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Confirmation and Extension of Association of Blood Lead with Attention-Deficit/Hyperactivity Disorder (ADHD) and ADHD Symptom Domains at Population-Typical Exposure Levels

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Abstract

BACKGROUND—Recent studies have suggested that child ADHD and its symptom domains are related to blood lead level, even at background exposure levels typical in western countries. However, recent studies disagreed as to whether lead was related to inattention or hyperactivity-impulsivity within the ADHD domain. More definitive evaluation of these questions was sought.

METHODS—236 children aged 6–17 years participated (61 ADHD-Combined type, 47 ADHD Predominantly Inattentive type, 99 non-ADHD control, 29 unclassified borderline, situational, or NOS cases). Formal diagnosis was reliably established by a best estimate procedure based on a semi-structured clinical interview and parent and teacher ratings. Lead was assayed from whole blood using inductively coupled plasma mass spectrometry with a method detection limit of 0.3 μg/dL.

RESULTS—Blood lead levels were slightly below United States and Western Europe population exposure averages, with a mean of 0.73 and a maximum of 2.2 μg/dL. This is the lowest level of blood lead ever studied in relation to ADHD. After statistical control for covariates including IQ and prenatal smoking exposure, blood lead was associated with ADHD-combined type but not inattentive type. Parent and teacher report indicated association of blood lead with Conners cognitive problems, but only teacher report showed effects on DSM-IV inattention symptoms. Blood lead was associated with hyperactivity-impulsivity in parent report regardless of measurement method, whereas teacher report effects depended on child treatment history.

CONCLUSIONS—These findings confirm that in children with typical U.S. population lead exposure, careful identification of children with ADHD also identifies children with slightly elevated blood lead.

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Keywords

ADHD; hyperactivity; inattention; blood lead

Attention deficit hyperactivity disorder (ADHD) occurs in 3 to 7% of children, with etiology believed to be multifactorial. The DSM-IV (APA, 2000) specifies three clinical subtypes: predominantly hyperactive (ADHD-PH), predominantly inattentive (ADHD-PI), and combined (ADHD-C). The subtypes are arrived at through combinations of two primary symptom dimensions: inattention-disorganization, and hyperactivity-impulsivity. These symptom domains may have partially distinct etiological inputs (Nigg, 2006). Because they appear to be an extreme of a behavioral continuum, the symptom dimensions also serve as useful foci to study etiology. Indeed, a factor analytic tradition has arrived at related but slightly different item sets than DSM-IV to capture population variation in “cognitive problems” and hyperactivity/impulsivity (e.g., Conners et al., 2007).

Lead exposure via water, soil, and other sources remains a worldwide health concern (Centers for Disease Control, 2005). Blood lead above 10 μg/dL has been associated reliably with ADHD and related behaviors, with the only real dispute being the magnitude of the effect (Burns et al., 1999; Silva, Hughes, Williams, & Faed, 1988; Thomson et al. 1989). Regulation of commercial uses of lead has markedly reduced the incidence of frank lead poisoning in recent decades in the U.S. (CDC, 2005), Western Europe (e.g., Delschen, Machtolf, Sugiri, & Wilhelm, 2008), and Scandinavia (Stromberg, Lundh, & Skerfving, 2008). Perhaps as a result, lead exposure has not been highlighted as an ongoing concern related to ADHD.

This reassuring picture, however, is eroding. Even at lower blood levels (< 10 μg/dL) lead has been linked to reduced intellectual functioning (IQ; Lanphear et al., 2005). Recent findings point to an association with ADHD as well, even at low exposures. Three years ago, Braun, et al. (2006), in a US population survey, found that blood lead was related to parent report that their child was diagnosed or treated for ADHD. This effect held even at blood levels below 5 μg/dL (i.e., children with blood lead > 2 μg/dL were more like to have ADHD than children with blood lead <0.7 μg/dL). One year later, Chiodo et al. (2007) reported that blood lead was related to teacher rated symptoms of inattention and activity, but not impulsivity, using the Conners rating scales and other standard scales in a high-risk sample. The next year Nigg et al (2008) conducted the first low-level lead study of children formally diagnosed with ADHD. Blood lead was related to ADHD and to parent reported DSM-IV symptoms of hyperactivity but not inattention. Those results supported an association to ADHD but appeared partially to contradict Chiodo et al (2007) as to the affected symptom domain.

