



## Full length article

## Low-level lead exposure and autistic behaviors in school-age children

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## ABSTRACT

**Introduction:** The association between lead exposure and autism spectrum disorder is inconclusive. We hypothesized an association between higher blood lead concentrations and more autistic behaviors, including impaired social interactions and communication, stereotypical behaviors, and restricted interests, among school-age children.

**Methods:** Data from 2473 Korean children aged 7–8 years who had no prior history of developmental disorders were analyzed. Two follow-up surveys were conducted biennially until the children reached 11–12 years of age. Blood lead concentrations were measured at every survey, and autistic behaviors were evaluated at 11–12 years of age using the Autism Spectrum Screening Questionnaire (ASSQ) and Social Responsiveness Scale (SRS). The associations of blood lead concentration with ASSQ and SRS scores were analyzed using negative binomial, logistic, and linear regression models.

**Results:** Blood lead concentrations at 7–8 years of age (geometric mean: 1.64  $\mu\text{g}/\text{dL}$ ), but not at 9–10 and 11–12 years of age, were associated with more autistic behaviors at 11–12 years of age, according to the ASSQ ( $\beta = 0.151$ ; 95% confidence interval [CI]: 0.061, 0.242) and SRS ( $\beta = 2.489$ ; 95% CI: 1.378, 3.600). SRS subscale analysis also revealed associations between blood lead concentrations and social awareness, cognition, communication, motivation, and mannerisms.

**Conclusion:** Even low blood lead concentrations at 7–8 years of age are associated with more autistic behaviors at 11–12 years of age, underscoring the need for continued efforts to reduce lead exposure.

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## 1. Introduction

Autism spectrum disorder (ASD) encompasses heterogeneous neurodevelopmental disorders characterized by impaired social interaction and communication skills, the presence of markedly repetitive behaviors, and restricted interests. It incurs a substantial social burden worldwide and is estimated to be a leading cause of disability in children (Baxter et al., 2014). In the United States, 1 of every 68 children is affected by ASD at the age of 8 years (Centers for Disease Control and Prevention, 2014).

The cause of ASD remains unclear. Although differences in the expression patterns of several genes are associated with a higher risk of ASD (Ch'ng et al., 2015), one twin study indicated that the proportion of cases attributable solely to genetic factors is limited (Hallmayer et al., 2011). Besides genetic factors, paternal and

maternal age (Reichenberg et al., 2006; Idring et al., 2014), duration of pregnancy, birth weight, and intrapartum hypoxia (Eaton et al., 2001; Glasson et al., 2004; Larsson et al., 2005) can increase the risk of ASD. Moreover, environmental pollutants may lead to ASD development by causing brain tissue damage and affecting brain function via oxidative stress, inflammation, and mitochondrial dysfunction in the central nervous system (Chauhan and Chauhan, 2006; James et al., 2006; Li et al., 2009; Pardo et al., 2005; Rossignol and Frye, 2012).

Lead is an established neurotoxicant that causes oxidative stress, inflammation, and mitochondrial dysfunction (Sanders et al., 2009; Velaga et al., 2014; Zhang et al., 2013). It profoundly and adversely affects neuropsychological functions such as intelligence (Canfield et al., 2003; Khalil et al., 2009), memory (Stewart and Schwartz, 2007), processing speed (Winneke et al., 1996), language (Lanphear et al., 2000), visuospatial skills (Ris et al., 2004), and motor skills (Chiodo et al., 2004). Particularly in school-age children, blood lead concentrations are associated with decreased cognitive function (Kim et al., 2009a; Kordas et al., 2004) and inattention-hyperactivity symptoms (Kim et al., 2010; Wang et al., 2008).

