Case–Control Study of Blood Lead Levels and Attention Deficit Hyperactivity Disorder in Chinese Children

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BACKGROUND: Attention deficit/hyperactivity disorder (ADHD) and lead exposure are high-prevalence conditions among children.

OBJECTIVE: Our goal was to investigate the association between ADHD and blood lead levels (BLLs) in Chinese children, adjusting for known ADHD risk factors and potential confounding variables.

METHODS: We conducted a pair-matching case–control study with 630 ADHD cases and 630 non-ADHD controls 4–12 years of age, matched on the same age, sex, and socioeconomic status. The case and control children were systematically evaluated via structured diagnostic interviews, including caregiver interviews, based on the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., revised criteria (DSM-IV-R). We evaluated the association between BLLs and ADHD using the Pearson chi-square test for categorical variables and the Student t-test for continuous data. We then performed conditional multivariable logistic regression analyses with backward stepwise selection to predict risk factors for ADHD.

RESULTS: There was a significant difference in BLLs between ADHD cases and controls. ADHD cases were more likely to have been exposed to lead during childhood than the non-ADHD control subjects, with adjustment for other known risk factors [children with BLLs ≥ 10 µg/dL vs. ≤ 5 µg/dL; OR = 6.0; 95% confidence interval (CI) = 4.10–8.77, p < 0.01; 5–10 µg/dL vs. ≤ 5 µg/dL; OR = 4.9; 95% CI = 3.47–6.98, p < 0.01]. These results were not modified by age and sex variables.

CONCLUSIONS: This was the largest case–control study to date to study the association between BLLs and ADHD in Chinese children. ADHD may be an additional deleterious outcome of lead exposure during childhood, even when BLLs are < 10 µg/dL.

KEY WORDS: attention deficit hyperactivity disorder, blood lead levels, case–control study. Environ Health Perspect 116:1401–1406 (2008). doi:10.1289/ehp.11400 available via http://dx.doi.org/

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Attention deficit hyperactivity disorder (ADHD) is one of the most common childhood psychiatric disorders, characterized by developmentally inappropriate levels of inattention, impulsivity, and hyperactivity [American Psychiatric Association (APA) 2000; Biederman and Faraone 2005; Rappley 2005; Remschmidt 2005]. Prevalence of ADHD in children has been reported to be 3–8% worldwide (Froehlich et al. 2007; Leung et al. 1996; Remschmidt 2005). Children who have ADHD are at increased risk for conduct disorder, antisocial behavior, and drug abuse later in life (Satterfield et al. 2007). Moreover, the costs associated with their medical care and education are substantial (Leibson et al. 2001).

Although the causes of ADHD remain unclear, both genetic and environmental factors are thought to influence the etiology of ADHD (Banerjee et al. 2007; Biederman and Faraone 2005; Castellanos and Tannock 2002; Durston 2003; Khan and Faraone 2006). Furthermore, many environmental risk factors and potential gene–environment interactions have also been shown to increase the risk for the disorder (Banerjee et al. 2007; Biederman and Faraone 2005; Millichap 2008; Thapar et al. 2007). Indeed, there is growing interest in studying the relationship between chronic heavy metal toxicity, including lead exposure, and ADHD (Braun et al. 2006; Konofal and Cortese 2007; Millichap 2008; Nigg et al. 2008).

Lead is one of the well-established environmental poisons, and its general toxic effects, particularly in children, continue to be a major public health issue worldwide [American Academy of Pediatrics (AAP) 2005; Lidsky and Schneider 2003; Needleman et al. 2004]. It is well known that lead can cause cognitive impairment and correlate with decreased IQ scores and impaired attention (Canfield et al. 2003; Koller et al. 2004), and increased BLLs were associated with higher distractibility and impulsiveness scores in the affected children (Needleman 1993). The World Health Organization (WHO) and the U.S. Centers for Disease Control and Prevention (CDC) recommended that child blood lead levels (BLLs) not exceed 10 µg/dL (CDC 1991; WHO 1995). As a result of rapid industrialization in China, it is estimated that tens of millions of children 1–18 years of age have BLLs ≥ 10 µg/dL (Huo et al. 2007; Ren et al. 2006; Wang and Zhang 2006). Furthermore, several recent studies have shown that cognitive deficits and behavioral problems in children still exist even with BLLs < 10 µg/dL (Binns et al. 2007; Braun et al. 2006; Canfield et al. 2003; Koller et al. 2004).

