

Original investigation

Secondhand Smoke Exposure and Low Blood Lead Levels in Association With Attention-Deficit Hyperactivity Disorder and Its Symptom Domain in Children: A Community-Based Case–Control Study

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Abstract

Aim: Secondhand smoke (SHS) is a major indoor pollutant. We examined the possible association between exposure to both SHS and low levels of lead and attention-deficit–hyperactivity disorder (ADHD) and its symptom domain in children.

Methods: This case–control study was based on the results of a community survey using the ADHD rating scale conducted in 49 elementary schools. Both cases and control subjects were confirmed by a child psychiatrist. Each case was matched with one control subject according to gender, school, and grade in school. Using a multivariate conditional logistic regression model, we analyzed 214 case–control pairs of children who ranged in age from 6 to 10 years. Urine and blood levels of cotinine and of lead were determined, and information pertaining to SHS exposure was obtained by means of a questionnaire.

Results: Exposure to low levels of lead (geometric mean = 1.65 µg/dL) was related to ADHD, particularly inattention (odds ratio [OR] = 1.67, 95% confidence interval [CI] = 1.07–2.59), whereas SHS exposure was associated mainly with hyperactivity/impulsivity (OR = 3.85, 95% CI = 1.55–9.56). In the pathway from blood lead to hyperactivity/impulsivity, children’s SHS exposure mediated and indirectly accounted for about 73% of this relationship. The combined exposure to lead and SHS synergistically increased the risk of ADHD, evident as both inattention and hyperactivity/impulsivity.

Conclusion: SHS, which is associated with hyperactivity/impulsivity in particular, combined with exposure to low blood levels of lead synergistically increased the risk of ADHD. Therefore, the exposure of children to both SHS and lead needs to be reduced.

Implications: Although exposure to low levels of lead has been shown to be associated with ADHD, there is little evidence of symptom domain specificity. In our study, low blood lead levels were related to inattention. In addition, prenatal or postnatal exposure to SHS increased the risk of ADHD, particularly hyperactivity/impulsivity. Combined exposure to lead and SHS synergistically increased the risk for both these ADHD symptom domains. To protect children from environmental risk factors related to ADHD, it is necessary to further reduce children's exposure to SHS and lead, even in those with low blood lead levels.

Introduction

Attention-deficit-hyperactivity disorder (ADHD), a common neuropsychiatric disorder characterized by behavioral problems, such as attention deficit, hyperactivity, and impulsivity, affects 2.0% to 7.6% of school-age children in Korea.^{1,2}

Lead is a heavy metal found naturally in the environment and is also widespread throughout the environment as a result of human activity. This well-known neurotoxicant is especially detrimental to neurodevelopment in childhood. Although many studies have shown the harmful effects of blood lead levels (BLLs) exceed 10 µg/dL, a growing body of evidence now shows that lower BLLs (eg, ≤5 µg/dL) also have adverse effects, suggesting that there is no threshold for developmental neurotoxicity.³⁻⁷

Recent studies have revealed an association between BLL and a diagnosis of ADHD.⁸ However, the results have been inconclusive regarding whether the impact of low levels of lead exposure is greater on hyperactivity/impulsivity than on inattention in children.⁸⁻¹⁰ Nevertheless, an association between postnatal lead exposure and impulsive operant response has been reported in animal studies,¹¹ as has a dominant association between blood lead and hyperactivity/impulsivity in children.¹²

On average, about 40% of children, 35% of women, and 33% of men continue to be regularly exposed to secondhand smoke (SHS), which is a common indoor pollutant worldwide.¹³ Studies have shown a relationship between prenatal maternal smoking or postnatal SHS exposure and neurodevelopmental and behavioral problems in children, including deficits in intellectual ability and academic achievement, decreased attention span, and hyperactivity^{14,15} and ADHD.¹⁶ Postnatal SHS exposure is associated with ADHD independently of prenatal maternal smoking,¹⁷⁻¹⁹ and ADHD symptoms have been reported in the children of women who smoked during pregnancy.²⁰

The reported association between prenatal maternal smoking and movement disorders in their offspring²¹ may suggest that SHS has a greater effect on hyperactivity/impulsivity than on inattention; however, studies to elucidate the dominant symptom domain linked to SHS exposure have rarely been performed.