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However, previous studies evaluating the association between lead exposure and ASD have reported inconclusive results, with evidence for positive (Adams et al., 2013; Blaurock-Busch et al., 2011; El-Ansary et al., 2011; Al-Farsi et al., 2013; Lakshmi Priya and Geetha, 2011), null (Abdullah et al., 2012; Albizzati et al., 2012; De Palma et al., 2012; Tian et al., 2011), and negative associations (Kern et al., 2007; Yorbik et al., 2010). These studies employed case-control designs with a maximum sample size of 105 children. Another study reported a positive association between hair lead concentrations and the severity of ASD symptoms among 44 children with ASD (Blaurock-Busch et al., 2012). Most of these studies (Abdullah et al., 2012; Albizzati et al., 2012; Blaurock-Busch et al., 2011; De Palma et al., 2012; Al-Farsi et al., 2013; Kern et al., 2007; Lakshmi Priya and Geetha, 2011; Yorbik et al., 2010) used biomarkers that are not well accepted or frequently used, such as hair and urine lead, and suggested a general deficit in the metabolism of heavy metals rather than a specific relation between lead and ASD.

Therefore, in the present study using a large-scale cohort of children, we evaluated the hypothesis that blood lead concentrations would be associated with more autistic behaviors among school-age children. To our knowledge, this study was conducted with the largest sample size to date.

## 2. Methods

### 2.1. Study participants and data collection

The Children's Health and Environment Research (CHEER) study was a cohort study conducted between 2005 and 2010 to investigate the relationships between environmental risk factors and neurodevelopmental and allergic disorders in school-age children. CHEER recruited children from 33 elementary schools in 10 Korean cities. The baseline, first, and second follow-up surveys were conducted in 2005–2006, 2007–2008, and 2009–2010, respectively. In 2005–2006, 5443 children 7–8 years of age were enrolled in the CHEER study. Among them, 3692 children then 9–10 years of age were followed up in 2007–2008, and 2631 children then 11–12 years of age in 2009–2010. In the 2007–2008 survey, 1548 children 7–8 years of age were newly

enrolled. Among them, 1055 children then 9–10 years of age were followed up in 2009–2010. Finally, in 2009–2010, 68 children 7–8 years of age were newly enrolled. Therefore, a total of 7059 children at 7–8 years of age were enrolled between 2005 and 2010. The parents of all participating children submitted written informed consent, and the Ethical Review Board of the Dankook University College of Medicine reviewed and approved the study protocol.

Among a total of 7059 children, 2609 were included in the ASD sub-study. These children were enrolled in 2005–2006 when they were 7–8 years of age, followed up in 2009–2010 when they were 11–12 years of age ( $n=2631$ ), and their parents agreed to answer the Autism Spectrum Screening Questionnaire (ASSQ) and Social Responsiveness Scale (SRS), because the ASSQ and SRS were used to assess children at 11–12 years of age. The data of participants for whom blood lead concentrations were not measured ( $n=131$ ), those with an ASD diagnosis reported by parents ( $n=4$ ), and those whose mothers were diagnosed with schizophrenia ( $n=1$ ) were excluded. The final analysis included data from 2473 children (Fig. 1).

Blood sampling and anthropometric measurements were performed at every survey. The questionnaire, which was completed by parents at every survey, contained questions about demographics, socioeconomic status, diet, and personal and familial medical histories. The ASSQ and SRS were administered only at the second follow-up survey when the children were 11–12 years of age.

### 2.2. Blood sample analysis

A whole blood sample (3–5 mL) was collected from each child, sealed in a heparin-containing tube, and sent to a laboratory (NeoDin Medical Institute, Seoul, Korea) for analysis. Blood lead concentrations were determined by atomic absorption spectrophotometry (Spectral AA-800 Zeeman correction; Varian, Belrose, NSW, Australia). The standardized quality control procedure was performed according to the manufacturer's instructions, and an internal control was used for every series of analyses. Accuracy was evaluated using a periodic external quality control program (inter-laboratory calibration program). The limit of detection for lead was

