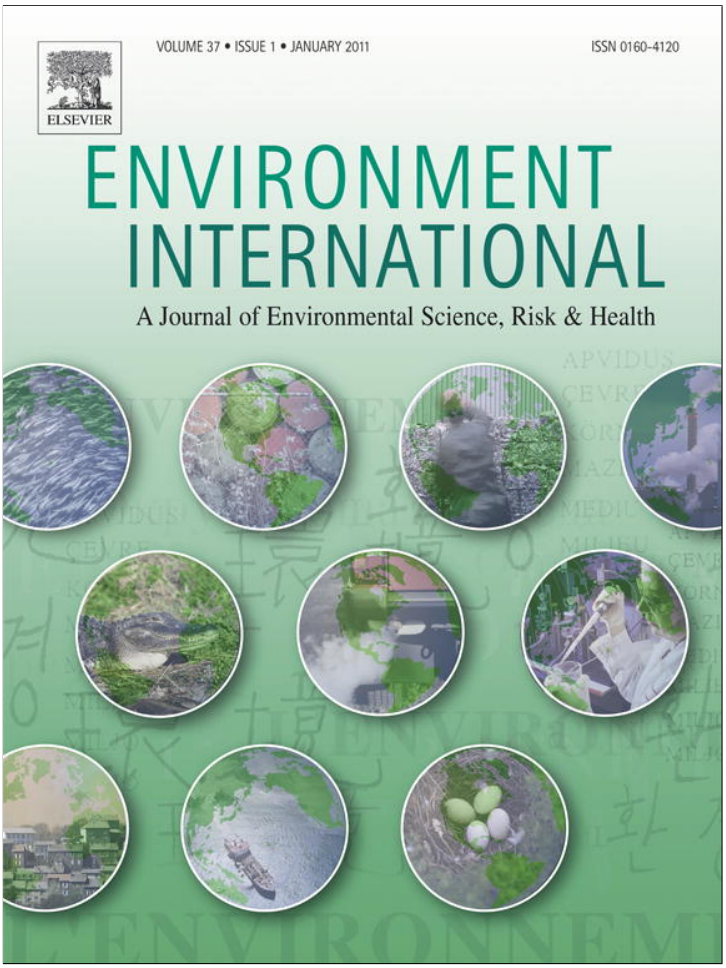

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Environment International 40 (2012) 88–96

Contents lists available at SciVerse ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Childhood blood lead levels and intellectual development after ban of leaded gasoline in Taiwan: A 9-year prospective study

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ARTICLE INFO

Article history:
Received 18 May 2011
Accepted 25 October 2011
Available online xxxx

Keywords:
Children health
Blood lead
Intelligence quotient (IQ)
Prenatal exposure
Postnatal exposure
Gasoline

ABSTRACT

Background: Lead (Pb) exposure is associated with children's neurodevelopment, even at low doses. Leaded gasoline was banned in Taiwan in 2000 to reduce environmental exposure to Pb.
Objectives: To evaluate the neurodevelopmental effect of low-level Pb exposure in young children.
Methods: In 2001–2002, we have recruited 430 pregnant women in the third-trimester in Taichung, Taiwan who answered detailed questionnaires in the obstetric clinic. A total of 119, 76, and 66 children were followed up at 2–3, 5–6 and 8–9 years, respectively. We collected blood samples from pregnant women, Umbilical cord and children, and evaluated children's neurodevelopment and cognition function at all three time points using Bayley and Wechsler tests. Blood samples were analyzed for whole blood lead (BPb) levels.
Results: Geometric mean of BPb in pregnant women, cord blood and children at 2–3, 5–6 and 8–9 years old were 2.21, 1.30, 2.48, 2.49 and 1.97 μg/dl, respectively. Low-level postnatal Ln BPb was significantly associated with not only decreasing intelligence quotient (IQ), but also delayed cognitive function in children at 5–8 years (β: −5.97, SE: 2.59, $p = 0.025$), after adjustment for maternal education, maternal BPb exposure, Home Observation for Measurement of the Environment Inventory (HOME), and gender of child, using linear mixed models. No significant relation was observed between prenatal and cord blood Pb levels and children's cognitive function in children 2–8 years.
Conclusions: Low-level postnatal BPb levels in children at 2–5 years may have lagged effects on neurodevelopment in those at 5 to 8 years. Action is warranted to reduce even very low environmental Pb levels to reduce the developmental burden of Pb on children.

1. Introduction

Lead (Pb) is a well-established neuron-toxic environmental pollutant. Sources of lead come from lead-gasoline combustion, coal incinerators, battery factories, paint and toys. Tetraethyl and tetramethyl lead were once used worldwide as gasoline additives to increase its octane rating. Epidemiological and experimental data indicate persistent deleterious effects of high blood lead (BPb) levels on hemoglobin synthesis, genotoxicity, behavior, reproduction and brain function, as significant adverse neurocognitive consequences in children (Ericson and Mishra 1990; Baghurst et al., 1992; Bellinger et al., 1992; Juberg et al., 1997; García-Lestón et al., 2010).

Longitudinal studies, including those in Yugoslavia and the Port Pirie cohort, show that prenatal and postnatal BPb levels of >10 μg/dl are inversely associated with cognitive function in pre-school (Wasserman et al. 1997, 2000) and teenage children (Tong et al., 1996, 1998). Recent studies further indicate that even lower BPb levels may delay intellectual development in children (Canfield et al., 2003; Jusko et al., 2008; Koller et al., 2004; Lanphear et al., 2005; Schnaas et al., 2006). However, little is known of the effect of prenatal and postnatal low-level BPb exposure on children's neurodevelopment.

Previous studies have revealed that banning leaded gasoline can significantly decrease Pb levels in the environment (Bellés et al., 1995) and BPb in adults, children and fetuses (Falq et al., 2011; Graber et al., 2010; Hwang et al., 2004; Mathee et al., 2006). The lead in gasoline in Taiwan was decreased from 0.34 g/l in 1983 to

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doi:10.1016/j.envint.2011.10.011

0.026 g/l in 1997, then banned in 2000 by the Taiwan Environmental Protection Agency (EPA). The ambient air lead in Taiwan then decreased significantly, from 0.47 μg/m^3 in 1989 to 0.09 μg/m^3 in 1997. Although unleaded gasoline use began in 2000, environmental lead levels decreased only gradually, delaying the effect of using unleaded gasoline on children by about 1.5 years (Hwang et al., 2004). Therefore, the health effect on children of low-level exposure to lead remains a public health concern (Levin et al., 2008).

To our knowledge, there is no safe level of BPb in children, although numerous studies have been conducted to evaluate the long-term effects of prenatal and postnatal low-level BPb exposure on children's neurodevelopment, there are few study to evaluate the effects after ban of leaded gasoline. We sought to understand the relations of prenatal and postnatal exposure to low-level lead on children's cognition function and intellectual quotient (IQ) and to determine which measure best predicts children's neurodevelopment later in life.