Regarding the combined or modifying effect of lead and SHS exposures on ADHD, a few studies have been reported. Blood lead along with prenatal maternal smoking,²² and their synergistic effects,²³ or blood lead and SHS exposure in children⁴ has been linked to childhood ADHD. However, no study has examined the symptom domain-specific effects of exposure to both lead and SHS in combination. Knowing the symptom domain-specific associations with different toxic agents, either alone or combined, can help us understand the toxicological mechanisms and target public health interventions.

Therefore, the purpose of this community-based, case-control study was to detect any associated risk for ADHD and specificity of its symptom domains with respect to low BLLs and SHS exposure, in combination and with mutual adjustment of each factor.

Methods

Study Subjects

This study was conducted between 2008 and 2010 in Cheonan, a medium-sized city in South Korea. A community survey for ADHD screening using the parent-rated Korean version of ADHD rating scale (K-ARS)²⁴ and the questionnaire on SHS exposure was conducted in the elementary schools. Of a target population of 49 570 children in 65 elementary schools, 30 227 children in 49 schools, with their respective parents, completed the questionnaire.

Children were considered positive for ADHD symptoms if they had a total score of not less than 19 on the K-ARS or had received a diagnosis of ADHD, as reported by their parents. We restricted our case-control study subjects to children in third grade (ie, 6 months ahead of children in the third grade in US elementary schools) and younger. Eligible controls were matched with the cases among those with a K-ARS score of less than 19 according to gender, school, and grade in school. To improve the comparability of the control subjects, we also tried to recruit children who were similar to the cases in terms of their background (eg, belonging to the same community), as well as matching them by age (school grade), gender, and school. We contacted the parents by telephone to get permission for the eligible cases and controls to participate in our study. After excluding children whose parents could not be contacted or denied permission, 249 potential cases and 229 potential control subjects were invited to visit the study hospital where a child psychiatrist performed a psychiatric and comprehensive health examination. Those children found to have a conduct disorder, severe mood disorder, pervasive developmental disorder, neurological disorder (including epilepsy; $n=12$), or mental retardation ($n=1$) were excluded. Finally, after additional post hoc matching, a total of 428 children (214 cases and 214 controls), ranging from 6 to 10 years of age, were included in the study.

This study was approved by the institutional review board of Dankook University Hospital (IRB no. 0801-006), and written informed consent was obtained from the parents or guardians of the children and from the children themselves prior to enrollment.

Measurement of BLLs

To measure lead concentrations in blood, 3–5 mL of whole blood was drawn from each child by syringe and was collected in heparin-containing tubes. BLLs were determined by atomic absorption spectrophotometry (Spectral AA-800, Varian, Sydney, Australia) at a commercial laboratory. The coefficient of variation for the BLLs was 4.9%. The limit of detection for blood lead was 0.2 µg/dL. None of the blood samples below the limit of detection are shown.

Determination of SHS Exposure and Measurement of Urinary Cotinine

Information concerning SHS exposure was obtained from the children's parents or guardians by means of a self-administered

questionnaire that included a set of standardized questions commonly used in previous studies. However, because of the Health Promotion Act of 2003, smoking has been banned in public spaces in Korea, we did not include exposure to SHS in the mothers' workplaces or the children's schools. The questions were constructed in two series: one for maternal smoking and the other for smokers in the home. If the mother was a current or ex-smoker (≥ 400 cigarettes smoked to date), we asked whether the mother ever smoked during pregnancy or ever smoked at the time of the child's birth or up to age 1 year and found that none of the mothers had smoked during pregnancy. Another series of questions whether someone else smoked in the home, beginning with the question "Have your children ever been exposed to SHS at home?" (At least one person at home smoked ≥ 1 cigarette/d.) We then asked during which periods did that person smoke in the home (during pregnancy, from birth to age 1 year, and/or longer than 1 year). If someone smoked at home during the pregnancy, we classified the prenatal maternal SHS exposure as "yes"; if the mother or someone else smoked at home for any period of time since the child's birth, we classified the postnatal SHS exposure as "yes."