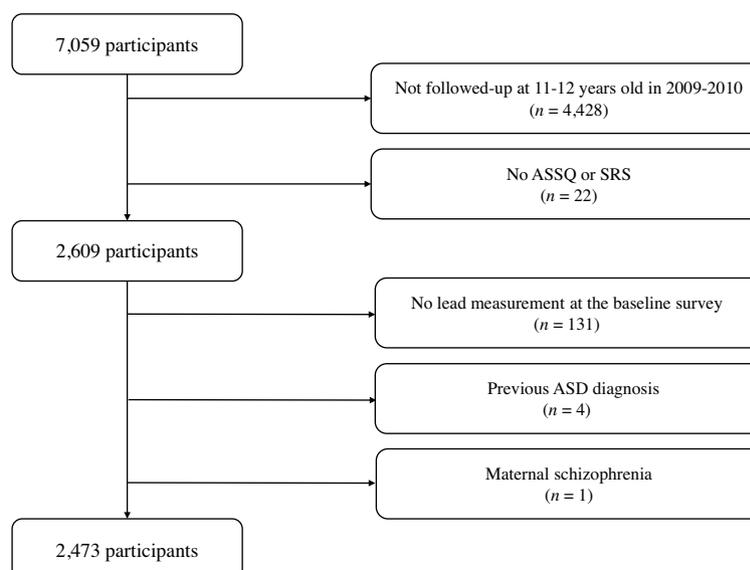


Fig. 1. Overview of study population sampling. ASSQ: Autism Spectrum Screening Questionnaire; SRS: Social Responsiveness Scale; ASD: Autism Spectrum Disorder.

0.03  $\mu\text{g}/\text{dL}$ , and lead concentrations below the limit of detection were imputed as the limit of detection divided by the square root of 2 (Hornung and Reed, 1990).

### 2.3. Autistic behaviors

The ASSQ, which consists of 27 items rated on a three-point scale, is a validated and reliable screening instrument for ASD within the general population (Ehlers et al., 1999; Posserud et al., 2009). The ASSQ score is calculated by summing the individual item scores. Higher scores indicate more autistic behaviors. In the current analyses, ASSQ scores were analyzed as continuous variables. For sensitivity analyses, the ASSQ scores were categorized as either  $<19$  or  $\geq 19$ , because a score  $\geq 19$  on the parent questionnaire has been reported to effectively screen for ASD (Ehlers et al., 1999).

Meanwhile, the SRS evaluates autistic behaviors as a continuum, rather than “all or none,” and gives an index of deficiency in reciprocal social interactions (Bölte et al., 2008; Constantino et al., 2003). It includes 65 Likert-scale items assessing subscales of social awareness, cognition, communication, motivation, and mannerisms. Each item’s score was summed to calculate the total scores, which were used as an outcome.

### 2.4. Covariates

Each child’s sex was reported in the baseline questionnaire. Fetal tobacco smoke exposure was considered present when the child’s mother reported having smoked during pregnancy or when there was another smoker in the home while she was pregnant. Environmental tobacco smoke exposure was considered present when the infant lived with a smoker in the home after delivery. Paternal and maternal education levels were categorized as less than a high school diploma, high school diploma, or higher. Family income was categorized as  $<\text{US}\$2000$  or  $\geq\text{US}\$2000$  per month. Low birth weight was defined as a birth weight  $<2.5$  kg. Breastfeeding was categorized as none,  $<3$ , 3–5, or  $\geq 6$  months. Gestational age at delivery was categorized as  $<31$ , 32–36, 37–41, or  $>41$  weeks. With regard to gestational age and breastfeeding, we used categories of the covariates obtained using the structured questionnaire and did not collapse categories, in order to conduct tight adjustment and consider potential nonlinear associations (Clark et al., 2006; Cooper et al., 2009). However, we collapsed categories of covariates regarding socioeconomic status, such as

paternal and maternal education and family income, to ensure sufficient sample size in each stratum, because we did not assume a nonlinear correlation with outcomes.

These covariates were selected *a priori* on the basis of earlier literature reviews (Al-Farsi et al., 2012; Hwang et al., 2013; Kim et al., 2010; Schultz et al., 2006). Model 1 contained covariates such as sex, fetal and environmental tobacco smoke exposure, paternal and maternal education levels, monthly family income, low birth weight, breastfeeding, and gestational age at delivery. Model 2 was additionally adjusted for log-transformed blood mercury concentration and fish intake of the children at the time that the lead levels were measured.