2. Methods

2.1. Subjects

The study subjects were pregnant women with no clinical complications, aged 20–40 years who delivered their babies in a medical center in central Taiwan, from December 1, 2001 to November 30, 2002 (Wang et al., 2004; Su et al., 2010). A total of 430 pregnant women were initially recruited at the third-trimester in this study. Blood samples of 323 paired women (at 3rd trimester) and newborns (at delivery) were obtained and ten babies did not provide detailed data of health status examination. Maternal blood lead concentration was used in modeling prenatal blood lead effects.

From the recruited mothers, we followed 119, 76 and 66 children at age 2–3, 5–6 and 8–9 years, respectively, during 2003 to 2009. The framework of this study is illustrated in Fig. 1. The pregnant women answered detailed questionnaires in the obstetric clinic, including

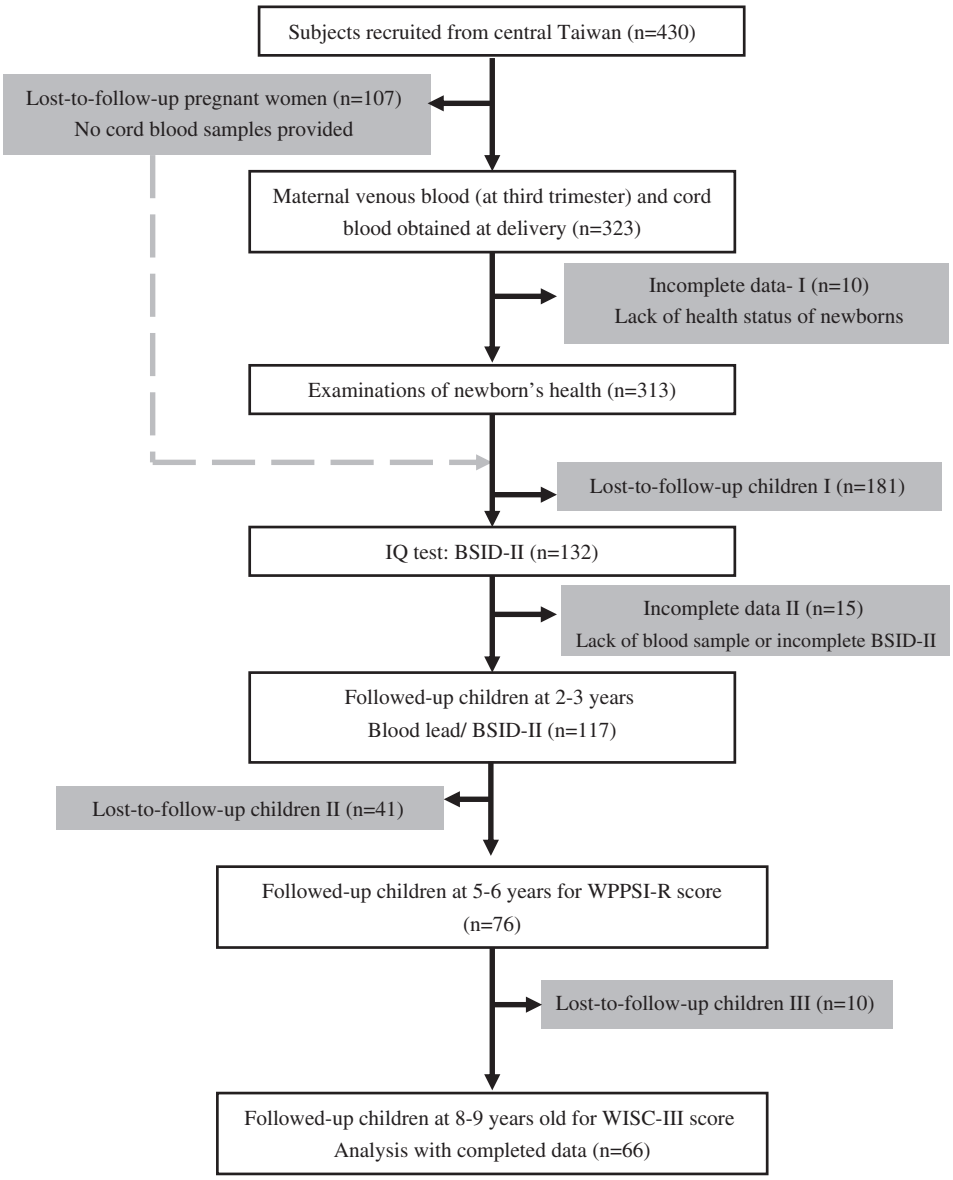

Fig. 1. Framework of this longitudinal study. Abbreviations: intelligence quotient (IQ); Bayley Scales of Infant Development–II (BSID-II); Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R); Wechsler Intelligence Scale for Children-version III (WISC-III).

their age, parity, education, medical history, cigarette smoking and alcohol use before and after pregnancy, and home pesticide use. Physicians measured general physical parameters of newborns, including gestational age, gender, birth weight and height, head and chest circumference and Apgar score. We collected veinous blood from pregnant women, cord blood at birth, and veinous blood from each child during the three follow-up points (2–9 years) to analyze for BPb levels. We assessed children's IQ using three different tools to evaluate cognitive development at 2–9 years. This protocol was approved by the Research Ethic Committee, National Health Research Institutes and written informed consent was obtained from participants before the study began.

2.2. BPb levels

Venous blood was collected from pregnant women at the third trimester, cord blood from newborns at delivery, and from children at 2–3, 5–6, and 8–9 years old using plastic and lead-free containers. The blood samples were analyzed for BPb levels at the Center of Toxic Substances and Drugs Residue Analysis, Kaohsiung Medical University Hospital. The analytic procedure for lead determination was previously published (Wang et al., 2002); briefly, the whole blood sample was diluted 1:9 with phosphate modifier. After pretreatment with cell lysis and digestion, blood samples were analyzed by Zeeman effect graphite furnace atomic absorption spectrometry (GF-AAS, Perkin-Elmer 5100 PC with AS 71 autosampler, PerkinElmer, Waltham, MA), with intralaboratory quality controls. With use of commercial standard materials (Betherning Institute, Bio-Rad, Hercules, CA), all coefficients of variation (CVs) were <6% for measurements at high (32.8–49.2 μg/dl) and medium levels (18.2–27.3 μg/dl), and <8% at low levels (5.9–8.9 μg/dl).