To measure urinary cotinine levels, we collected urine samples (maximum = 50 mL), under supervision, from each subject, by means of enzyme-linked immunosorbent assay kits (Calbiotech, Spring Valley, CA, USA). The limit of detection was 1.0 ng/dL, with limit of detection/2 substituted for lower levels. The coefficients of variation were 5.8% to 14.7% for interassay values and 4.2% to 8.4% for intra-assay values at environmental exposure levels.

ADHD and Symptom Domain Diagnosis

The children who screened positive according to the K-ARS were assessed by a child psychiatrist using the standard procedures for diagnosing ADHD, including the Attention-deficit Diagnosis System, the Korean version of a modified computerized continuous performance test,²⁵ and clinical evaluation based on *DSM-IV* criteria. The child psychiatrist identified the dominant ADHD symptom domain for each case based on all the results: the K-ARS score, Attention-deficit Diagnosis System score (≥ 60), and *DSM-IV* criteria.

Confounders and Covariates

Information about basic demographic variables and other potential risk factors for ADHD was obtained from the questionnaire, that is, mother's education level (<12 , 12, or >12 years of schooling), family history of ADHD (yes or no), parental marital status (couple, single, separated, divorced, or widowed), and teenage mother (maternal age at child's birth <20 or ≥ 20 years old). In the multivariate model, we did not include parental marital status as a confounder because of multicollinearity. To account for dilution-dependent sample variation in urine concentration of cotinine, the urine creatinine level was considered as a covariate in the multivariate model.

Statistical Analysis

Risk of ADHD was estimated using the conditional logistic regression model adjusted for potential confounders and covariates, and the odds ratios (ORs) and 95% confidence intervals (CIs) were recorded. Crude ORs and 95% CIs were estimated using unadjusted conditional logistic models, and adjusted ORs and 95% CIs in model 1 were estimated based on models adjusted for maternal education level and ADHD family history, while those in model 2 were estimated by additional adjustment for SHS exposure (Table 2) or blood lead (Table 3) in the corresponding model 1. Assessment

of the interaction effect between blood lead and SHS exposure on ADHD risk was performed using the likelihood ratio test in the corresponding conditional logistic regression models with and without an interaction term for multiplicative interaction. Statistical analyses were conducted using R version 3.0.1,²⁶ with a significance level of 0.05.

Results

Compared with the control subjects, the ADHD cases were more likely to have a single parent, to have a less well-educated mother, and to be exposed to prenatal and postnatal SHS. There was no significant difference between the cases and the control subjects with respect to family history of ADHD or maternal age at the time of the child's birth. Geometric means (geometric standard deviation) of blood lead and urinary cotinine levels, respectively, were 1.65 $\mu\text{g}/\text{dL}$ (1.45) and 1.79 ng/mL (3.81) in the cases and 1.49 $\mu\text{g}/\text{dL}$ (1.48) and 1.19 ng/mL (2.81) in the controls (Table 1). Levels of blood lead and urinary cotinine did not differ between the symptom domains of inattention and hyperactivity/impulsivity.

BLL was significantly associated with all types of ADHD (OR = 1.46; 95% CI = 1.02–2.10), whereas this significance disappeared, with a smaller risk, after adjustment for postnatal SHS exposure (OR = 1.28; 95% CI = 0.89–1.83). Nevertheless, the estimate of risk for inattention was not attenuated when the model was adjusted for postnatal SHS exposure (OR = 1.63; 95% CI = 1.03–2.58; Table 2).