The present study sought more definitive evaluation in a larger, well-diagnosed sample. The aim was to scrutinize relations with both DSM-IV and Conners ratings, by both parent and teacher report, so as to confirm and extend prior findings as well as to clarify the apparent contradiction in the last two studies reported. Dozens of potential confounds have been ruled out in relation to lead exposure and ADHD (Chiodo et al. 2007; Silva, et al., 1988; Thomson et al. 1989), but mostly at higher lead exposure levels. Thus, an expanded set of confounders and covariates was also considered here, as outlined in Methods.

Confirmation of the association of ADHD with lead exposure even at very low blood lead levels would be of major importance to public health, because exposure levels in the range of 1–5 μg/dL remain very common. Yet, most public authorities continue to use 10 μg/dL as the criterion of concern. If the association of low levels of lead exposure with ADHD is

verified, it opens the potential for new insights into the etiology of ADHD, because lead can serve as a model insult affecting frontal-striatal circuitry in ways that are relatively well understood. It also could open potential new opportunities for study of susceptibility-insult or gene by experience models. It could also provide clues to prevention via dietary supplementation (Kordas et al., 2007), via renewed caution before introducing new toxins into children's environments, or via aggressive efforts to continue to eliminate all lead exposure.

METHODS

Participants

Recruitment and Evaluation—Participant recruitment and characterization followed the same procedures as Nigg et al. (2008), but this was an entirely new sample. In all, 236 children aged 6–17 completed the study. Because some of these children also participated in our sib-pair study of genetics of ADHD, the sample included 78 sibling pairs (n=156 siblings). All children were recruited via mailings to parents in regional school districts, public advertisements, and outreach to local clinics. Parents provided written informed consent and children provided written informed assent. All procedures were approved by the University Institutional Review Board and complied with NIH and APA guidelines for protection of human participants.

Families entered a multi-stage screening process to establish diagnostic groupings. To confirm ADHD and comorbid diagnoses, a semi structured clinical interview (Kiddie Schedule for Affective Disorders and Schizophrenia (*K-SADS-E*) was completed with a parent by a trained clinician. Interviewers had a master's degree in clinical psychology or social work. Each interviewer double coded 20 tapes with a criterion interviewer to ensure process fidelity and inter-interviewer reliability (all disorders $k > .80$ in this report). In addition, parents and teachers completed the *ADHD Rating Scale* (DuPaul et al., 1998) and the Conners et al (1997) *ADHD Rating Scale, Revised* (hereafter, Conners).

Exclusion criteria—Rule outs were long-acting psychotropic medication (e.g. antidepressants), history of seizure, neurological impairments, a prior diagnosis of mental retardation or autistic disorder, head injury with loss of consciousness, sensorimotor handicap, or other major medical conditions in the child, as reported by the parent. At the diagnostic interview youth were ruled out if they had substance addiction, bipolar disorder, history of psychosis, sleep disorder, medical or neurological condition discovered at the clinical screen, or IQ <75. Control children were also excluded for ADHD, learning disability, or conduct disorder.

Establishment of Final ADHD and Other Diagnoses—Using all available data, a best estimate diagnosis was arrived at independently by two experienced clinicians (a board certified child psychiatrist and a fully licensed child clinical psychologist) blind to study hypotheses and blood lead levels. Their agreement rates for ADHD, conduct disorder, and oppositional defiant disorder were acceptable (all $k > .80$). Disagreements were resolved by discussion. Consistent with DSM-IV ADHD criteria, the clinicians required that another disorder did not better account for symptoms, evidence of impairment, and evidence of cross-situational symptoms. When ADHD symptoms were situational (only noticeable at home or school) or were subthreshold (5 symptoms), a diagnosis of ADHD-NOS was assigned. Those youth were included in this report for purposes of regression analysis of symptom scores but not for between-group analyses.