2.3. Intellectual development evaluation

2.3.1. Bayley Scales of Infant Development–II (BSID-II): 2–3 years old

All intellectual evaluation was administered to children by qualified psychologists using a standardized protocol. At age 2–3 years, intelligence was assessed using the Bayley Scales of Infant Development–II (BSID-II) (Bayley 1993), which measures: acquisition of object constancy, memory learning and problem solving, sensory/perceptual acuity, discrimination and response, vocalization and beginning of verbal communication, basis of abstract thinking, complex language, habituation, mental mapping, and mathematical concept formation. The resulting score is called the mental development index (MDI). Meanwhile, BSID-II also assesses degree of body control, large muscle coordination, finer manipulatory skills of the hands and fingers, postural imitation, dynamic movement, and stereognosis to yield the psychomotor development index (PDI).

2.3.2. WPPSI-R and WISC-III: 5–6 and 8–9 years old

We used the Chinese version of the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) (Wechsler 1989) and the Wechsler Intelligence Scale for Children-version III (WISC-III) (Wechsler 1991) to assess children's IQ at 5–6 and 8–9 years, respectively. We labeled these scores IQ_5 and IQ_8 to indicate scores by age. WPPSI-R and WISC-III are not only universally acknowledged tools to evaluate pre-school children's IQ, they also provides a thorough sampling of the abilities of children with lower than average IQ scores (Jusko et al., 2008; Lanphear et al., 2005; Schnaas et al., 2006; Wasserman et al., 2000). The WPPSI-R has five subtests of verbal skill (arithmetic, comprehension, information, similarities and vocabulary) and five subtests of visual–spatial skill (block design, geometric design, mazes, object assembly and picture completion). Verbal IQ_5 (VIQ_5), the combined scores of verbal tests, and performance IQ_5 (PIQ_5), the combined scores of visual–spatial test, were standardized to yield the full-scale IQ ($FSIQ_5$). Similarity, WISC-III also has five subtests of verbal skill, which yield verbal IQ_8 (VIQ_8), and five subtests of performance (picture completion, coding, picture arrangement, block design and object assembly), which yield performance IQ_8 (PIQ_8). Full-scale IQ_8 ($FSIQ_8$) was obtained by combining VIQ_8 and PIQ_8 scores.

2.4. Questionnaire and covariates

Information on demographic, socioeconomic and other factors that could confound the relationship between pre- and postnatal lead exposure, and children's cognitive development was collected. We used an administrated questionnaire to obtain demographic data (socioeconomic status, health status, lifestyle and habits) of pregnant women. A parent also completed the Home Observation for Measurement of the Environment Inventory (HOME) (Caldwell and Bradley 1984) at the three time points in the clinic. The HOME score was used to evaluate the quality and quantity of emotional and cognitive stimulation in the home environment.

2.5. Statistical analysis

We assessed the relationship between prenatal (maternal and cord blood) and postnatal lead exposure (at 2–3 years, 5–6 years, 8–9 years and average of the three), and children's cognitive development (BSID-II, WPPSI-R and WISC-III IQ scores). All variables were assessed for normal distribution, or nature logarithm-transform to approximate normal distribution. For example, all IQ scores were normal distribution and all blood Pb levels were nature logarithm-transformed. Covariates assessed included maternal age at delivery, maternal education, prenatal smoking and alcohol consumption, child's gender, birth weight, and HOME score. Due to twins shared the same household, they will be more highly correlated than children from different households. We randomly included one of them for statistical analysis.

We used independent sample *t* test to assess the difference in characteristics between followed and lost-to-follow up subjects as well as differences in follow-up subjects by IQ scores, socioeconomic status and other variables. For nominal variables, the chi-square test was applied. Trend test and Kendall's tau-c were utilized to evaluate the change in children's IQ by level of maternal or child BPb levels and other covariates. Pearson correlation was used to explore the relationship between IQ scores, BPb levels and potential covariates. Significance was set at $P<0.05$.

We used multivariate multiple regressions to assess the effects of BPb level on IQ score at each age. The significance was set at $P<0.05$. To consider repeat measures spontaneously, we utilized linear mixed model (LMM) to evaluate the relationship of BPb levels at 2–3 and 5–6 years to children's IQ. We used $FSIQ_5$ and $FSIQ_8$ to represent children's IQ at 5–9 years old as the dependent variable in the LMM. Covariates in the model included children's BPb levels and HOME scores at 2–3, 5–6 and 8–9 years, maternal education, prenatal Pb level and maternal age. We first put in children's BPb levels, HOME score, birth weight and gender to assess the impact of individual factors (Model 1). In Model 2, we additional added in three maternal factors: maternal BPb level, education and age. In Model 3, we included three environmental factors (pesticide use, pre-pregnancy smoking, and post-pregnancy alcohol drinking). We treated the subjects as random effect and controlled for fixed covariates in three models. Model selections were based on the value of Akaike's Information Criterion (AIC) (smaller is better). We also used compound symmetry (CS) and first-order autoregressive (AR(1)) to evaluate the covariance structure and random effects in the LMM. Two indexes, logarithm Likelihood and AIC, were used to evaluate the goodness of fit statistics. The compound symmetry and variance components were constructed as the covariance structures. We used Shapiro–Wilk test to evaluate the normality of residual distribution. Residual and influence

analyses were conducted and no outliers and influential data points were observed. All analyses were performed using SAS 9.13 software (SAS Inc., Cary, NC).

3. Results

3.1. Characteristics of followed and lost-to-follow up subjects

Demographic characteristics of children followed and lost-to-follow up are shown in Table 1. No significant differences in physiological factors (age, BMI, menarche age), socioeconomic status (parent's education, annual income), maternal lifestyle (cigarette smoking and alcohol consumption) or medical history (hormone therapy) were observed in the pregnant women between groups. Children followed in this study had a longer gestational age and slight heavier birth weight than those lost to follow up. In addition, both maternal and cord BPb geometric mean (GM) levels were slight lower (around 10%) in those followed than in those lost to follow up. Gender ratio of subjects followed was 1.08, similar to the sex ratio in the general population, and most were singletons. Mean and range of age of children at each period for cognitive function testing were 26.1 (21.5–30.7), 62.7 (57.0–71.0) and 98.2 (93.6–111.6) months, respectively. The estimated gestational age of BPb measurement in pregnant women was all above 28 weeks (at the third trimesters).

3.2. Mental development evaluation and BPb levels

Table 2 shows the long-term evaluation of intellectual development in followed children at different ages. Mean IQ score of children were 95.4 ± 12.4 points (MDI), 105.9 ± 13.7 points ($FSIQ_5$) and 110.2 ± 13.7 points ($FSIQ_8$) at 2–3, 5–6 and 8–9 years old, respectively. MDI was significantly positively correlated with $FSIQ_5$ (Pearson correlation (R) = 0.414, P<0.001, n = 76) and $FSIQ_8$ (R = 0.405, P<0.001, n = 66). Also, $FSIQ_5$ was significant positively correlated with $FSIQ_8$ (R = 0.646, P<0.001, n = 66, data not shown). Besides, average $HOME_2$ score was 40.2 ± 4.0, and increased slightly to 45.6 ± 5.2 and 46.7 ± 5.5 for ages 5–6 to 8–9 years, respectively.