SHS exposure during the prenatal and postnatal periods was significantly associated with ADHD, and a strong association was observed in the hyperactivity/impulsivity symptom domain with postnatal SHS exposure even after adjustment for BLL (OR = 3.85; 95% CI = 1.54–9.61). Urinary cotinine levels also showed a significant association with all types of ADHD and the inattention symptom domain (Table 3).

Figure 1 shows the association between the combined exposures to lead and SHS and ADHD and its symptom domains.

The combined exposure to prenatal and/or postnatal SHS and to lead also showed significantly increased joint effects in both the inattention and the hyperactivity/impulsivity domains, with a stronger effect on hyperactivity/impulsivity. SHS exposure during both the prenatal and the postnatal periods was more strongly associated with the hyperactivity/impulsivity symptom domain. In the group with high BLLs, the joint ORs were 3.16 for inattention and 17.06 for hyperactivity/impulsivity after SHS exposure during prenatal and postnatal periods (Figure 1 and Supplementary Table S1). A stronger association between SHS exposure and hyperactivity/impulsivity was mainly due to postnatal SHS exposure in children rather than to prenatal maternal SHS exposure (Supplementary Table S2).

Discussion and Conclusions

In this study, we found that lead exposure at very low concentrations is related to ADHD in children, particularly inattention symptoms, while SHS exposure is associated mainly with the hyperactivity/impulsivity symptom domain of ADHD. In addition, the results revealed a significant association between ADHD and both prenatal maternal SHS exposure and postnatal SHS exposure in childhood, even after mutual adjustment for prenatal and postnatal SHS exposure, with significant synergism of the combined exposures to SHS during these two periods, particularly in association with the

Table 1. Characteristics of Community-Based ADHD Cases and Matched Control Subjects, 2008–2010, Cheonan, Korea

Characteristics	Case (n = 214)	Control (n = 214)	p value
Inattention, N (%)	155 (72.43)		
Hyperactivity/impulsivity, N (%)	59 (27.57)		
Age (y), N (%)			.55
≤7	134 (62.62)	138 (64.49)	
>7	80 (37.38)	76 (35.51)	
Elementary school grade, N (%)			.73
1st	130 (60.75)	132 (61.68)	
2nd	58 (27.1)	52 (24.3)	
3rd	26 (12.15)	30 (14.02)	
Gender, N (%)			1.00
Male	153 (71.5)	153 (71.5)	
Female	61 (28.5)	61 (28.5)	
Maternal educational level (y) ^a , N (%)			.02
≤12	126 (58.88)	104 (48.6)	
>12	83 (38.79)	109 (50.93)	
Unknown	5 (2.34)	1 (0.47)	
ADHD family history, N (%)			.81
No	192 (89.72)	192 (89.72)	
Yes	9 (4.21)	7 (3.27)	
Unknown	13 (6.07)	15 (7.01)	
Parental marital status ^a , N (%)			.01
Couple	150 (70.09)	179 (83.64)	
Single, separated, divorced or widowed	54 (25.23)	29 (13.55)	
Unknown	10 (4.67)	6 (2.8)	
Maternal age at child birth (y), N (%)			.17
<20	3 (1.40)	1 (0.47)	
≥20	197 (92.06)	206 (96.26)	
Unknown	14 (6.54)	7 (3.27)	
Postnatal secondhand smoke exposure ^a , N (%)			.0002
No	109 (50.93)	147 (68.69)	
Yes	104 (48.6)	65 (30.37)	
Unknown	1 (0.47)	2 (0.93)	
Prenatal secondhand smoke exposure ^a , N (%)			.0008
No	65 (30.37)	95 (44.39)	
Yes	144 (67.29)	114 (53.27)	
Unknown	5 (2.34)	5 (2.34)	
Blood lead (ug/dL) ^a , gMean (gSD)	1.65 (1.45)	1.49 (1.48)	.003
Urinary cotinine (ng/mL) ^a , gMean (gSD)	1.79 (3.81)	1.19 (2.81)	<.0001
U. cotinine with creatinine adjusted (μg/g crea.) ^a	2.06 (3.54)	1.26 (2.75)	<.0001
ADHD rating scale, parent-rated ^a , Mean (SD)	24.48 (8.62)	7.15 (8.91)	<.0001
Inattention ^a	13.6 (4.97)	4.15 (4.93)	<.0001
Hyperactivity/impulsivity ^a	10.88 (4.78)	2.99 (4.29)	<.0001
Continuous performance test ^a , Mean (SD)			
Visual omission errors ^a	72.26 (33.89)	53.28 (19.11)	<.0001
Visual commission errors ^a	70.06 (26.03)	53.23 (18.84)	<.0001
Visual response time	52.30 (15.46)	50.53 (11.87)	.16
Visual response time standard error ^a	72.45 (26.05)	53.61 (17.14)	<.0001
Auditory omission errors ^a	58.6 (16.88)	46.65 (10.6)	<.0001
Auditory commission errors ^a	56.98 (18.58)	45.92 (13.96)	<.0001
Auditory response time	57.00 (18.51)	57.25 (14.61)	.88
Auditory response time standard error ^a	62.91 (14.94)	52.47 (12.57)	<.0001