Measures

Blood Lead—Over 90% of children approached agreed to the blood draw for the lead assay. Children had 2 ml whole blood drawn through venipuncture in the arm. The blood was drawn into a 2 ml purple-top Vacutainer tube (tubes were lot checked for lead by lab prior to use). Blood samples were labeled with a study number, frozen and stored at −20C prior to analysis. Samples were assayed using the process of inductively coupled plasma mass spectrometry (ICPMS). This method had a detection limit for lead of 0.3 μg/dL; inter-run precision was 5.8% (coefficient of variation) at a lead value of 2.9 μg/dL. The process began with whole blood samples brought to room temperature and vortexed so no particulate matter remained at the bottom of the sample. Samples were diluted 1:50 with a diluent composed of 1.0% tetramethylammonium hydroxide, internal standard (iridium), 1.0% isopropyl alcohol, 0.01% ammonium pyrrolidene dithiocarbamate (APDC), and 0.05% wetting solution (Triton X). Samples were then mixed by inverting 3–4 times. The analysis then entailed quantitating the sum of masses 206, 207, and 208 based on three replicates per sample on a Perkin Elmer Elan DRC Plus ICP-MS. Three children were below the limit of detection. Following Braun et al (2006; p. 1905), those levels were scored as 0.2 ($0.3/\sqrt{2}$). Following Burns et al. (1999), the blood lead score was $\log_{10}$ transformed to reduce influence of outliers.

IQ and achievement—To estimate full scale IQ, children completed a 3-subtest short form of the Wechsler (2003) Intelligence Scales for Children-4th Edition comprised of Vocabulary, Block Design, and Information,[1] with reliability of .93 and validity in relation to the full WISC-IV of r=.88 (Sattler, 2001, p. 771). All completed the word reading and spelling subtests of the Wechsler (2005) Individual Achievement Test-2nd edition to estimate academic achievement and enable evaluation of learning disability by the team.

Behavior Disorders and Symptoms—Total KSAD symptom counts were used for parent DSM-IV ADHD symptom dimensions. To reduce collinearity, oppositional and conduct symptom scores (r=.63) were summed into an “externalizing” total score. For teachers, ADHD symptoms were assessed on the *ADHD Rating Scale* (symptoms scored as absent if rated 0, 1 and as present if rated 2, 3) and summed. The Conners ratings served as additional dimensional measures. Age and sex adjusted T scores were computed for oppositional, hyperactive-impulsive, and cognitive problems/inattention for teachers and mothers.

Other Covariates and Confounders—Total gross annual income in the child’s primary household was reported by parents. Maternal smoking during pregnancy has been of keen interest as a possible contributor to ADHD, yet also tends to be correlated with low income and thus with lead exposure (Braun et al., 2006). Maternal smoking during pregnancy was reported retrospectively by the mother and coded as “none” (0) or “any” (1). Although retrospective recall limits the ability to verify these reports, maternal recollection of smoking in pregnancy at child age of six years has agreed with post-partum report at 90% (Hensley-Alford, Lappin, Peterson, & Johnson, 2008). Due to recent interest in nutritional status, particularly the role of iron in the lead-ADHD relationship (Kordas et al., 2007), blood hemoglobin was assayed by standard methods to assess iron status. Normal hemoglobin values for children are 11–13 gm/dL, and in adolescents, 12–16 (women) or 14–18 (men). Values in the current sample ranged from 11.0–15.6. Child history of stimulant medication treatment was reported by mothers on the KSADS interview, and was coded as a 0 or 1 (no

[1]Children over the age of 16 completed the same 3 subtests on the WAIS-III; it has reliability=.95 and validity=.91; Sattler, 2001, p. 825.

history of stimulants, versus treatment history; 43 children had stimulant treatment). It was examined as a potential moderator of teacher reports.

Data Reduction and Analysis

Unless otherwise noted, analyses were conducted in MPLUS v5.1 (Muthen & Muthen, 1998–2008), with family as a clustering value and analysis set to "type=complex;" this procedure removes variance due to siblings being from the same family. Missing data were handled using full information maximum likelihood procedures in MPLUS. Missing data were minimal with the exception of income (7% missing). Three extreme outliers for the income variable were truncated. All effects were evaluated with the following covariates: household income, maternal smoking, and child age, sex, and blood hemoglobin level. Low IQ is a possible complication yet there is controversy as to whether it represents part of the ADHD syndrome. Results are therefore reported with and without covarying IQ. For regression models, standardized parameter estimates were computed. For continuous measures, these were standardized on X and Y variables. The resulting coefficient is interpreted as the amount of change in Y in standard deviation units for a one standard deviation change in X. For the categorical (0, 1) variables (sex and prenatal smoking), they were standardized on the Y variable--yielding amount of change in Y (in standard deviation units) for a change in the X variable from 0 to 1.