Table 2 shows the BPb levels in maternal blood, cord blood and children's blood at 2–3, 5–6, and 8–9 years, and the average for children at 2–9 years. We found that the GM of BPb level of maternal blood (2.21, 95%CI: 2.01–2.44 μg/dl) was 1.7 fold higher than that of cord blood (1.30, 95%CI: 1.21–1.40 μg/dl). In children, GM of BPb levels were highest at 2–3 years (2.48, 95%CI: 2.27–2.70 μg/dl) and at 5–6 years (2.49, 95%CI: 2.27–2.73 μg/dl), and lowest at 8–9 years (1.97, 95%CI: 1.77–2.20 μg/dl). Average (2–9 years) BPb GM levels in children was 2.33 (95%CI: 2.13–2.55) μg/dl. Children's BPb levels at 2–3 years were significantly positively correlated with those at 5–6 years (R = 0.662, P<0.001, n = 64) and 8–9 years (R = 0.519, P<0.001, n = 63). Also, children's BPb level at 5–6 years was significant positively correlated with that at 8–9 years (R = 0.607, P<0.001, n = 62) (data not shown). In addition, children's lifetime average BPb level was significant positively correlated with that at 2–3 years (R = 0.865, P<0.001, n = 62), 5–6 years (R = 0.894, P<0.001, n = 62) and 8–9 years (R = 0.798, P<0.001, n = 62). However, neither maternal BPb level nor cord BPb level was correlated with children's BPb at any age (data not shown).

3.3. Children's IQ and related factors

We categorized children's IQ scores by tertile of maternal BPb level (data not shown). We found that children's PDI decreased marginally significantly as maternal BPb level increased (IQ point = −5.5, p = 0.066). We also categorized children's IQ scores by tertile of children's BPb level by age. We found no significant trend between children's BPb at age 2–3 years, children's BPb at age 8–9 years and IQ scores. Although children's IQ scores at 5–9 years decrease as BPb levels increase, we observed a

Table 1
Demographic characteristic of followed and lost-to-follow-up subjects.

Demographic characteristics		Followed up (n = 119)		Lost-to-follow-up (n = 298)		P-value[a]
Continuous variables		Mean (GM)	SD (95%CI)[a]	Mean (GM)	SD (95%CI)[a]	
Maternal age (years, n[b] = 119/276)		29.2	4.0	28.5	4.5	0.165
Maternal BMI (n = 117/269)		21.0	3.1	20.7	3.2	0.433
Menarche (years, 117/270)		13.6	1.3	13.7	1.3	0.428
Birth weight (gram, n = 115/252)		3160	407	3062	490	0.063#
Birth length (cm, n = 114/249)		51.2	2.5	51.1	2.8	0.715
Gestational age (weeks, n = 118/246)		39.3	1.3	38.8	1.7	0.014*
Head circumference (cm, n = 114/247)		33.5	1.3	33.3	1.6	0.161
Chest circumference (cm, n = 113/246)		33.0	1.6	32.5	2.0	0.050*
Apgar score lst min (n = 115/246)[c]		8.4	0.8	8.1	0.9	0.003†
Apgar score 5th min (n = 115/246)[c]		9.7	0.5	9.6	0.6	0.161
Maternal blood Pb (μg/dl, n = 119/298)		2.53 (2.21)	1.3 (2.01–2.4)	2.85 (2.31)	1.8 (2.13–2.5)	0.089#
Cord blood Pb (μg/dl, n = 105/218)		1.39 (1.30)	0.5 (1.21–1.4)	*1.52* (1.41)	0.6 (1.34–1.49)	0.056#
Categorical variables		n	%	n	%	
Gender	Male	62	52.1	135	53.1	0.850
	Female	57	47.9	119	46.9	
Singleton	Yes	118	99.2	176	95.1	0.095#
	No (Twin)	1	0.8	9	4.9	
Maternal education	≤12 years	54	45.8	141	49.3	0.518
	>l2 years	64	54.2	145	50.7	
Paternal education	≤12 years	49	41.5	131	47.5	0.278
	>l2 years	69	58.5	145	52.5	
Family annual income ($US/year)	<20,000	59	51.3	115	42.1	0.097#
	≥20,000	56	48.7	158	57.9	
Lactation	Yes	104	92.0	224	89.6	0.467
	No	9	8.0	26	10.4	
Before pregnancy						
Active smoker	Yes	8	6.8	22	7.9	0.712
	No	109	93.2	256	91.9	
Passive smoke	Yes	51	43.6	129	46.6	0.587
	No	66	56.4	148	53.4	
During pregnancy						
Active smoker	Yes	2	1.7	6	2.2	1.000
	No	117	98.3	271	97.8	
Alcohol consumption	Yes	2	1.7	11	4.0	0.360
	No	117	98.3	*266*	96.0	
Pesticide use at home	Yes	35	29.4	92	33.2	0.457
	No	84	70.6	185	66.8	

[a] Statistical method: Independent t-test, chi-square test; #p<0.10; *p<0.05; †p<0.01.
[b] Number of followed and lost-to-follow-up subjects (n = follow/lost-followed up).
[c] Apgar score is the sum score of five vital sign, including appearance, pulse, grimace, activity, respiration, in newborns.

Table 2
Neurodevelopment evaluation and blood lead concentrations of followed up children at 2–9 years.

Neurodevelopment evaluation	Children with completed data				
	n	Mean	SD[a]	Median	Range
BSID-II (at 2–3 years)[a]					
PDI	117	97.7	11.0	97.0	61–126
MDI	117	95.4	12.4	96.0	54–126
$HOME_2$ score	115	40.2	4.0	41.0	30–47
WPPSI-R (at 5–6 years)[a]					
VIQ_5	76	103.7	13.2	106.0	73–140
PIQ_5	76	106.9	14.1	107.0	69–141
FSIQ5	76	105.9	13.7	106.0	78–136
$HOME_5$ score	75	45.6	5.2	46.0	29–54
WISC-III (at 8–9 years)[a]					
VIQ_8	66	110.8	12.3	110.0	75-137
PIQ_8	66	108.2	12.4	109.0	82–136
$FSIQ_8$	66	110.2	11.9	111.0	86–138
$HOME_8$ score	64	46.7	5.5	48.0	31–55
Blood lead levels (μg/dl)	n	Geometric mean	95%CI[a]	Median	Range
Maternal blood (at third-trimester)	119	2.21	2.01–2.44	2.30	0.4–7.2
Cord blood	105	1.30	1.21–1.40	1.29	0.26–2.92
Children blood (at 2–3 years)	119	2.48	2.27–2.70	2.50	0.5–8.4
Children blood (at 5–6 years)	64	2.49	2.27–2.73	2.30	1.1–4.8
Children blood (at 8–9 years)	63	1.97	1.77–2.20	2.10	0.9–5.3
Average blood Pb (2, 5, 8 years)	62	2.33	2.13–2.55	2.32	1.13–4.63