ADHD: attention deficit hyperactivity disorder. gMean, gSD = geometric mean, geometric standard deviation. p-value calculated using χ^2 test or *t* test for a simple comparison between cases and controls.

^a*p* < .05 showed a statistical significance.

hyperactivity/impulsivity symptom domain. Moreover, the combined exposure to lead and SHS resulted in an additive increase in risk for ADHD in both the inattention and the hyperactivity symptom domains.

To the best of our knowledge, this is the first study to evaluate the symptom domain-specific association between ADHD in children

and the adjusted and/or combined effects of exposure to lead and SHS. One reason for the inconsistent association between lead exposure and specific symptom domains of ADHD in other studies might have been the possible misclassification of these symptom domains.⁸

In our study, we diagnosed and confirmed the cases and control subjects at two stages in the study process: screening in community

Table 2. Association Between Blood Lead ($\mu\text{g}/\text{dL}$) and ADHD With Symptom Domains in a Community-Based Matched Case–Control Subjects, 2008–2010, Cheonan, Korea

Symptom domain	No. of pairs	Crude		Adjusted			
		OR	(95% CI)	Model 1		Model 2	
				OR	(95% CI)	OR	(95% CI)
All ADHD	214	1.51 ^a	(1.10, 2.06)	1.46 ^a	(1.02, 2.10)	1.28	(0.89, 1.83)
Inattention	155	1.55 ^a	(1.06, 2.26)	1.67 ^a	(1.07, 2.59)	1.63 ^a	(1.03, 2.58)
Hyperactivity/impulsivity	59	1.43	(0.83, 2.48)	1.15	(0.63, 2.10)	1.04	(0.53, 2.07)

ADHD = attention-deficit-hyperactivity disorder; OR = odds ratio; CI = confidence interval; BLL = blood lead level; SHS = secondhand smoke. Case and control matched by gender, school, and grade. Crude: unadjusted OR and 95% CI was estimated for BLL ($\mu\text{g}/\text{dL}$) using conditional logistic regression model. Adjusted: model 1, adjusted for ADHD family history and maternal educational level in the corresponding crude model; model 2, additionally adjusted for postnatal SHS in the corresponding model 1.

^a $p < .05$ showed a statistical significance.