Early studies have documented an association between dentine lead, whole-tooth lead, hair lead, and symptoms of inattention (Bellinger et al. 1994a, 1994b; Ferguson et al. 1993; Needleman and Leviton 1979; Needleman et al. 1979; Turhill 1996), and subsequent studies showed that lead exposure can cause attention deficit disorder and impulsivity (Brockel and Cory-Slechta 1998; Burns et al. 1999; Eppright et al. 1997; Kahn et al. 1995; Minder et al. 1994; Silva et al. 1988; Thomson et al. 1989; Wasserman et al. 1998, 2001). However, these studies may not be conclusive. First, few studies have investigated the effect of lead exposure on ADHD formally diagnosed with the established criteria in International Classification of Diseases, 10th Revision (ICD-10) (WHO 2007) or in Diagnostic and Statistical Manual of Mental Disorders, 4th ed., revised (DSM-IV–R; APA 2000).
Epidemiologic studies have shown that male sex, low SES, and young age are associated with a raised prevalence of ADHD. Moreover, its prevalence falls with age (Biederman and Faraone 2004; Doyle 2004; Sechill and Schwab-Stone 2000). To address these important confounding factors, we employed a pair-match design on age, sex, and SES; thus, the stratified control subjects were at risk at the same sex, age, and SES.

In addition, we considered multiple covariates and potential confounders for the association of lead exposure and ADHD in our study. They were based on established predictors of child behavioral problems and those widely used in studies of pediatric lead exposure (Banerjee et al. 2007; Biederman and Faraone 2005; Linnet et al. 2003; Mick et al. 2002; Millichap 2008; Scahill and Schwab-Stone 2000). The following variables were used: family history of ADHD (ADHD in parents and siblings, diagnosed by psychiatrists, obtained from clinical reports), household composition (normal: child lives with biological parents; single: child lives with only one parent; or recombined: child lives in remarried family), maternal tobacco use during pregnancy (at least one cigarette per day during the daytime and during the same study period. By the pair-matched design, each ADHD case and control set had the same sex, the same age (difference between birthdays within 6 months), and almost the same level of socioeconomic status (SES). The controls were given the same full diagnostic assessment as the ADHD cases and screened only for the absence of ADHD without exclusion of any other diagnosis except for the same exclusion criteria applied to cases. SES is measured by poverty-to-income ratio (PIR), and PIR is the ratio of family income to the poverty threshold for the year of the interview. Low SES was defined as having PIR values < 1 in our analysis and high SES as having PIR > 3. The others were regarded as middle SES. The study was approved by our institutional review boards and complied with all applicable requirements of the United States. The parents of all the children in this study provided written informed consent at enrollment.

Blood sampling and analysis. Blood samples (2 mL/child) were collected in heparinized syringes. Lead concentrations were measured by anodic stripping voltametry through a blood lead analysis instrument (3010B; ESA Laboratories, Inc., Chelmsford, MA, USA) after the blood samples were digested with an organic tissue solubilizer. The limit of detection was 1.0 µg/dL. No detectable values were given values of 0.70 (1.0 divided by the square root of 2). Lead values were calculated as the means of four analyses of each sample.

**Covariates.** Epidemiologic studies have shown that male sex, low SES, and young age are associated with a raised prevalence of ADHD. Moreover, its prevalence falls with age (Biederman and Faraone 2004; Doyle 2004; Sechill and Schwab-Stone 2000). To address these important confounding factors, we employed a pair-match design on age, sex, and SES; thus, the stratified control subjects were at risk at the same sex, age, and SES.

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during the last trimester), maternal drinking
during pregnancy (at least two glasses per
week during the entire pregnancy), labor
complications, cesarean delivery, perinatal
distress [low birth weight and admission to a
neonatal intensive care unit (NICU) as mark-
ers], parents’ age at childbirth, and parents’
education. Because all the cases recruited were
of Chinese Han nationality, the variable of
ethnic origin could not be used in our analy-
sis. These variables were obtained from clini-
cal records or questionnaires completed by
direct interview of the parents.

Study factors were defined as binary vari-
able or categorical variables. For example,
maternal smoking and drinking habits during
pregnancy were recorded as binary vari-
able—that is, drinker or nondrinker, ciga-
rette smoker or nonsmoker. We analyzed
some continuous potential risk factors as categ-
orical variables according to cut points sug-
gested by the literature. For example, low
birth weight is typically defined as < 2,500 g
(St Sauver et al. 2004). Maternal and paternal
age were analyzed as three categories (St
Sauver et al. 2004): < 20 years, 20–30 years,
and > 30 years of age. Maternal and paternal
education were analyzed as ≤ 9 years of com-
pulsory education, high school education
(9–12 years), or some college or advanced
training (> 12 years).