### 2.5. Statistical analysis

The right-skewed distribution of blood lead concentrations was natural log-transformed to approximate a normal distribution. The negative binomial regression model, a generalization of the Poisson model applied to analyze over-dispersed count data (Musliner et al., 2014), was used to assess the association between blood lead concentrations and ASSQ scores, as ASSQ scores are count data that aggregate specific items, and the distribution variance was considerably larger than the mean (Fig. 2). The total SRS and subscale scores were modeled as normal distributions, and linear regression analyses were performed after visually examining the linearity of the associations between blood lead concentrations and the total SRS or subscale scores using a generalized additive model. In the present analyses, we used both ASSQ and SRS to assess the robustness of the results independent of the selection of assessment instrument and to decrease the misclassification of outcomes. Furthermore, the ASSQ is a tool widely used for general elementary school populations (Posserud et al., 2009), which is the case for the present study, and SRS provides quantitative measures for autistic symptomatology across the whole range of severity and subscales for each domain of autistic traits (Constantino et al., 2003), which is suitable for the aim of the current study.

After multivariate analyses were conducted, cross-product interaction terms between the lead concentration and each covariate were sequentially added to the initial models. Log likelihood ratio tests were performed to assess the significance of each interaction term.

Several sensitivity analyses were conducted to test the robustness of the results. First, to assess whether blood lead

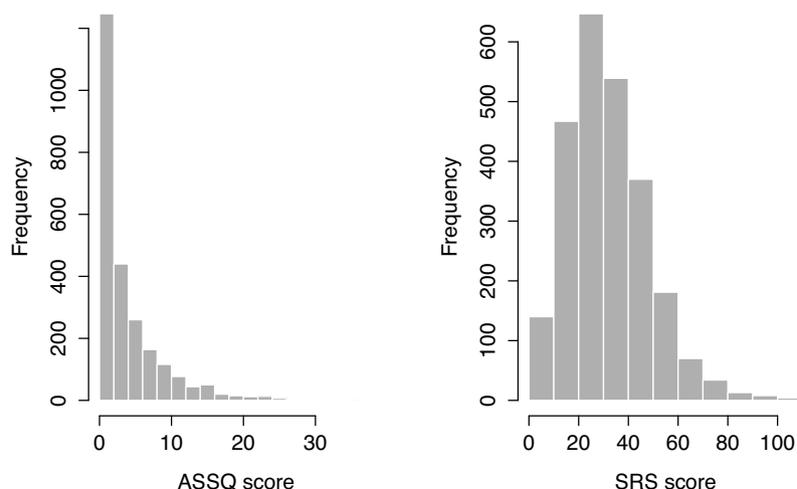


Fig. 2. Distributions of total ASSQ and SRS scores. ASSQ: Autism Spectrum Screening Questionnaire; SRS: Social Responsiveness Scale.

levels are associated with positive screening test results according to predefined criteria, the ASSQ scores were dichotomized using cutoff values of 19 and 17, which have been suggested to be the most efficient when using parent-evaluated ASSQ scores and combining parent- and teacher-evaluated ASSQ scores, respectively (Ehlers et al., 1999; Posserud et al., 2009). Second, we conducted analyses after excluding children with attention-deficit/hyperactivity disorder (ADHD) symptoms, defined as Dupaul Parent ADHD Rating Scale scores  $\geq 19$  (So et al., 2002), to disentangle autistic and ADHD symptoms associated with lead exposure. The Dupaul Scales were completed by the parents of the participating children when children were 11–12 years of age. We also conducted analyses adjusting for continuous Dupaul score as a covariate. Third, to consider potential location bias, we repeated analyses with additional adjustment for the city where each child resided.

We did not present the results adjusted for multiple comparison because we reported all results conducted under specific pre-established hypothesis (Rothman, 1990) and assumed that the results mutually supported each other rather than being independent. All analyses were performed with SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA) and R, version 3.1.0 (The Comprehensive R Archive Network, Vienna, Austria: <http://cran.r-project.org>).

### 3. Results

The demographic characteristics of the children ( $n=2473$ ) are shown in Table 1. Among them, 50.2% were boys, 36.9% had a mother with more than a high school degree, 49.6% had a father with more than a high school degree, and 34.0% were from families with a monthly income <US\$2000. Compared to the excluded children, those included in the analysis were more likely to be girls, exposed to fetal tobacco smoke, and have a body mass index <23 kg/m<sup>2</sup>.