[a] Abbreviations: Bayley Scales of Infant Development–II (BSID-II); confidence interval (CI); full-scale IQ at 5 years ($FSIQ_5$) and 8 years ($FSIQ_8$); Home Observation for Measurement of the Environment Inventory (HOME); intelligence quotient (IQ); mental development index (MDI); psychomotor development index (PDI); performance IQ (PIQ_5) and verbal IQ (VIQ_5) at 5 years; performance IQ (PIQ_8) and verbal IQ (VIQ_8) at 8 years; standard deviation (SD); Wechsler Preschool & Primary Scale of Intelligence-Revised (WPPSI-R); Wechsler Intelligence Scale for Children-version III (WISC-III).

marginally significant decreasing trend between BPb levels at age 5–6 years and $FSIQ_8$ (IQ point = −8.1, p = 0.074). However, when we used average BPb for ages 2–9 years as a predictor, we found a significant trend for PIQ_8 (P_{trend} = 0.039) and $FSIQ_8$ (P_{trend} = 0.018), and a marginally significant trend for VIQ_8 (P_{trend} = 0.071). We further assessed the relationship between categorical variables, like socioeconomic status, and children's IQ scores at each age (Table 3). We found significant differences in children's MDI by education level of pregnant women and annual family income. These factors also differed significantly by VIQ_5, $FSIQ_5$ and $FSIQ_8$, and differed marginally significantly by PIQ_8 and VIQ_8. We found no significant difference in IQ scores by child's gender, maternal passive smoking or home pesticide use.

We used Pearson correlation to evaluate the relationship between covariates and children's IQ scores (Table 3). Maternal BPb levels were marginally significantly negatively correlated with child's PDI (R = −0.166, P = 0.077), whereas children's BPb level at 2–3 years was inversely correlated with MDI (R = −0.164, P = 0.074). Children's BPb level at 2–3 years was also significantly negatively correlated with PIQ_5 (R = −0.240, P = 0.037) and $FSIQ_5$ (R = −0.229, P = 0.047), and marginal significantly negative correlated with VIQ_5 (R = −0.197, P = 0.088) and $FSIQ_8$ (R = −0.215, P = 0.083). Besides, children's BPb level at 5–6 years was significantly negatively correlated with PIQ_5 (R = −0.277, P = 0.026), PIQ_8 (R = −0.270, P = 0.031) and $FSIQ_8$ (R = −0.296, P = 0.018), and marginally significantly negatively correlated with VIQ_8 (R = −0.235, P = 0.062). Average children's BPb levels for ages 2–9 years was significantly negatively correlated with $FSIQ_8$ and marginally significantly negatively correlated with PIQ_8 and VIQ_8. However, we found no significant correlation between children's BPb levels at ages 8–9 years and $FSIQ_8$.

Table 3
Correlations[a] between maternal and cord blood Pb levels in pregnant women, and blood Pb levels in children at 2–3, 5–6, 8–9 years, children's IQ and other factors.

Pearson correlation	BSID-II[b] (N = 117)			n	WPPSI-R[b] (N = 76)			n	WISC-III[b] (N = 66)		
	n	MDI[b]	PDI[b]		PIQ_5[b]	VIQ_5[b]	$FSIQ_5$[b]		PIQ_8[b]	VIQ_8[b]	$FSIQ_8$[b]
Blood Pb (BPb)[c]											
Maternal BPb (3rd trimester)	117	0.013	**−0.166**#	76	−0.061	−0.054	−0.064	66	−0.118	−0.027	−0.082
Cord BPb	104	0.020	**0.289**†	69	0.005	−0.048	−0.025	60	0.101	−0.073	0.014
Children BPb (2–3 years)	117	**−0.164**#	−0.139	76	**−0.240***	**−0.197**#	**−0.229***	66	−0.182	−0.190	**−0.215**#
Children BPb (5–6 years)	64	–	–	64	**−0.277***	−0.025	−0.149	64	**−0.270***	**−0.235**#	**−0.296***
Children BPb (8–9 years)	63	–	–	63	–	–	–	63	−0.136	**−0.208**#	−0.201
Average BPb (2–9 years)	62	–	–	62	–	–	–	62	**−0.224**#	**−0.248**#	**−0.277***
Pregnant women											
Maternal age	117	0.079	0.123	76	0.132	0.146	0.152	66	**0.297***	**0.346**†	**0.366**†
BMI[b]	115	0.001	0.101	76	−0.178	−0.149	−0.173	66	−0.006	0.174	0.098
Maternal education	116	**0.266**†	0.073	76	0.117	0.297†	0.255#	66	**0.216**#	**0.221**#	**0.244***
Newborn											
Gestational age	116	0.045	0.112	76	0.131	0.016	0.089	66	−0.096	0.109	0.006
Apgar score 1st min	113	−0.064	−0.133	74	−0.123	−0.163	−0.171	64	−0.008	−0.201	−0.131
Apgar score 5th min	113	−0.022	−0.122	74	−0.183	−0.153	−0.188	64	−0.043	−0.168	−0.136
Birth weight	113	0.064	0.008	74	0.107	−0.035	0.037	64	0.034	0.183	0.123
Birth height	112	0.004	0.003	74	0.147	0.088	0.135	64	0.073	0.154	0.132
Head circumference	112	0.112	−0.008	74	0.171	0.055	0.124	64	0.007	0.044	0.021
Chest circumference	111	0.114	−0.031	74	0.051	−0.044	0.007	64	−0.087	0.068	−0.016

[a] Pearson correlation coefficient; #p<0.10; *p<0.05; †p<0.01.
[b] Abbreviations: Bayley Scales of Infant Development–II (BSID-II); blood lead (BPb); body mass index (BMI); intelligence quotient (IQ); mental development index (MDI); performance IQ (PIQ_5) and verbal IQ (VIQ_5) at 5 years; performance IQ (PIQ_8) and verbal IQ (VIQ_8) at 8 years; psychomotor development index (PDI); Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R); Wechsler Intelligence Scale for Children-version III (WISC-III).
[c] All the blood lead were natural logarithm transformed.

Table 4
Multivariate multiple regression[a] results of children BPb[b] levels and IQ[b] scores (BSID-II[b], WPPSI-R[b] and WISC-III[b]) at 2–3, 5–6, and 8–9 years.