RESULTS

Descriptive Overview

The sample comprised four groups: non-ADHD, ADHD-PI, ADHD-C, and ADHD-NOS. "NOS" meant subthreshold, 5 symptoms, or situational. Note that ADHD primarily hyperactive type was rarely identified (n=2). Those two cases were assigned to the "NOS" group. Table 1 provides a descriptive and clinical overview of the sample groups. It supports the validity of the clinical groupings. Only the ADHD-PI and ADHD-C groups consistently exceeded clinical cutoffs on the Conners ADHD Index. The ADHD-NOS group was intermediate on several clinical measures between the control group and the ADHD groups. Groups differed in exactly the way suggested by the diagnostic assignments in teacher and parent ratings. Some suppression of symptoms in teacher ratings was expected, because some children were in treatment (Table 1).

The groups were similar on IQ, but they differed in age, gender ratio, and household income (leading to differences in rate of families estimated to reside in poverty). As shown in Table 1, the sample as a whole was relatively more well off economically than the U.S. national average. The ethnic breakdown of the sample was 75% Caucasian, 7% African American, 3% Latino, 1% Native American, and 14% mixed or other. Race was unrelated to blood lead and was not covaried or analyzed further.

Child blood lead ranged from less than 0.3 μg/dL (undetectable, n=3) to 2.20 μg/dL with a mean of 0.73 (SE=0.04). Table 2 shows that blood lead in the current sample was even lower than in Nigg et al (2008), and equal to or lower than recent averages in the U.S., Scandinavia, and Western Europe (Braun et al., 2006, used the NHANES sample shown in Table 2). Thus, the sample had typical background exposure. This blood lead level was the lowest ever evaluated in relation to ADHD to date.

As expected, and as in prior studies, blood lead was related to lower family income (B=−.15, p<.05), male sex (B= −43, p<.01), and younger age (B=−.23, p<.01). Before covariates, blood lead was correlated to KSAD inattention (B=.19, p<.01), hyperactivity/impulsivity, (B=.28, p<.01), the externalizing composite, (B=.21, p<.01) and to all Conners scales. Blood

lead in siblings was correlated at r=.47 (p<.001), supporting the supposition that it might be a shared environment effect and the importance of controlling sibling status.

Association of ADHD Diagnosis with Blood Lead Level

The three-group ANCOVA (omitting the "NOS" group; see Method) was conducted in SPSS v. 17. It yielded nearly a medium effect size for group assignment, F(2,200)=5.16, partial eta squared=.049, p=.007 (sibling status not controlled). Follow up simple comparisons were conducted using effect coding in MPLUS (controlling for sibling status; blood lead was the dependent variable and all covariates were included). The ADHD-C group had higher lead level than the control group (B=.141, p=.033; with IQ covaried, B=.057, p=.041). The ADHD-PI group did not differ from the control group (p=.27). Thus, group effects were confined to ADHD-C.

Regression Analysis of ADHD and Externalizing Symptom Dimensions

Parent Report—Regression models were conducted for symptom domains as dependent variables (n=236, see Method). Table 3 summarizes the results for parents for both DSM-IV symptoms (KSADS) and the Conners, with and without IQ as a covariate. As it shows, blood lead level was marginally associated with attention problems, but not after covarying IQ. Blood lead was reliably associated with hyperactivity/impulsivity regardless of covariates. On the Conners, both cognitive problems and hyperactivity/impulsivity were reliably related to blood lead.

The KSADS externalizing composite was also related to blood lead (B=.21, p<.01; with IQ covaried, B=.20, p<.05); the same held for oppositional behavior on the Conners (B=.22, p<.01, with IQ covaried, B=.21, p<.01). Specificity was examined for each model by making blood lead the outcome variable. To conserve power, IQ was omitted and other covariates removed in stepwise fashion (income, p>.50, and hemoglobin, p>.20, were thus removed in all models). In the DSM-IV model, hyperactive symptoms were specifically related to blood lead (B=.144, p=.043), whereas externalizing symptoms were shy of significant (B=.136, p=.121). The same held using the Conners: blood lead was related to hyperactivity (B=.18, p=.034) but not oppositional behaviors (B=.09, p=.34) or cognitive problems (p=ns).