The geometric means (and 95% confidence interval [CI]) of the blood lead concentrations at 7–8, 9–10, and 11–12 years of age were 1.64 (1.60, 1.68), 1.58 (1.55, 1.61), and 1.58 (1.55, 1.61)  $\mu\text{g}/\text{dL}$ , respectively. The geometric standard deviations at each age were 1.76, 1.55, and 1.56  $\mu\text{g}/\text{dL}$ , respectively. The distributions of blood lead concentrations are presented in Table S1. The children's ASSQ and SRS scores are shown in Fig. 2. Among the total of 2473 children included in the present study, 54 (2.2%) had an ASSQ score  $\geq 19$ . For the SRS, 2091 (84.6%), 340 (13.8%), and 42 (1.7%) children had T-scores of  $\leq 59$  (normal), 60–75 (mild to moderate), and  $\geq 76$  (severe), respectively.

A one-unit increment in the log-transformed blood lead concentration at 7–8 years of age was positively associated with the ASSQ score ( $\beta=0.151$ ; 95% CI: 0.061, 0.242) and total SRS score

( $\beta=2.489$ ; 95% CI: 1.378, 3.600) at 11–12 years of age, whereas similar associations were not observed for lead concentrations at either 9–10 or 11–12 years of age (Table 2).

Linear relationships between lead concentrations at 7–8 years of age and total SRS and subscale scores were observed in generalized additive models (Fig. 3). Lead concentration at 7–8 years of age was also associated with social awareness ( $\beta=0.438$ ; 95% CI: 0.227, 0.649), social cognition ( $\beta=0.492$ ; 95% CI: 0.209, 0.774), social communication ( $\beta=0.997$ ; 95% CI: 0.576, 1.418), social motivation ( $\beta=0.346$ ; 95% CI: 0.121, 0.570), and social mannerisms ( $\beta=0.217$ ; 95% CI: 0.009, 0.425). However, we could not find associations between lead concentrations at 9–10 or 11–12 years of age and SRS subscale scores, except for an association between lead concentrations at 11–12 years and social mannerisms ( $\beta=0.281$ ; 95% CI: 0.015, 0.547) (Table 3). When the interaction terms between lead concentration and each covariate were added sequentially and assessed, no interactions were observed at an  $\alpha$ -level=0.10.

In the sensitivity analyses, when we dichotomized the ASSQ scores, blood lead concentrations at 7–8 years of age were associated with positive screening test results according to the cutoff of 19 (odds ratio [OR]=1.793; 95% CI: 1.010, 3.184) and 17 (OR=1.949; 95% CI: 1.175, 3.232) (Table S2). The results were robust when the children with ADHD symptoms ( $n=179$ ) were excluded. When we included Dupaul ADHD score as a covariate, the association between blood lead levels and SRS remained, while the association with ASSQ was attenuated. The results did not change appreciably when we conducted analyses further adjusted for the cities where the children resided (data not shown).

### 4. Discussion

Blood lead concentrations in the present study were comparable to those reported in US children (1.8  $\mu\text{g}/\text{dL}$ ) (Jones et al., 2009), while lower than those of Chinese children (7.1  $\mu\text{g}/\text{dL}$ ) (Liang et al., 2010; Wang et al., 2015). The results demonstrated an association between blood lead concentration at 7–8 years of age and more autistic behaviors at 11–12 years of age according to ASSQ and SRS assessment. Moreover, blood lead concentration at 7–8 years of age was associated with the SRS subscales of social awareness, cognition, communication, motivation, and mannerism. However, these results should be interpreted cautiously because some observed associations might occur by chance due to multiple analyses.

The current analyses considered autistic behaviors as a continuum with incremental severity. Although lead concentration was associated with an ASSQ score  $\geq 19$  (Table S2), this finding should be interpreted cautiously because the ASSQ is not a