Table 3. Association Between SHS Exposure and ADHD With Symptom Domains in a Community-Based Matched Case–Control Subjects, 2008–2010, Cheonan, Korea

	No. of pairs	Crude		Adjusted			
		OR	(95% CI)	Model 1		Model 2	
				OR	(95% CI)	OR	(95% CI)
Urinary cotinine level ($\mu\text{g}/\text{mL}$)							
All ADHD	214	1.05 ^a	(1.01, 1.09)	1.09 ^a	(1.03, 1.15)	1.10 ^a	(1.03, 1.16)
Inattention	155	1.05 ^a	(1.01, 1.09)	1.11 ^a	(1.03, 1.19)	1.11 ^a	(1.02, 1.21)
Hyperactivity/impulsivity	59	1.07	(0.98, 1.16)	1.06	(0.97, 1.16)	1.06	(0.97, 1.17)
Prenatal maternal SHS exposure (yes vs. no)							
All ADHD	209	1.78 ^a	(1.18, 2.67)	1.69 ^a	(1.10, 2.61)	1.67 ^a	(1.08, 2.58)
Inattention	150	1.61 ^a	(1.00, 2.58)	1.60	(0.97, 2.65)	1.49	(0.89, 2.49)
Hyperactivity/impulsivity	59	2.38 ^a	(1.04, 5.43)	1.86	(0.78, 4.48)	1.91	(0.76, 4.78)
Postnatal SHS exposure (yes vs. no)							
All ADHD	213	2.15 ^a	(1.43, 3.23)	1.98 ^a	(1.25, 3.12)	1.83 ^a	(1.15, 2.91)
Inattention	155	1.67 ^a	(1.03, 2.67)	1.50	(0.87, 2.57)	1.27	(0.72, 2.24)
Hyperactivity/impulsivity	58	4.00 ^a	(1.75, 9.16)	3.85 ^a	(1.55, 9.56)	3.85 ^a	(1.54, 9.61)
Pre and postnatal SHS exposure (both yes vs. both no) ^b							
All ADHD	124	2.43 ^a	(1.30, 4.53)	2.41 ^a	(1.21, 4.79)	2.41 ^a	(1.20, 4.81)
Inattention	88	1.83	(0.91, 3.70)	2.00	(0.89, 4.47)	1.85	(0.80, 4.26)
Hyperactivity/impulsivity	36	6.00 ^a	(1.34, 26.81)	5.68 ^a	(1.14, 28.44)	5.55 ^a	(1.12, 27.58)

ADHD = attention deficit hyperactivity disorder; SHS = secondhand smoke; BLL = blood lead level; OR = odds ratio; CI = confidence interval. Case and control matched by gender, school, and grade. Crude: OR and 95% CI were estimated for BLL ($\mu\text{g}/\text{dL}$) using conditional logistic regression model, adjusted for urinary creatinine level (analysis for cotinine). Adjusted: model 1, adjusted for ADHD family history and maternal educational level in the corresponding crude model; model 2, additionally adjusted for in the blood lead concentration in the corresponding model 1.

^a $p < .05$ showed a statistical significance.

^bThe SHS exposure variable categorized as both no (referent), prenatal yes and postnatal no, prenatal no and postnatal yes, and both yes. In this table, only the OR and 95% CIs for both yes category was presented.

level and a comprehensive clinical interview and an examination by a child psychiatrist.

Lead is known to play an important role in the etiology of ADHD, even after exposure to lower lead levels ($<10 \mu\text{g}/\text{dL}$).^{7,8,22,27} Because lead crosses the blood–brain barrier, young children are more vulnerable to such exposure because their blood–brain barrier is still not mature, and the lead is absorbed at a higher rate. The presence of lead affects mostly the prefrontal cortex, hippocampus, basal ganglia, and cerebellum,²⁸ and it disrupts the dopaminergic, glutamatergic, and cholinergic neurotransmission circuitry.²⁹

In contrast to the results of previous studies showing that lead exposure had a similar effect size in the inattention and hyperactivity domains⁸ or that a very low level of lead exposure had a dominant

effect on hyperactivity/impulsivity,^{9,12} we found an association between blood lead and inattention rather than hyperactivity, in which the BLL was extremely low (ranging from 0.42 to 4.70 $\mu\text{g}/\text{dL}$ [geometric mean = 1.65]). Furthermore, postnatal SHS exposure, as a confounding factor, explained the association between blood lead and ADHD of 6% and 73% in inattention and hyperactivity/impulsivity symptom domains, respectively (as shown in the adjusted model 2 in Table 2). Children of lower socioeconomic status are more likely to be exposed to lead³⁰ as well as to SHS,³¹ meaning that lead and SHS may commonly coexist as pollutants. Therefore, confounding by SHS in association with lead and ADHD is highly likely and might even be exaggerated when the level of lead exposure is very low because the effect size caused by exposure to lead may be