Teacher Report—Table 4 shows the complete models for teacher reported DSM-IV symptoms and Conners ratings. On the ADHD Rating Scale, blood lead was unrelated to inattention or hyperactivity-impulsivity. On the *Conners Rating Scale*, results were similar to those reported for teachers by Chiodo et al (2007) and different from the ADHD Rating Scale results. As Table 4 shows, cognitive problems were related to blood lead level, whereas hyperactivity-impulsivity was related to blood lead prior to covarying IQ, but not after.

Conners oppositional behavior was also related, weakly, to blood lead (B=.13, p<.05), though not after IQ was covaried (B=.11, p=.07). The specificity model was computed just as with parent data. Cognitive problems were uniquely related to blood lead (B=.16, p=.031), whereas oppositional behavior (p=.76) and hyperactivity (p=.34) were not.

Interaction of Teacher Findings with Child Treatment Status—The interaction of child treatment history with blood lead was examined (all covariates included). For DSM-IV inattention, there was no interaction (p>.50), but for DSM-IV hyperactivity/impulsivity, there was (B=−.193, p=.009). For children never treated (including controls), there was a reliable relation of blood lead to hyperactivity (with all covariates; B=.151, p=.017). For the children who had been treated, the relation disappeared (B=−.177, p=.19). This result suggested that medication treatment masked the relation of lead to teacher-rated DSM-IV

hyperactive symptoms. For the Conners ratings, the interaction of treatment status with blood lead was shy of significance for hyperactivity (B=−.11, p=.064), but robust for cognitive problems (B=−.18, p=.002). Again, for children not in treatment, the effect of blood lead on cognitive problems was easily seen (with all covariates, B=.17, p=.004); but not in the treated children (B=−.13, p=.446). These interactions did not reproduce when checked in the smaller Nigg et al (2008) sample (all p> .20).

DISCUSSION

Whereas ADHD carries well-established genetic influences on susceptibility (Waldman & Gizer, 2006), environmental risk factors may interact with that susceptibility in complex ways (Purcell, 2002). Several studies have linked blood lead with ADHD, but usually in samples with lead levels much higher than current population averages in the U.S. or Western Europe. More recent studies have begun to show that even very low levels of lead exposure (< 5 μg/dL), blood lead is associated with ADHD. Nigg et al. (2008) was the first low-lead study to look at children formally diagnosed with ADHD by standardized methods and the first to use ICPMS technology to measure blood lead. That technology is important because it has detection limits 3–8 fold lower than other methods typically used clinically or in most prior studies of ADHD. ICPMS was used again in the current report in a new sample.

The present study provides a more definitive confirmation of Nigg et al (2008) in a larger sample, with additional covariates, with more examination of teacher ratings, and at the lowest levels of blood lead ever measured in relation to ADHD. It confirms that in a sample selected for ADHD, there are reliable relations of blood lead with lifetime symptoms of hyperactivity-impulsivity as assessed by structured clinical interview of the parent. Hyperactivity effects are either weak or are moderated by treatment history when based on teacher report. On the other hand, the association of blood lead with inattention (or cognitive problems) was observed in parent and teacher Conners ratings and in teacher but not parent DSM-IV ratings.

Thus, like Nigg et al (2008), we found that blood lead was reliably associated with hyperactivity but not inattention when using DSM-IV ratings. However, like Chiodo et al (2007), we also found that Conners ratings revealed a clearer association of blood lead with cognitive problems than with hyperactivity-impulsivity in teacher ratings. This apparent disagreement across methods and raters could be readily understood. The Conners scales have slightly different items than the DSM-IV and are selected to be sensitive to intervention effects (lead may be an intervention). The Conners scales also had somewhat better normal distribution properties (for inattention, Shapiro-Wilk > .90 for maternal and >. 80 for teacher ratings, versus weaker values for the respective DSM-IV scales). Furthermore, it is sensible to expect that teachers would have more opportunity to observe cognitive problems (relevant to classroom behavior), whereas parents and teachers might be equally good observers of hyperactive or impulsive behaviors.