**Table 1**  
Study participants' baseline characteristics.

Variable	Included ( $n=2473$ )	Excluded ( $n=4586$ )	$p$ -Value
Sex: male	1242 (50.2)	2436 (53.1)	0.0202
Fetal tobacco smoke exposure <sup>a</sup>	514 (22.1)	769 (19.7)	0.0223
Environmental tobacco smoke exposure <sup>b</sup>	772 (33.2)	1208 (30.9)	0.0658
Maternal education (>high school diploma)	841 (36.9)	1317 (36.8)	0.9304
Paternal education (>high school diploma)	1140 (49.6)	1822 (50.0)	0.7654
Monthly family income (<US\$2,000)	825 (34.0)	1363 (32.8)	0.3347
Low birth weight (<2.5 kg)	76 (3.5)	141 (3.9)	0.4134
Breastfeeding ( $\geq 6$ months)	565 (25.0)	833 (23.6)	0.5866
Gestational age ( $\leq 36$ weeks)	350 (15.1)	178 (14.8)	0.8305
Blood mercury level ( $\geq 2.03$ $\mu\text{g}/\text{L}$ )	1190 (50.0)	121 (51.8)	0.6265
Fish intake ( $\leq$ once/week)	710 (50.8)	1354 (51.0)	0.8808
BMI ( $\geq 23$ kg/m <sup>2</sup> )	68 (2.8)	161 (4.3)	0.0013

Data are shown as  $n$  (%). Denominators vary across strata due to missing values

<sup>a</sup> Active maternal smoking or presence of a smoker in the home during pregnancy.

<sup>b</sup> Presence of a smoker in the home after delivery. BMI: body mass index.

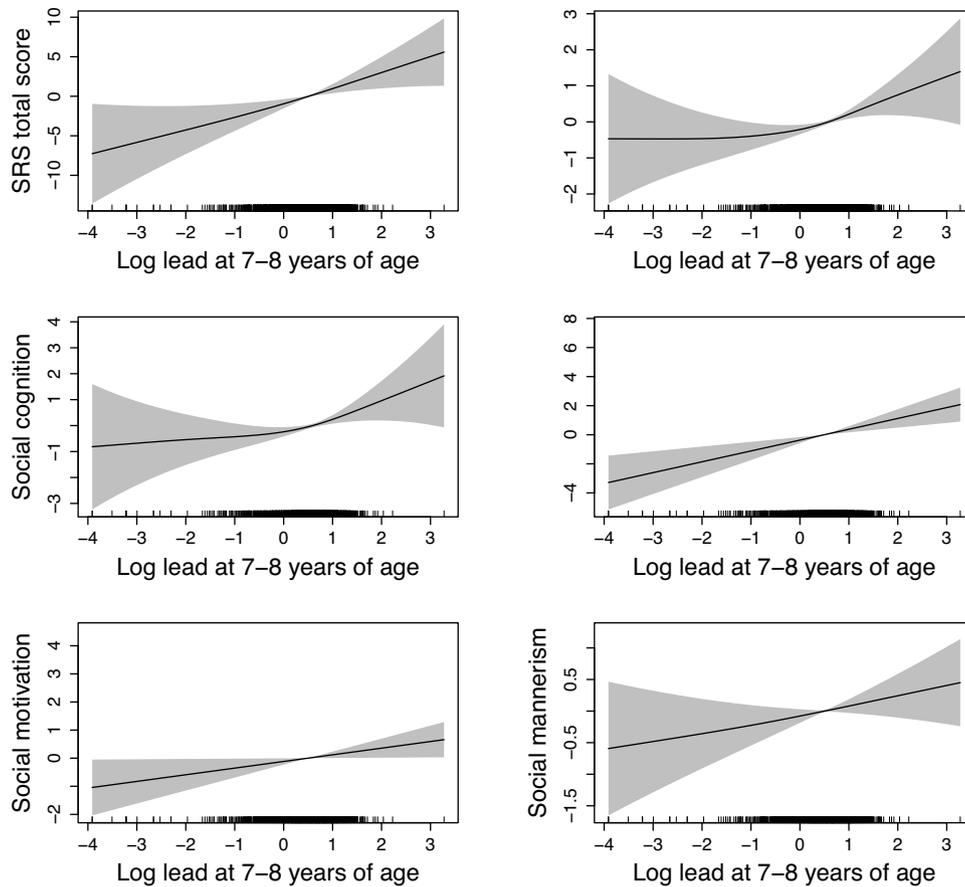
**Table 2**

Associations of blood lead concentration with ASSQ scores via negative binomial regression and SRS scores via linear regression at 11–12 years of age.