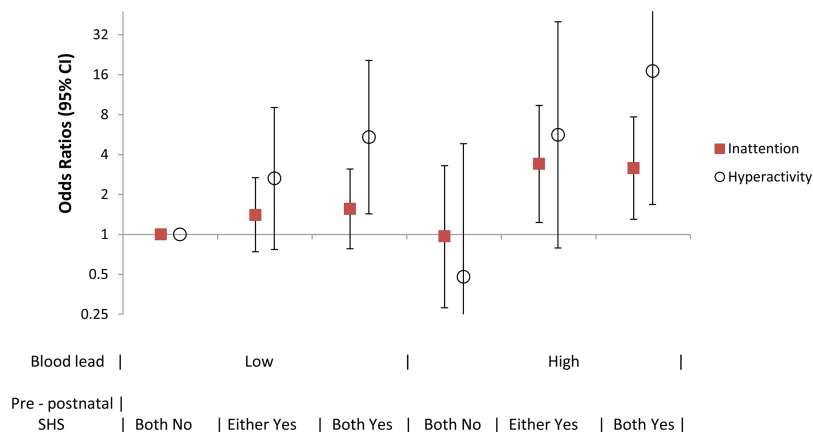


Figure 1. Combined exposure to blood lead and secondhand smoke (SHS) in association with attention-deficit–hyperactivity disorder (ADHD) in a community-based matched case–control subjects, 2008–2010, Cheonan, Korea. Cases and control subjects were matched according to gender, school, and grade in school. Odds ratios and 95% confidence intervals were estimated using the conditional logistic regression model adjusted for ADHD family history, urinary creatinine level, and maternal education level. Blood lead levels (BLLs; $\mu\text{g}/\text{dL}$): low = 0.38–1.90 (Q1 to Q3); high = 1.90–6.16 (Q4). *p* values for multiplicative interaction for all ADHD, for inattention, and for hyperactivity, respectively: .19, .48, and .41 between BLLs and prenatal and postnatal SHS exposure.

small while that of SHS may be relatively large because it is a major indoor pollutant, with exposure in 40% of children and 35% of women worldwide.¹³

Although urinary cotinine showed a significant association with ADHD, it did not show a distinctively different effect size between inattention and hyperactivity symptom domains (Table 3 and Supplementary Table S1). Urinary cotinine is a biomarker reflecting current exposure to SHS, but it is not a reliable indicator of past and long-term exposure to SHS because of its short half-life (15–19 hours), nor is it a comprehensive indicator for the numerous toxicants present in cigarette smoke.^{23,32} Information about SHS exposure obtained from the questionnaire, although this source may be less sensitive owing to its subjective nature, can sometimes be a better indicator than urinary cotinine in terms of past and long-term exposure to SHS, which contains several hundred chemical toxicants as well as nicotine. On the other hand, it is well-known that people with ADHD symptoms have much higher rates of tobacco smoking because of its nicotinic effect in improving cognition.³³ Compared with the information on SHS obtained from the questionnaire, urinary cotinine is more likely to be affected by the reverse causality because this biomarker can reflect current exposure. In the present study, the rate of the hyperactivity/impulsivity type of ADHD was higher than the rate for the inattention type with respect to postnatal SHS exposure (61.0% and 43.9%, respectively), whereas the levels of cotinine in the urine were the opposite: 1.50 ng/mL and 1.86 ng/mL for the hyperactivity/impulsivity type and inattention type, respectively.