With all that in mind, the pattern that emerges is still rather clear. Inattention/cognitive problems were related to blood lead when measured via the Conners but not when measured via DSM-IV symptoms. This finding, which explains the prior difference between Chiodo et al (2007) and Nigg et al (2008), is due to either the different item set or the better psychometric properties of the Conners T score. Further study to see which of those events is true will be of interest. In contrast, hyperactivity/impulsivity is related to blood lead when rated by parents, but based on these data we tentatively suggest that this effect may be suppressed in teacher ratings by child treatment history. Overall, the conclusion is that both ADHD symptom domains are related to blood lead, but that further consideration of the

measurement scale and treatment effects remains important in quantifying these associations.

Limitations of this study should be noted. Most important, it is unclear how well concurrent lead levels reflect risks that probably occurred earlier in development. Effects of lead on the brain may depend on age of exposure (Manton et al., 2000). The ages of exposure and the peak early exposure level of the children in this study are unknown. However, the exposure levels observed are consistent with U.S. national levels in children at this age. Those U.S. surveys indicate that even preschool children average less than 5 μg/dL of exposure (CDC, 2005). Second, it is possible that hyperactive children ingested more lead, rather than that lead influenced hyperactivity. However, the only study we are aware of to test that question (David et al., 1977) found that lead levels were not elevated in hyperactive children with a known organic etiology (e.g., head injury), but were elevated in other hyperactive children. Further, an extensive animal experimental literature suggests lead has causal effects on neurodevelopment that make it a plausible influence on ADHD (Cory-Slechta, 1995). Thus, the most parsimonious summary of the data is likely that lead influenced ADHD rather than the reverse.

Last, this was not a random population sample, so sampling biases cannot be ruled out (characteristics of refusers were unknown). The sample was economically somewhat more well off, less representative of minority groups, and less lead-exposed than the nation as a whole. This may have resulted in under-estimation of effect magnitudes in relation to lead exposure and ADHD, although effect sizes reported were similar to those reported by Chiodo et al (2007) in a lower income, African American sample. In short, this study confirms that ADHD, both as a diagnosis and as symptom dimension, is associated with blood lead level at low exposure levels, even below 2.5 μg/dL.

In conclusion, background-levels of lead exposure were associated with ADHD in a clinically characterized sample, at the lowest levels of blood lead ever studied in relation to ADHD, and in both parent and teacher reports. This evidence that ADHD and its symptom domains are associated with blood lead has rather significant implications, because exposures in the range studied here remain widespread by definition. Lead exposure is a plausible neurobiological candidate for involvement in ADHD because it disrupts midbrain dopamine and other neurotransmission circuitry (Cory-Slechta, 2005), systems that are also implicated in ADHD (Nigg, 2006). It contributes to what is now an emerging body of literature linking ADHD to lead exposure even at population typical exposures. Implications for prevention, practice, and policy warrant further discussion.

Key points

- Lead is a known neurotoxicant previously associated with ADHD at high exposure
- Recent studies suggested low, population typical exposures may also related to ADHD
- Current study obtained fresh confirmation in a sample with very low, population typical lead exposure
- Children with ADHD had higher lead level than children without ADHD
- Both parent and teacher reports confirm the association of blood lead with ADHD symptoms.
- Further review of actionable lead level exposure in children is indicated

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ABBREVIATIONS

dL	deciliter=.1 (or $1/10^{th}$) liter
µg	microgram=.001 milligrams
B	standardized regression coefficients
ICPMS	inductively coupled plasma mass spectrometry
NOS	not otherwise specified
CDC	Centers for Disease Control

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Table 1

Sample Summary Statistics (Mean and Standard Deviation)