Variables	MDI (BSID-II)[b] (n = 116)			PDI (BSID-II)[b] (n = 116)			$FSIQ_5$ (WPPSI-R)[b] (n = 76)			$FSIQ_8$ (WISC-III)[b] (n = 66)		
	B	95%CI	p	β	95%CI	p	β	95%CI	p	β	95%CI	p
Ln BPb 2–3 years	−0.132	−8.32 ~ 1.42	0.163	−0.107	−6.91 ~ 1.94	0.268	**−0.210**	−13.7 ~ −0.825	**0.082**#	**−0.220**	−12.4 ~ 0.537	**0.071**#
Maternal education	**0.244**	0.396 ~ 2.73	**0.009**†	0.052	−0.765 ~ 1.46	0.580	**0.249**	0.162 ~ 3.20	**0.031***	**0.235**	0.058 ~ 2.67	**0.041***
Gender	−0.043	−5.61 ~ 3.49	0.644	−0.026	−4.71 ~ 3.56	0.785	0.020	−5.67 ~ 6.78	0.860	**0.199**	−0.802 ~ 10.2	**0.093**#
Ln BPb 3rd trimester[c]	0.017	−3.80 ~ 4.57	0.855	−0.152	−6.87 ~ 0.734	0.113	−0.018	−6.07 ~ 5.20	0.878	0.017	−4.45 ~ 5.15	0.883
Maternal age	0.030	−0.478 ~ 0.664	0.747	0.075	−0.315 ~ 0.723	0.780	0.111	−0.409 ~ 1.18	0.336	**0.331**	0.30 ~ 1.66	**0.005**†
Alcohol consumption[c]	−0.097	−26.7 ~ 8.30	0.300	−0.069	−21.7 ~ 10.1	0.470	0.001	−27.3 ~ 27.6	0.990	0.054	−17.1 ~ 27.5	0.644
Ln BPb 5–6 years	–	–	–	–	–	–	−0.134	−14.9 ~ 5.27	0.342	**−0.313**	−17.1 ~ −2.16	**0.012***
Maternal education	–	–	–	–	–	–	0.205	−0.346 ~ 3.02	0.117	**0.222**	−0.006 ~ 2.49	**0.051**#
Gender	–	–	–	–	–	–	0.000	−7.37 ~ 7.38	1.000	**0.212**	−0.59 ~ 10.3	**0.080**#
Ln BPb 3rd trimester[c]	–	–	–	–	–	–	−0.002	−6.60 ~ 6.48	0.986	0.011	−0.460 ~ 5.07	0.924
Maternal age	–	–	–	–	–	–	0.126	−0.453 ~ 1.29	0.341	**0.331**	0.294 ~ 1.58	**0.005**†
Alcohol consumption[c]	–	–	–	–	–	–	0.017	−26.9 ~ 30.7	0.130	0.038	−17.8 ~ 24.8	0.743
Ln BPb 8–9 years	–	–	–	–	–	–	–	–	–	**−0.219**	−11.7 ~ 0.547	**0.074**#
Maternal education	–	–	–	–	–	–	–	–	–	**0.263**	0.174 ~ 2.69	**0.026***
Gender	–	–	–	–	–	–	–	–	–	0.146	−1.89 ~ 8.43	0.209
Ln BPb 3rd trimester[c]	–	–	–	–	–	–	–	–	–	0.010	−4.32 ~ 4.71	0.932
Maternal age	–	–	–	–	–	–	–	–	–	**0.376**	0.398 ~ 1.67	**0.002**†
Alcohol consumption[c]	–	–	–	–	–	–	–	–	–	0.060	−15.7 ~ 26.5	0.611

[a] Multivariate multiple regression; #: $p<0.10$; *: $p<0.05$; †: $p<0.01$.
[b] Abbreviations: Bayley Scales of Infant Development–II (BSID-II); blood lead (BPb); confidence interval (CI); intelligence quotient (IQ); mental development index (MDI); natural logarithm (Ln); psychomotor development index (PDI); Wechsler Preschool & Primary Scale of Intelligence-Revised (WPPSI-R); Wechsler Intelligence Scale for Children-version III (WISC-III).
[c] $\text{Ln BPb}_{\text{3rd trimester}}$: prenatal BPb from pregnant women at 3rd trimester; alcohol consumption: alcohol consumption of pregnant women during pregnancy.

For other covariates, we found a positive correlation between maternal age and PIQ_8, VIQ_8 and $FSIQ_8$. Maternal education was significantly positively correlated with most children's IQ scores. HOME score at each age stage was significantly positively correlated with children's IQ.

3.4. Association of BPb levels and children's IQ

Table 4 shows the multivariate multiple regression analysis of children's Ln BPb levels and IQ scores at 2–9 years old. After adjusting for gender, maternal education and age, maternal BPb and alcohol consumption during pregnancy, children's Ln BPb levels at 2–3 years was marginal significantly negative associated with $FSIQ_5$ (β = −0.210, 95%CI: −13.7 — −0.825, P = 0.082) and $FSIQ_8$ (β = −0.220, 95%CI: −12.4 — −0.537, P = 0.071). Children's Ln BPb levels at age 5–6 years (β = −0.313, 95%CI: −17.1 — −2.16, P = 0.012) were significantly inversely associated with $FSIQ_8$ after adjustment for same covariates. However, we observed only a marginally significant negative association between children's Ln BPb levels at age 8–9 years and $FSIQ_8$ (β = −0.219, 95%CI: −11.7 — 0.547, P = 0.074). Children's Ln BPb levels at age 2–9 years (β = −0.289, 95%CI: −16.9 — −1.48, P = 0.020) were significantly and inversely associated with $FSIQ_8$, after adjusting for same covariates (Supplemental Table A and B).

Table 5
Results of postnatal BPb[a] exposure in children at 2–3 and 5–6 years and IQ[a] scores in children at 5–6 and 8–9 years using linear mixed model[b].

Linear mixed models	Beta	SE	p-value
Model 1 (No = 134)			
Intercept	86.9	13.4	<0.001
Children's Ln BPb[b]	−6.56	2.59	0.014
HOME score	0.476	0.194	0.017
Count[c]	3.03	1.35	0.029
Model 2 (No = 134)			
Intercept	59.1	16.0	<0.001
Children's Ln BPb[a]	−5.69	2.53	0.030
Maternal Ln Pb	−0.885	2.24	0.694
HOME[a] score	0.347	0.199	0.088
Maternal education	1.452	0.627	0.024
Maternal age	0.616	0.308	0.050
Count[c]	2.99	1.32	0.028
Model 3 (No = 133)			
Intercept	52.0	20.2	0.012
Children's Ln BPb[a]	−5.97	2.59	0.025
Maternal Ln BPb	−0.299	2.23	0.894
HOME[b] score	0.378	0.199	0.063
Maternal education	1.34	0.621	0.035
Maternal age	0.663	0.304	0.034
Count[c]	2.93	1.33	0.031

[a] Abbreviations: intelligence quotient (IQ); blood lead (BPb); Home Observation for Measurement of the Environment Inventory (HOME); natural logarithm (Ln); number of observations (No); standard error (SE).
[b] Model 1: adjusted for gender, HOME score, and birth weight. Model 2: adjusted for gender, HOME score, birth weight, maternal BPb, maternal education, and maternal age. Model 3: adjusted for gender, HOME score, birth weight, maternal BPb, maternal education, maternal age, pesticide use, pre-pregnancy smoking, and post-pregnancy alcohol drinking.
[c] "Count" represent separated fixed effect term for each BPb period.