Among the several neurotransmission circuitries that can be affected by lead, the cholinergic systems have been reported to be related to sustained attention and working memory.³³ The brain's nicotinic acetylcholine receptors are thought to play important roles in attention, memory, and cognition by modulating synaptic transmission and plasticity in the corticolimbic circuits.^{34,35} Nicotine, an acetylcholine agonist, is also reported to alleviate inattentiveness in patients with ADHD.³⁶ Moreover, nicotine exposure induces changes in the dopamine neurotransmission system that affect the function of the dopamine transporter and of dopamine receptors in particular,^{37,38} including stimulation of phasic dopamine release in the striatum,^{39,40} which has been linked to ADHD symptoms. Therefore, the

finding that SHS exposure is more strongly associated with hyperactivity than with inattention may be partially interpretable. However, we still have a long way to go to understand the effects of numerous toxicants other than the nicotine present in cigarette smoke, given that exposure of the developing brain to smoke leads to attention problems later on.⁴¹

Another interesting finding in the present study was the independent and combined effects of prenatal maternal and postnatal children's SHS exposure in association with ADHD. We found that prenatal maternal SHS exposure showed a significant association with ADHD independently from postnatal SHS exposure in children, which was consistent with a previous study.²⁰ Moreover, exposure to SHS during both the prenatal and the postnatal periods synergistically increased the risk of ADHD on an additive scale. Our results regarding the association between postnatal SHS exposure and ADHD are consistent with the findings from two recent studies.^{42,43} Postnatal SHS exposure seems to have a more direct effect on children than does maternal SHS exposure during pregnancy and shows a stronger effect size on ADHD. This makes sense because the toxic chemicals present in smoke need to cross the placental blood barrier as well as the blood–brain barrier of the fetus to reach the fetal brain during prenatal SHS exposure, whereas these chemicals can reach a child's brain by crossing only the latter barrier during postnatal SHS exposure.

This study has some limitations. First, the intelligence level of children, which is also affected by lead exposure, may be a confounding factor in assessing the association between lead exposure and attention/hyperactivity.¹² In the present study, we did not measure children's IQ and therefore could not adjust for it in the multivariate model. Instead, when we repeated the multivariate analyses by adding a variable for learning performance in school, as evaluated by the parents/guardians, the pattern of the association was not materially changed even by slightly higher effect estimates (Supplementary Table S3). Therefore, the effect size in the present study might be underestimated if IQ has a confounding effect.

Second, we did not adjust for some potential confounding factors, including those not recognized. In terms of parental marital status⁴⁴ and maternal age at the time of childbirth,⁴⁵ the effect sizes estimated by the multivariate model after these two variables were

added did not change, although the CIs became wider and sometimes lost statistical significance (data not shown).

Third, a case-control study is potentially subject to recall bias, especially with respect to the information related to outcomes. The information provided by the children's parents or guardians regarding prenatal and postnatal SHS exposure might be biased, particularly when the children have ADHD-like problems. However, in the present study, most of the cases were newly diagnosed during the study process (those already having been diagnosed with ADHD made up 3.8% [8 of 214]), and these parents/guardians did not recognize ADHD in their children at the time of enrollment. Therefore, we can assume that recall bias, if any, might have been minimal.

Fourth, our sample was recruited from a community in Korea, and the results may not be generalizable to the population of the nation as a whole, to different regions, or to other racial or ethnic groups.

In conclusion, low BLLs were associated with ADHD, with inattention symptoms being dominant, and prenatal maternal and/or postnatal SHS exposure in children was associated with ADHD, particularly hyperactivity/impulsivity symptoms. The combined exposure to lead and SHS increased the risk of ADHD synergistically in both symptom domains. In order to protect children from exposure to environmental risk factors for ADHD, further reductions in exposure to lead, even in children whose BLLs are extremely low, as well as cessation of smoking in the home and in children's play areas, are necessary to decrease SHS exposure in pregnant women and children.

Supplementary Material

Supplementary Tables 1 to 3 can be found online at <http://www.nt.oxfordjournals.org>

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Declaration of Interests

None declared.

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