	Model 1 <sup>a</sup>				Model 2 <sup>b</sup>			
	ASSQ		SRS		ASSQ		SRS	
	$\beta$	95% CI	$\beta$	95% CI	$\beta$	95% CI	$\beta$	95% CI
[Pb] at 7–8 y	0.152	0.062, 0.243	2.439	1.337, 3.541	0.151	0.061, 0.242	2.489	1.378, 3.600
[Pb] at 9–10 y	–0.031	–0.146, 0.084	0.930	–0.547, 2.397	–0.023	–0.143, 0.097	1.295	–0.235, 2.825
[Pb] at 11–12 y	0.048	–0.066, 0.162	0.652	–0.777, 2.081	0.054	–0.061, 0.170	0.724	–0.727, 2.176

<sup>a</sup> Model 1 was adjusted for sex, fetal and environmental tobacco smoke exposure, paternal and maternal education levels, family income, low birth weight, breastfeeding, and gestational week at delivery.

<sup>b</sup> Model 2 was further adjusted for children’s fish intake and blood mercury concentration, which were measured with the same survey. ASSQ: Autism Spectrum Screening Questionnaire; [Pb]: lead concentration; SRS: Social Responsiveness Scale; CI: confidence interval.



**Fig. 3.** Penalized regression spline of log-transformed blood lead concentrations at 7–8 years of age with respect to total Social Responsiveness Scale (SRS) scores and subscale scores.

Solid lines: spline curve; shaded area: 95% confidence interval.

Models were adjusted for sex, fetal and environmental tobacco smoke exposure, paternal and maternal education levels, family income, low birth weight, breastfeeding, gestational week at delivery, and children’s fish intake and blood mercury concentration, which were measured using the same survey.

diagnostic tool. Therefore, it is more appropriate to interpret the current results as indicative of a positive association between blood lead concentrations and more autistic behaviors. The current analysis has the strength to identify the effect of lead exposure upon earlier or subclinical manifestations of ASD (Kim et al., 2009b). Although these subclinical features may be shared with other neurobehavioral disorders such as ADHD (Reiersen et al., 2007), the results remained robust after excluding children with ADHD symptoms assessed using the Dupaul ADHD Rating Scales.

Blood lead concentrations in early school-age children have been reported to be associated with neuropsychiatric outcomes such as cognitive function (Kim et al., 2009a; Kordas et al., 2004), as well as with inattention and hyperactivity symptoms (Kim et al.,

2010; Wang et al., 2008). Although the prenatal and early infancy periods are critical for ASD development (Bilder et al., 2009), the present results agree with previous findings that suggested a child’s lead exposure up to early school age might also affect neuropsychiatric function maturation and could induce more autistic behaviors. Subtle changes in the distributions of ASSQ and SRS in association with lead exposure at an early school age could produce relatively large changes in the prevalence of children above a particular threshold, such as that for ASD diagnosis, thus suggesting the potential clinical importance of lead exposure at an early school age.

Several mechanisms have been suggested to explain the effect of lead exposure on the nervous system. First, lead exposure might

**Table 3**  
Associations between blood lead concentrations and SRS subscale areas.

	[Pb] at 7–8 y		[Pb] at 9–10 y		[Pb] at 11–12 y	
	$\beta$	95% CI	$\beta$	95% CI	$\beta$	95% CI
Social awareness	0.438	0.227, 0.649	0.218	−0.062, 0.499	−0.027	−0.302, 0.248
Social cognition	0.492	0.209, 0.774	0.207	−0.168, 0.583	0.202	−0.162, 0.567
Social communication	0.997	0.576, 1.418	0.376	−0.183, 0.936	0.135	−0.409, 0.679
Social motivation	0.346	0.121, 0.570	0.098	−0.201, 0.397	0.071	−0.220, 0.361
Social mannerisms	0.217	0.009, 0.425	0.046	−0.227, 0.318	0.281	0.015, 0.547

The model was adjusted for sex, fetal and environmental tobacco smoke exposure, paternal and maternal education levels, family income, low birth weight, breastfeeding, gestational week at delivery, and children's fish intake and blood mercury concentration (measured using the same survey).