**Data analysis.** The association between
BLLs and ADHD was evaluated using the
Pearson chi-square test for categorical vari-
able and the Student t-test for continuous
data. We also performed a conditional logistic
regression analysis with a binary outcome of
ADHD in relation to BLLs, adjusting for
other potential confounding factors (Hosmer
and Lemeshow 2000). In the regression model,
BLLs were analyzed as an ordered categorical
variable and recorded as three categories:
≤ 5 µg/dL, 5–10 µg/dL, and ≥ 10 µg/dL. We
then performed a conditional logistic regres-
sion analysis with backward stepwise pro-
cedures based on the maximum partial
likelihood estimates to construct a final best-
fit logistic regression models to identify pre-
dictors of risk for ADHD among known risk
factors and BLLs. We estimated odds ratios
(ORs) and 95% confidence intervals (CIs) for
differing levels of exposure. All statistical
tests were considered to be significant at an alpha
level of 0.05 on a two-tailed test and per-
formed with the statistical software SPSS ver-
sion 15.0 (SPSS Inc., Chicago, IL, USA).

**Results**

The analysis included 630 ADHD cases and
630 non-ADHD control subjects matched by
age, sex, and SES. There were 434 sets of
boys and 196 sets of girls. The average ages
were 7.9 ± 2.1 years. The mean BLLs were
5.76 ± 3.39 µg/dL in the control group. The
ADHD group had higher BLLs (p < 0.05, see
Table 1). There was no significant difference
in BLLs between males and females.

Figure 1 shows BLL distribution and
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cumulative distribution of ADHD children and
controls. Only 10.1% of non-ADHD children
had BLLs > 10 µg/dL, whereas this percentage
increased significantly to 24.4% in ADHD
children. (χ² = 237, p < 0.01). In addition,
49.8% of non-ADHD children had BLLs
> 5 µg/dL, whereas of the ADHD cases, 74.7%
had BLLs > 5 µg/dL (χ² = 116, p < 0.01).

Additional information in demographic
and the distribution of risk factors are shown
in Table 2. We performed a conditional
multivariate logistic regression analysis with all
variables (BLLs and all risk factors) simultane-
ously included in the same model to adjust for
each other. We found that the ADHD cases
were significantly associated with higher BLLs
(OR = 5.19, p < 0.01 for children with BLLs
5–10 µg/dL; OR = 7.15, p < 0.01 for with
BLLs ≥ 10 µg/dL, using the sample with BLLs
≤ 5 µg/dL as referent) and family history
of ADHD (OR = 4.54, p < 0.01, compared
with the sample without familial ADHD his-
tory). The risk for ADHD decreased as the
mother’s education level increased (OR = 0.69,
p = 0.017, using the sample of ≥ 9 years
maternal education as referent). The analysis
also found an association between ADHD and
maternal smoking during pregnancy, but the p-value is near the significant threshold