Table 5 shows the results of the LMM of the lagged effects of postnatal Pb exposure at 2–3 and 5–6 years on IQ scores in children at 5–6 and 8–9 years. Children's Ln BPb levels were significantly negatively associated with their IQ score (β = −6.56; SE:2.59, p = 0.014) after adjusting for gender and birth weight (Model 1), whereas HOME score was significantly positively associated with children's IQ (β = 0.476; SE:0.194, p = 0.017). Maternal age and education were significantly positive associated with children's IQ, whereas children's Ln BPb levels were significantly negatively associated with their IQ score (β = −5.69; SE:2.53, p = 0.030), after further adjusting for maternal Ln BPb level (Model 2). After adjustment for environmental factors (Model 3), children's Ln BPb was still negatively associated with their IQ score (β = −5.97; SE:2.59, p = 0.025), whereas maternal age and education were positively associated with their IQ (for maternal age, β = 0.663; SE: 0.304, p = 0.034; for maternal education, β = 1.34; SE: 0.621, p = 0.035). The assessment of gender, sub-parts of the IQ and prenatal BPb on LMM and evaluation of normality, covariance structure, residual on LMM were detailed presented at Supplemental materials (Supplemental Table C–E and F–G). Fig. 2 illustrated the scatter plot of children's intelligence quotient (IQ) at 5 and 8 years vs Ln BPb levels in children at 2 and 5 years using LMM with formula and 95% confidence interval of fitted line.

4. Discussion

We found a significant negative association between low-level postnatal Pb levels and the 3-years lagged effects of children's IQ at 2–9 years. For two decades, studies have focused on the effect of lead exposure (mostly 10–20 μg/dl) on children's IQ (Bellinger et al., 1987, 1992; Schnaas et al., 2006; Tong et al., 1996, 1998; Wasserman et al., 2000). Based on robust dose–response relationship from previous long-term studies, the World Health Organization and U.S. Centers for Disease Control and Prevention (CDC) recommended a threshold blood lead level of <10 μg/dl in children (CDC, 1991; WHO, 1995). In the past decade, studies have questioned how low is low enough for lead exposure in children (Canfield et al., 2003; Gilbert and Weiss, 2006; Rogan and Ware, 2003). A prospective cohort study by Krakow provided evidence of the effect of low prenatal BPb levels on delayed

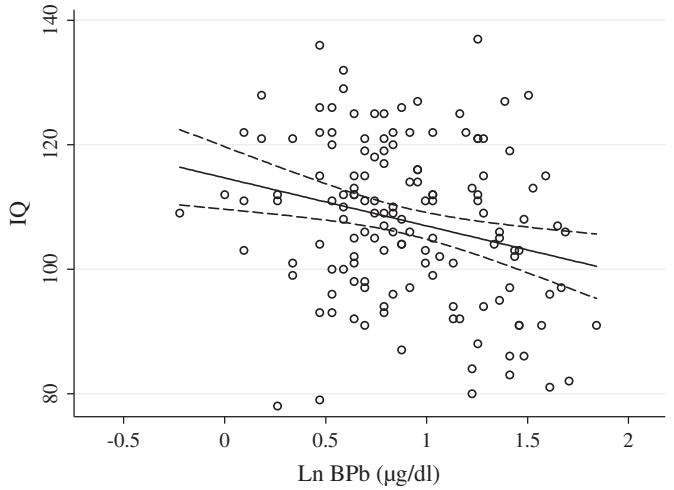

Fig. 2. Scatter plot of children's intelligence quotient (IQ) at 5 and 8 years vs. nature logarithm blood lead (Ln BPb) levels in children at 2 and 5 years using mixed model with formula and 95% confidence interval of fitted line (YIQ = 113.11 − 6.28X Ln BPb, PLnBPb = 0.021, AIC = 1076).

mental development in infancy; however, it lacked postnatal BPb levels and evaluation of long-term effects (Jedrychowski et al., 2007). Our study provided both prenatal and postnatal BPb levels, and long-term follow up of neurodevelopment of children at 2–9 years. Using LMM analysis, we found that low-level postnatal lead exposure has a significant negative and delayed effect on children's cognitive function.

We did not observe a significant effect of maternal or cord blood BPb levels on neurodevelopment, which is not consistent with previous studies (Schnaas et al., 2006; Wasserman et al., 2000). At least two recent animal studies have indicated that prenatal Pb levels in the mother can cross the placenta and affect monoamine oxidase (MAO) activity in the rat brain, especially for postnatal Pb exposure (Foltinova et al., 2007; Shin et al., 2007). Shin et al. also found that Pb exposure increased MAO activity in most brain regions in the rat and that toxicity gradually decreased as rats developed. Therefore, the relatively lower prenatal BPb level in our study compared to other studies, and the low postnatal BPb levels may have more subtle effects on children's long-term neurodevelopment than we were able to measure.

The findings of this study are relevant to the effect of banning Pb in gasoline on BPb level and cognitive development in children. We found that children's BPb levels in Taiwan decreased as they aged, consistent with results from the NHANES study (Supplemental Table H). The most recent children's BPb levels at 1–5 years in Taiwan were half those of children in an earlier investigation in Kaohsiung City (5.86 ± 2.62 μg/dl, n = 249) (Yang et al., 1995). However, these levels are still around twice those in the US (Jones, et al., 2009). In addition, we found a 40% reduction in cord BPb levels in the Taichung population compared to those in a Taipei study for the same timeframe (Hwang et al., 2004). Several studies have indicated that airborne Pb from gasoline is the primary exposure source for human adults, fetuses and children (Hwang et al., 2004; Levin et al., 2008). According to records of the Taiwan EPA, Taichung has around 30% fewer automobiles than Taipei. The levels of maternal and cord BPb (prenatal Pb exposure) in our study were similar to those found in mid-1990s Montreal, Canada (Smargiassi et al., 2002) and late-1990s agricultural Greece (Dussias et al., 1997). While our results indicate that banning leaded gasoline has largely reduced BPb levels in Taiwan, children's Pb exposure remains from other sources such as paint and toys.