[Pb]: lead concentration; SRS: Social Responsiveness Scale; CI: confidence interval.

affect the nervous system by hindering neurotransmitter release, interfering with energy metabolism, generating reactive oxygen species, and activating apoptosis (Brookes et al., 2004; Markovac and Goldstein, 1988). Second, lead might influence the nervous system by increasing the risks of conditions such as hypertension, vitamin D deficiency, and impaired thyroid or renal function (Abadin et al., 2007). Third, the presence of lead might affect the nervous system by inhibiting the formation of key molecules during the mature differentiation of glial cells (Bressler and Goldstein, 1991; Silbergeld, 1992). However, no specific pathway is known to lead to autistic behaviors. Therefore, further mechanistic studies of this subject are warranted.

The current study has some limitations that should be addressed. First, only blood lead concentrations that reflect acute exposure were used; therefore, the results do not precisely reflect the effects of cumulative exposure, which may be more relevant. Previous studies suggest that children with ASD could not efficiently eliminate heavy metals by excretion and, therefore, store them in brain and other tissue (Holmes et al., 2003; Quig, 1998). The association between blood lead concentration and ASD traits observed in the present study may also be affected by the poor heavy metal excretion and detoxifying ability of the children with ASD traits. However, the direction of the effect of low lead excretion capacity on blood lead levels among children with ASD was not clear because lead could be sequestered in tissue such as bone, keeping blood lead level low. Therefore, to fully understand the association between body burden of lead and ASD, further study measuring lead concentrations in various specimens and tissues, especially bone, is warranted. Second, the underreporting of disease history is a major concern. Relatively few parents reported an ASD diagnosis for their children at the baseline survey ( $n=4$ ), whereas 54 children had an ASSQ score  $\geq 19$  at 11–12 years of age. This might be due to the social stigma of ASD or the fact that in Korea most children with severe neurological disorders or intellectual disabilities are educated in special schools or classes (Kwon, 2005). Third, the ASSQ and SRS scores were evaluated only once when the children were 11–12 years of age and not at enrollment. Although we excluded children diagnosed with ASD at enrollment, clinical ASD and autistic behaviors evaluated using tools such as the ASSQ or SRS are not the same, which limits the ability to exclude children with subclinical ASD, despite the study design to measure blood lead levels at each time point and assess autistic behaviors at 11–12 years of age. Furthermore, it is potentially problematic to assess autistic behaviors only once because there may be variation and measurement error in outcome assessment over time. Although ASSQ and SRS scores evaluated 1–4 years apart showed a relatively high correlation in the United States (Braun et al., 2014) and Norway (Sivertsen et al., 2012), to our knowledge, there have been no studies investigating the reliability and validity of ASSQ and SRS among Korean populations. This is a limitation of the present study, despite the similar distributions of ASSQ and SRS scores in the present study

and those conducted abroad, as well as the correlation between ASSQ and SRS scores (data not shown). Fourth, because blood lead levels are inversely associated with intelligence quotient (IQ) scores in children (Canfield et al., 2003) and intellectual disability frequently overlaps with ASD and is related to some ASD symptoms (Cervantes and Matson, 2015), the IQ of children needs to be considered as a potential mediator or confounder. Therefore, it is a limitation of the current study that IQ scores were not considered due to lack of information.

The current study also has some strengths worth mentioning. To our knowledge, this study was conducted with the largest sample size to date, which supplied sufficient statistical power. In addition, all models used in the current study were adjusted for extensive confounders to increase the likelihood of detecting a true relationship.

In conclusion, elevated blood lead concentrations, even at low levels, are associated with increased autistic behaviors in school-age children. In developed countries, the incidence of ASD has increased in recent decades despite the decline in blood lead levels, possibly due to changes in various factors also associated with ASD risk, such as parental age, low birth weight, breastfeeding, and gestational age at delivery in the same period. Because children might continue to be exposed to lead through sources such as paint or toys, despite the ban on leaded gasoline (Huang et al., 2012), and because low-level lead exposure observed in the present study could be associated with autistic behaviors, the present results emphasize the importance of lead exposure as a major public health issue.

### Conflict of interest

The authors declare that there are no conflicts of interest.

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### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.neuro.2016.02.004>.

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