**Table 2. Demographic and distribution of risk factors of ADHD cases and controls.**

| Characteristic                          | ADHD (n = 630) | Controls (n = 630) | OR*  | p-Values* |
|----------------------------------------|---------------|-------------------|------|-----------|
| Matched factors                        |               |                   |      |           |
| Age (years)                            |               |                   |      |           |
| 4–6                                    | 172           | 172               | —    | —         |
| 7–9                                    | 303           | 303               | —    | —         |
| 10–12                                  | 195           | 155               | —    | —         |
| Sex                                    |               |                   |      |           |
| Male                                   | 434           | 434               | —    | —         |
| Female                                 | 196           | 196               | —    | —         |
| SES (PIR)                              |               |                   |      |           |
| ≤ 1                                     | 58            | 58                | —    | —         |
| > 1                                     | 436           | 436               | —    | —         |
| > 3                                     | 136           | 136               | —    | —         |
| Child factors                          |               |                   |      |           |
| Blood lead (µg/dL)                     |               |                   |      |           |
| ≤ 5                                     | 101           | 316               | 5.19 | < 0.01    |
| > 5                                     | 326           | 255               | 7.15 | < 0.01    |
| ≥ 10                                    | 203           | 59                | —    | —         |
| Household composition                  |               |                   |      |           |
| Two parent                             | Referent      | Referent          |      |           |
| Single parent                          | 27            | 23                | 1.05 | 0.89      |
| Recombined                             | 15            | 17                | 0.50 | 0.11      |
| Low birth weight (< 2,500 g)           | 55            | 64                | 0.68 | 0.13      |
| Twin                                   | 4             | 10                | 0.29 | 0.08      |
| Family history of ADHD                 | 21            | 4                 | 4.54 | 0.02      |
| Pregnancy, labor, or delivery character|               |                   |      |           |
| Labor or delivery complications        | 58            | 70                | 0.71 | 0.16      |
| Surgical procedure required            | 59            | 67                | 0.63 | 0.06      |
| Premature labor                        | 27            | 22                | 0.84 | 0.65      |
| NICU required                          | 39            | 45                | 0.57 | 0.08      |
| Parental factors                       |               |                   |      |           |
| Age of mother (years)                  |               |                   |      |           |
| ≤ 20                                   | 81            | 65                | 0.92 | 0.75      |
| 20–30                                  | 461           | 459               | —    | —         |
| ≥ 30                                   | 88            | 106               | 1.15 | 0.41      |
| Age of father (years)                  |               |                   |      |           |
| ≤ 20                                   | 20            | 16                | —    | —         |
| 20–30                                  | 479           | 493               | —    | —         |
| ≥ 30                                   | 131           | 121               | —    | —         |
| Maternal education (years)             |               |                   |      |           |
| ≤ 9                                     | 154           | 127               | 0.69 | 0.017     |
| > 9–12                                  | 393           | 371               | —    | —         |
| ≥ 12                                    | 83            | 132               | —    | —         |
| Maternal education (years)             |               |                   |      |           |
| ≤ 9                                     | 123           | 103               | 1.07 | 0.97      |
| > 9–12                                  | 373           | 376               | —    | —         |
| ≥ 12                                    | 134           | 151               | —    | —         |
| Maternal drinking during pregnancy     | 11            | 6                 | 1.20 | 0.77      |
| Maternal smoking during pregnancy      | 6             | 9                 | 4.04 | 0.047     |

*Obtained from the multivariate logistic regression model that simultaneously included all the risk factors and the BLLs.
We also performed a conditional multivariate stepwise logistic regression analysis stratified by sex and age. As with the total sample, ADHD cases were significantly associated with higher BLLs than the lower BLLs in all subdefinitions (Table 4), which indicates that increased risk for ADHD associated with BLLs is not modified by age and sex.

### Table 3. Risk factors identified in stepwise logistic regression model.a

| Variables                  | β²   | SE  | Wald test | p-Value | OR (95% CI) |
|----------------------------|------|-----|-----------|---------|-------------|
| BLL                        |      |     |           |         |             |
| ≤ 5                        |      |     |           |         |             |
| 5–10                       | 1.59 | 0.18 | 79.86     | < 0.01  | 4.92 (3.47–6.98) |
| ≥ 10                       | 1.79 | 0.19 | 89.79     | < 0.01  | 6.00 (4.11–8.77) |
| Family history of ADHD     | 1.73 | 0.63 | 7.51      | < 0.01  | 5.65 (1.64–19.46) |
| Maternal education (years) |      |     |           |         |             |
| ≤ 9                        |      |     |           |         |             |
| 9–12                       | -0.13| 0.17 | 0.60      | 0.438   | 0.62 (0.43–0.88) |
| ≥ 12                       | -0.49| 0.19 | 6.90      | < 0.01  | 0.62 (0.43–0.88) |

*Variable(s) entered on step 1: BLLs, household composition, birth weight, twin, family history of ADHD, labor complications, cesarean, premature labor, NICU, mother’s age, father’s age, maternal education, paternal education, prenatal tobacco exposure and prenatal alcohol exposure. aβ² values are the estimated unstandardized regression coefficients.

This table is obtained from the multivariate logistic regression model that simultaneously included all the risk factors and the BLL. OR indicates likelihood of an ADHD.

### Table 4. Increased risks for ADHD associated with BLLs in different sample definitions.

| BLL (μg/dL) | OR (95% CI) | p-Value |
|------------|-------------|---------|
| Total sample (n = 1,280) |          |         |
| ≤ 5        | 1           |         |
| 5–10       | 4.92 (3.47–6.98) | < 0.01 |
| ≥ 10       | 6.00 (4.11–8.77) | < 0.01 |
| Male sample (n = 866) |          |         |
| ≤ 5        | 1           |         |
| 5–10       | 4.49 (2.97–6.80) | < 0.01 |
| ≥ 10       | 6.69 (4.20–10.67) | < 0.01 |
| Female sample (n = 392) |          |         |
| ≤ 5        | 1           |         |
| 5–10       | 5.62 (2.79–11.0) | < 0.01 |
| ≥ 10       | 7.36 (3.66–14.88) | < 0.01 |
| Age 4–6 years sample (n = 344) |          |         |
| ≤ 5        | 1           |         |
| 5–10       | 6.86 (3.17–14.86) | < 0.01 |
| ≥ 10       | 13.41 (5.04–35.69) | < 0.01 |
| Age 7–9 years sample (n = 606) |          |         |
| ≤ 5        | 1           |         |
| 5–10       | 5.78 (3.33–10.00) | < 0.01 |
| ≥ 10       | 8.53 (4.72–15.42) | < 0.01 |
| Age 10–12 years sample (n = 310) |          |         |
| ≤ 5        | 1           |         |
| 5–10       | 3.89 (1.82–8.32) | < 0.01 |
| ≥ 10       | 4.13 (2.01–8.49) | < 0.01 |