We found a delayed effect of low-level children's lead exposure on cognitive function using LMM. Previous studies have suggested that current Pb exposure is the best predictor of children's neurodevelopment (Jusko et al., 2008; Surkan et al., 2007). Different results may be due to variations in exposure dose of BPb, or the extent of timing of observation of biological effects. Several animal studies (Barkur et al., 2011; Dribben et al., 2011; Graham et al., 2011; Prins et al., 2010) have revealed the chronic effects of low-level lead exposure during and after pregnancy on brain and neuron development of offspring. Dribben et al. have reported that low-level Pb exposure in infant mice significantly increased apoptotic neurodegeneration in the brain, such as hippocampus and frontal cortical regions (Dribben et al., 2011). Recent studies reported that low-level Pb exposure during fetal and early development can cause significant effects on auditory neuron and memory impairment, even last into adulthood (Barkur et al., 2011; Prins et al., 2010). Besides, epidemiological studies also provide evidences to support the link between attentions or attention-deficit hyperactivity disorder (ADHD) related symptoms and Pb exposure in children (Winneke, in Press). Our data revealed that even children exposed to low-level BPb may have chronic or lagged effects on their neuron development. In addition, no significant gender difference was observed in the relationship of Pb exposure and cognitive function in children.

Some studies have reported that gender-difference may have some effects on early brain development (Graham et al., 2011; Weinstock, 2007). However, we evaluated the cognitive function from 2 to 9 years old children, which may not detect the crucial window of gender-difference on cognitive function, in current study. One study (Graham et al., 2011) reported that male rat was more sensitive to the low-level Pb prenatal exposure, which may result in dysregulation of steroid hormones, like cortisol, and neuronal damage. It may explain why the influence of Pb exposure on boy's cognitive function (β: −6.54) was higher than that in girls (β: −5.46) (Supplemental Table C). We further analyzed the effects of lowe-level BPb on PIQ and VIQ, respectively, during 2 to 9 years old using LMM (Supplemental Table D). We found that children's Ln BPb was significantly negative associated with PIQ (β: −5.95; SE: 2.75, p = 0.035) after adjustment, whereas marginal significant negative correlation was observed for VIQ (β: −5.07; SE: 2.7, p = 0.065). It is indicated that children's PIQ, which represented the development of visual–spatial skill, was more sensitive to low-level or chronic BPb exposure as compared to VIQ.

Some studies have found that high level exposure to mercury (Hg) may inversely affect children's cognitive function (Axelrad et al., 2007; Jedrychowski et al., 2007). Although some longitudinal studies, such as those conducted in the Faroe Islands and the Seychelles (Axelrad et al., 2007; Jedrychowski et al., 2007), found that prenatal mercury exposure had a dose–response relationship to children's IQ scores, the Seychelles study (Myers et al., 2009) recently showed an inconsistent pattern of associations from postnatal methyl Hg (MeHg) exposure. Fish consumption is considered a primary exposure source to Hg or MeHg in adults. Milk products are primary food sources of toddlers, whose diets gradually change to solid food, such as rice, meat, fish and vegetables as they become children. Our subjects came from a metropolitan area and are unlikely to have a similar exposure scenario to Hg in fish as those in coastal villages.

Some cross-sectional studies have shown that exposure to manganese (Mn) may affect intelligence in school-aged children (Kim et al., 2009; Wright et al., 2006). Mn is a neurotoxicant that has been associated with Parkinson's disease, especially in occupational worker and nearby residents. However, Mn is also an essential micronutrient for proper development at low dose, especially in early stage of infancy. The main source of early infant exposure to Mn is not through take-home occupational exposure but rather through use of soy-based formula in nursing infants who are not breast-feeding or less tolerate other milk-based formula preparations. According to the data from questionnaire, none of the children's parents worked in Mn-related factories and only nine women (7.6%) reported that they have no breastfeeding for their infant. Therefore, Mn may not be a confounder in cognitive function in our population.

This study provides solid scientific evidence of the effect of low-level Pb exposure on children's neurodevelopment. To avoid misclassification

of exposure, BPb was measured at three time points, from toddler to pre-adolescence, as well as during pregnancy and at birth. Multiple measurements of BPb provided a reliable representation of children's Pb exposure during 2–9 years old, an important period of neurodevelopment. At least two studies suggest that prenatal and postnatal Pb levels are independently associated with adverse cognitive function (Schnaas et al., 2006; Wasserman et al., 2000). We completely assessed the effects of low-level prenatal and postnatal Pb exposure to neurodevelopment function using a longitudinal birth cohort design. We also included several covariates in statistical analysis to reduce the potential residual confounding. Potential covariates selected from several longitudinal studies included child's gender, birth weight, HOME score, maternal education, maternal BPb and age, home pesticide use, pre-pregnancy smoking and alcohol use during pregnancy.

Our study has some limitations. First, our study is limited to describing the relationship between BPb levels and IQ at very low BPb concentrations. Second, the sample size is small when compared with several longitudinal studies (Schnaas et al., 2006; Wasserman et al., 2000). Although we took pains to follow subjects, many factors (e.g., divorce, migration, accident, personal reasons), lowered the participation rate to around 22 to 37%. Third, we did not evaluate the intelligence of the pregnant mothers, which may have biased our evaluation of prenatal Pb exposure. We used maternal education level to substitute for maternal intelligence in this study.

Although no threshold BPb levels have been established for lower cognitive function in children, the effect of low levels of prenatal and postnatal Pb exposure have not been well-characterized in preschool and school-age children. Gilbert and Weiss proposed a BPb action level of 2 μg/dl instead of the current 10 μg/dl set by the CDC in 1991 (Gilbert and Weiss, 2006). Our data support the adoption of 2 μg/dl as an actionable level for BPb and support the assertion that even these very low levels harm children's neurodevelopment.

5. Conclusions

Overall, we found that greater postnatal blood Pb levels are associated with lower IQ scores in children at 2–9 years. Postnatal low-level Pb exposure significantly delayed children's cognitive function. Although prenatal and postnatal Pb exposure in children was greatly reduced with the ban of leaded gasoline in Taiwan, these results indicate that avoiding even small amounts of lead exposure in children, from paint and toys, will reap public health benefits.

Competing financial interests

The authors have no such financial interests.

Acknowledgments

We are grateful for the financial support from National Health Research Institutes (grants no.: EO-90PP03, EO-092PP05, EO-095PP06, EO-098PP03 and NSC98-2314-B-400-001-MY3). We are greatly indebted to the clinics of the Department of Pediatrics and Department of Obstetrics and Gynecology, Chung-Shan Medical University Hospital, especially for Dr. Jia-Yuh Chen, Dr. Long-Yau Lin, Dr. Tsung-Ho Ying and Dr. Chin-Yi Lin. We appreciate the training of the Bayley Scales by professor Nai-Wen Guo, comments from Prof. Saou-Hsing Liou and our colleagues, especially for Dr. How-Ran Chao, Dr. Jein-Wen Chen, Ms. Hsiao-Yen Chen at the National Health Research Institutes, Miaoli, Taiwan, also for subject recruitment and sample collection.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.envint.2011.10.011.

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