	Control	"NOS"	ADHD-PI	ADHD-C	p
N	99	29	47	61	
% male	43%[a]	48%[a]	68%[b]	74%[b]	<.05
% White	73%[a]	33%[b]	81%[a]	81%[a]	<.05
Child age (years)	11.8(2.5)[a]	11.8(2.4)[ab]	12.4 (2.5)[s]	10.6(2.6)[b]	.05
Annual home income ($k)	87.1(41)[a]	67.4(27)[ab]	81.4(42)[ab]	63.9(42)[b]	.05
% under poverty line ($21,200)	4.0%[a]	3.1%[a]	4.2%[a]	21.1%[b]	<.01
Child Full Scale IQ	107.9(12)	104.9(13)	102.2(15)	103.4(15)	ns
KSADS Inattention Lifetime	0.6(1.1)[a]	4.5(2.7)[b]	7.6(1.1)[c]	7.8(1.5)[c]	<.01
KSADS Hyperactive Lifetime	0.4(0.8)[a]	2.8(2.9)[b]	2.1(2.1)[b]	6.9(1.7)[c]	<.01
KSADS Inattention Current	0.6(1.1)[a]	4.3(2.7)[b]	7.4(1.1)[c]	7.8(1.5)[c]	<.01
KSADS Hyperactive Current	0.4(0.8)a	2.7(2.8)[b]	1.7(1.8)[b]	6.6(1.8)[c]	<.01
Teacher ADHD RS Inatt Sx	0.33(1.1)a	1.4(2.6)[a]	3.1(3.3)[b]	4.3(3.4)[b]	<.01
Teacher ADHD RS Hyp Sx	0.2(0.8)a	1.1(2.4)[b]	0.7(1.9)[b]	3.2(3.4)[c]	<.01
% Conduct Disorder (Life)	0%a	9.4%[b]	7.4%[b]	13%[c]	<.01
% ODD (Lifetime)	2%	19%[b]	15%[b]	38%[c]	<.01
P-Conners Cognitive	46.5(6)[a]	61.9(11)[b]	71.6(9)[c]	71.4(11)[c]	<.01
P-Conners Hyperactivity	46.7 (4)[a]	59.1(14)[b]	58.2(12)b	72.7(12)[c]	<.01
P-Conners Oppositional	45.7(7)[a]	55.7(13)[b]	58.7 (14)[b]	64.3(15)[c]	<.01
P-Conners ADHD Index	46.4(6)[a]	61.5(10)[a]	70.2(10)[b]	72.7(10)[b]	<.01
T-Conners Cognitive	48.2(7)[a]	55.3(10)[b]	57.4(9)[b]	60.2(10)[b]	<.01
T-Conners Hyperactive	49.5(9)[a]	53.8(11)[ab]	54.2(11)[b]	61.7(13)[c]	<.01
T-Conners Oppositional	47.1(4)[a]	52.8(12)[b]	51.3(9)[b]	57.7(12)[c]	<.01
T-Conners ADHD Index	49.1(9)[a]	57.3(13)[b]	60.4(10)[b]	66.3(11)[c]	<.01
% treated stimulants (lifetime)	0%	7%	25%	48%	<.01
% pregnancy smoke	8.2%	13.8%	10.6%	13.1%	ns
Child unadjusted blood lead	0.2(.30)[a]	0.78(.24)[ab]	.72(.35)[ab]	.88(.44)[b]	<.01

Notes to Table 1: KSADS symptom scores and diagnoses are lifetime unless otherwise marked. For dimensional scores, post-hoc Tukey tests were conducted if variances were homogenous; or the Dunnet T3 post hoc if variances were not homogenous. Different superscripts indicate pair-wise differences on post-hoc tests at $p<.05$. For example, “a” under control Conners’ Cognitive indicates a significant difference from “b” for ADHD-PI for the same variable; because ADHD-C also has a “b” it differs from controls also, but not from ADHD-PI. “ab” indicates does not differ from the group with the “a” or “b” superscript. ADHD-PI =Inattentive type; ADHD-C=combined type. Poverty is defined as < 50% of the median household income of $50,233 in the U.S. in 2007 (16% of national population below that cutoff), in keeping with one type of convention for defining poverty. The comparisons in this table do not control for sibling non-independence.

Table 2

Median Blood Lead Level of Current Replication Sample, Nigg et al (2008), U.S. National Sample, and Selected European Data By Two Age Groups

Sample	Years Surveyed	%Male	Age in years	Mean/median blood lead µg/dL
Adolescents				
U.S.A. (CDC[1] NHANES)	1999, 2002	50%	12–19	0.94–1.10
Western Europe[2]	1996–2000	50%	0–18	3.5
Nigg et al 2007 (n=115)	2005–2006	64%	12–17	1.03 (SE=.05)
Current sample (n=96)	2006–2008	53%	12–17	0.68 (SE=.03)
Children				
U.S.A. (CDC NHANES)	1999, 2002	50%	6–11	1.25–1.51
Sweden[3]	2005, 2007	50%	7–11	1.31–1.32
Chiodo et al (2007)	1996–1997	51%	6–7	5.0
Nigg et al 2007 (n=35)	2005–2006	63%	8–11	1.04 (SE=.09)
Current sample (n=140)	2006–2008	63%	6–11	0.77(SE=.03)

[1] CDC=Centers for Disease Control; the U.S. national (from the CDC NHANES sample) reflect surveys at two points in time, one in 1999 and one in 2002. The lower value represents the 2002 value, and the higher value represents the 1999 value.

