036	−26.48 (115.63)	0.819	−41.32 (76.51)	0.590	171.68 (141.67)	0.226
Episodic memory (#correct)	−0.03 (0.06)	0.608	−0.23 (0.14)	0.106	0.04 (0.08)	0.646	0.05 (0.15)	0.735
Episodic memory (time ms)	7.80 (13.14)	0.553	−73.49 (33.27)	**0.028**	34.59 (14.86)	**0.021**	12.09 (27.47)	0.660
Sensorimotor (time ms)	0.20 (1.85)	0.916	0.72 (4.68)	0.877	3.23 (2.27)	0.156	−5.76 (4.19)	0.171
Motor speed (time ms)	0.64 (0.35)	0.063	−0.93 (0.87)	0.286	0.62 (0.79)	0.429	−0.31 (1.44)	0.832

[a]Covariates include: Child age at Wave 1, residence location (city, town, rural), mother and father occupation (unemployed, skilled/unskilled, professional) and education, and adolescent IQ.