This table is obtained from the multivariate logistic regression model that simultaneously included all the risk factors and the BLL. OR indicates likelihood of ADHD.
on ADHD incidence via genotype by environmental interaction (Swanson et al. 2007).

**Strengths of the study.** The strengths of this study are as follows: a) Our sample size was the largest to date in case–control studies to investigate BLLs and ADHD. b) The ADHD diagnosis was made through an extensive clinical evaluation based on the DSM-IV-R diagnostic instrument and performed by child and adolescent psychiatrists. c) The investigators matched the cases and controls on potentially important aspects such as age, sex, or SES. This is important because lead levels are highest among younger children compared with adolescents, and ADHD is of higher prevalence among children of elementary and middle-school age.

**Clinical implications.** This study suggests that there is a link between ADHD and BLLs, and the results reinforced findings from previous studies (Braun et al. 2006; Nigg et al. 2008). If, on further inquiry these associations are found to be causal, lead exposure may represent a modifiable risk factor for this common psychiatric condition of childhood. Considering that ADHD typically starts in early childhood and that lead poisoning is one of the most common and entirely preventable pediatric problems (AAP 2005; CDC 1991), strategies in public health must focus on practicing primary and secondary prevention of lead exposure in children. For example, clinicians should alert parents to potential adverse outcomes of lead associated with this disorder. In addition, routine screening for lead exposure may be necessary if lead symptoms emerge, so that these can be managed at an early stage.

Moreover, BLLs < 10 µg/dL also indicated a risk factor. This may suggest that the lower standard may effectively protect children from the harmful effects of lead, which is consistent with previous investigations (AAP 2005; Canfield et al. 2003; Surkan et al. 2007).

Some studies (Ruff et al. 1993; Tong et al. 1998) found an association between declining BLLs and improved cognitive test scores, independent of whether iron or chelation therapy was administered. However, other works (AAP 2005; Canfield et al. 2003) indicated that the damage caused by blood lead exposure is irreversible. Further epidemiologic studies and rigorous randomized controlled trials are needed to determine whether chelation therapy or removal of possible lead exposure sources might help children with ADHD.

**Limitations.** This study has several limitations. First, temporality between high BLLs and ADHD could not be ascertained definitely in this case–control design. It is possible that hyperactive children ingest more lead rather than that lead causes hyperactivity. Therefore, further studies with serial lead measurements, even from the antenatal to the postnatal period, and more continuous measures of ADHD symptoms or of specific underlying neurobehavioral domains may be required to document the temporal relationship between lead exposure and development of ADHD. Second, some might argue that concurrent blood lead tests are not an adequate biomarker of a child’s lifetime exposure. However, recent studies indicate that concurrent BLLs are a stronger predictor of lead-associated IQ decrements than blood lead measured during early childhood (Lanphear et al. 2005). Third, recall bias is one of the problems of the case–control study. In this study, the main variable of interest was the BLLs, which were objectively measured. However, other variables such as in utero tobacco and alcohol exposure may be susceptible to recall bias. Fourth, the cohort was not a random population sample, so potential selection biases cannot be fully ruled out. In addition, because all our sample was Chinese Han, no children living in foster families were included, and none of the sample had health insurance, our results may not generalize to children with different socioeconomic or ethnic backgrounds. Finally, it is interesting that Nigg et al. (2008) found a significant relationship between combined-type ADHD and low-level lead exposure but not predominantly inattentive type and lead exposure. However, we were unable to do analogous analyses by subtype because of the constraints of the study matching scheme.

**Conclusions**

This hospital-based case–control study suggests a strong relationship exists between ADHD and lead exposure, even low-level lead exposure (< 10 µg/dL, BLL), in Chinese children. If this finding is confirmed in future studies, the potential to prevent ADHD by reducing childhood lead exposure should be considered.

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