[2] Western Europe represents a meta-analytic average computed by Fewtrell et al (2004) from studies in Denmark, Sweden, Germany, France, Israel, and Greece in the late 1990's.

[3] Stromberg et al. 2007. The recent data represent two cities measured two years apart.

Table 3

Regression Analyses of Lead association with Parent–Reported ADHD Symptoms, Standardized Results Showing Parameter (standard error)

	KSADS Lifetime		Conners	
	Inattention	**Hyp-Imp**	**Cognitive**	**Hyp-Imp**
Without IQ covaried				
Age	.06(.07)	−.09(.07)	.13(.07)$^{+}$	.07(.08)
Sex	−.43(.15)**	−.30(.14)*	−.01(.15)	−.04(.14)
Income	−.14(.06)*	−.19(.07)**	−.09(.06)	−.18(.07)**
Hemoglobin	−.02(.07)	.02(.07)	−.11(.08)	−.07(.08)
Smoking	.29(.20)	.03(.23)	.27(.22)	−.19(.19)
Blood lead	.12(.07)$^{+}$	.19(.06)***	.21(.07)**	.26(.07)***
With IQ Covaried				
Age	.05(.07)	−.10(.07)	.12(.07)	.06(.08)
Sex	−.44(.14)**	−.30(.14)*	−.02(.15)	−.05(.14)
Income	−.10(.06)	−.17(.07)*	−.05(.06)	−.17(.08)*
Smoking	.24(.21)	.01(.23)	.22(.22)	−.20(.19)
Hemoglobin	.01(.06)	.04(.07)	−.09(.08)	−.06(.08)
IQ	−.12(.07)$^{+}$	−.09(.06)	−.12(.07)$^{+}$	−.05(.07)
Blood Lead	.11(.07)	.18(.06)***	.20(.07)**	.25(.07)***

Parameter estimates are standardized as explained in Method. Sex is coded 1=male, 2=female.

$^{+}$ p<.10;

* p<.05,

** p≤.01,

*** p≤.001.

Table 4

Regression Results for Association of Child Blood Lead with Teacher Behavior Ratings, Showing Standardized Parameter Estimates (standard error)

	ADHD Rating Scale		Conners	
	Inattention	**Hyp-Imp**	**Cognitive**	**Hyp-Imp**
Without IQ covaried				
Age	−.08(.07)	−.25(.07)***	.10(.08)	.08(.08)
Sex	−.60(.12)***	−.43(.10)***	−.02(.13)	.32(.13)*
Income	−.16(.07)*	−.07(.07)	−.33(.07)***	−.20(.07)**
Hemoglobin	−.05(.07)	−.05(.06)	.01(.08)	.02(.09)
Smoking	−.03(.24)	−.07(.20)	.12(.27)	−.42(.17)*
Blood lead	.09(.06)	.11(.06)+	.19(.07)**	.14(.06)*
With IQ Covaried				
Age	−.10(.07)	−.26(.06)***	.02(.02)	.06(.08)
Sex	−.62(.12)***	−.44(.10)	−.03(.06)	.30(.13)*
Income	−.12(.06)	−.04(.07)	−.23(.06)***	−.12(.07)+
Smoking	−.11(.24)	−.14(.21)	−.02(.26)	−.53(.15)**
Hemogl	−.02(.06)	−.03(.06)	.05(.07)	.05(.08)
IQ	−.19(.08)*	−.15(.07)*	−.35(.06)***	−.30(.07)***
Blood Lead	.06(.06)	.09(.06)	.15(.06)*	.11(.06)+

Parameter estimates are standardized as explained in Method. Sex is coded 1=male, 2=female.

+ p<.10;

* p<.05,

** p≤.01,

*** p≤.001.