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ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND URINARY METABOLITES OF ORGANOPHOSPHATE PESTICIDES IN U.S. CHILDREN 8–15 YEARS

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Abstract

Context—Exposure to organophosphate (OP) pesticides is common, and although these compounds have known neurotoxic properties, few studies examined risks for children in the general population.

Objective—To examine the association between the concentrations of urinary dialkyl phosphate (DAP) metabolites of OPs and attention deficit/hyperactivity disorder (ADHD) in children age 8 to 15 years.

Participants and Methods—Cross-sectional data from the National Health and Nutrition Examination Survey (2000–2004) were available for 1,139 children representative of the general U.S. population. A structured interview with a parent was used to ascertain ADHD diagnostic status, based on slightly modified criteria of the Diagnostic and Statistical Manual of Mental Disorders-IV.

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Author contributions

Maryse Bouchard had access to all of the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

- Study concept and design: Bouchard, Weisskopf, and Bellinger
- Acquisition, analysis, and interpretation of data: Bouchard
- Drafting of the manuscript: Bouchard
- Critical revisions of the manuscript for important intellectual content: Bouchard, Wright, Weisskopf, and Bellinger

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Results—One hundred nineteen children met the diagnostic criteria for ADHD. Children with higher concentrations of urinary DAPs, especially dimethyl alkylphosphates (DMAP), were more likely to be diagnosed with ADHD. A 10-fold increase in DMAP concentration was associated with an odds ratio (OR) of 1.55 (95% confidence intervals [CI], 1.14–2.10), after adjusting for sex, age, race/ethnicity, poverty-income ratio, fasting duration, and urinary creatinine concentration. For the most commonly detected DMAP metabolite, dimethylthiophosphate, children with levels higher than the median of detectable concentrations had double the odds of ADHD (adjusted OR, 1.93 [95% CI, 1.23–3.02]) compared with those with non-detectable levels.

Conclusions—These findings support the hypothesis that OP exposure, at levels common in U.S. children, may contribute to ADHD prevalence. Prospective studies are needed to establish whether this association is causal.

Keywords

attention deficit/hyperactivity disorder; ADHD; pesticides; organophosphates; OP; National Health and Nutrition Examination Survey; NHANES; Center for Health Statistics; NCHS; Centers for Disease Control and Prevention; CDC

INTRODUCTION

Approximately 40 organophosphate (OP) pesticides are registered with the U.S. Environmental Protection Agency (EPA) for use in the United States.¹ In 2001, 73 million pounds of OP were used in both agricultural and residential settings. The EPA considers food, drinking water, and residential pesticide use as important sources of exposure.² Residential pesticide use is common, but the major source of exposure to pesticides for infants and children would be the diet according to the National Academy of Sciences.³ The U.S. Pesticide Residue Program's 2008 Report indicates that detectable concentrations of the OP malathion were found on 28% of frozen blueberry samples, 25% of strawberry samples, and 19% of celery samples.⁴

Children are generally considered to be at greatest risk from OP toxicity because the developing brain is more susceptible to neurotoxicants,⁵ and the dose of pesticides per body weight is likely to be larger in children. Children age 6–11 years have the highest urinary concentrations of dialkyl phosphate (DAP) metabolites -- markers of OP exposure -- compared to other age groups in the U.S. population.⁶ Contributing to their vulnerability, children have reduced expression of detoxifying enzymes.^{7, 8} Epidemiological studies linking exposure to OPs and neurodevelopment have focused on populations with high exposure relative to the general population.^{9, 10} Prenatal exposure to OP was associated with increased risk of pervasive developmental disorders as well as delays in mental development at 2–3 years old.^{11, 12} Postnatal OP exposure has been associated with behavioral problems, poorer short-term memory and motor skills, and longer reaction time in children.^{13–15}

A few epidemiological studies suggest that exposure to OP is associated with adverse neurodevelopmental outcomes, but no study have addressed possible risks in children with average level of exposure. Using data on a representative sample of U.S. children, we examined the cross-sectional association between urinary DAP metabolite concentrations and ADHD prevalence in children of ages 8–15 years.

PARTICIPANTS AND METHODS

Study Design and Population

The National Health and Nutrition Examination Survey (NHANES) is a population-based health survey of non-institutionalized U.S. residents conducted by the National Center for

Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). NHANES uses a complex, multistage probability sampling design, with oversampling of certain subgroups. Participants completed household surveys, which included questions about demographics and health history, and blood and urine samples were collected during a physical examinations at mobile centers.¹⁶ We used data from 2000–2004, years for which ADHD was assessed in children 8–15 years; a diagnosis was available for 3,998 children. Urinary DAP metabolites were measured on a random subsample of the NHANES participants. From 2000 to 2002, the sampling rate was 1/2 for ages 6–11 years and 1/3 for ages 12–15 years. From 2003 to 2004, the sampling rate was 1/3 across all ages. Measurements of urinary DAPs were available for 1,481 children among those with an ADHD diagnosis. NHANES was approved by the NCHS institutional review board, and all participants provided written informed consent.

Children who received newborn care in an intensive care unit or premature nursery (n=167) and those with birth weight below 2,500 grams (n=126) were excluded because these are important risk factors for developmental disorders.¹⁷ We excluded 24 children with extremely diluted urine (creatinine < 20 mg/dL) and 1 outlier for urinary DAP concentration. Children with missing data were excluded (poverty-income ratio [PIR] [n=43], fasting duration [n=38], and urinary creatinine [n=1]).

ADHD Assessment

The Diagnostic Interview Schedule for Children (DISC-IV) a structured diagnostic interview designed for use in epidemiologic studies,¹⁸ was used to assess the presence of ADHD based on slightly modified criteria of the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV).¹⁹ The interview was conducted over the telephone by trained interviewers with the mother or another caretaker, two to three weeks after the physical examination. The interview was conducted by bilingual interviewers in English or Spanish. The DISC-IV has evidence of substantial validity,¹⁸ reliability for both its English¹⁸ and Spanish^{20, 21} versions, and successful use via telephone in the DSM-IV field trials.²² The use of DISC-IV data is restricted for confidentiality reasons, thus, we accessed the data through the NCHS Research Data Center.

The DISC-IV scoring algorithms determine ADHD diagnostic status for the past year, as well as ADHD subtype: i) predominately inattentive subtype, ii) predominately hyperactive-impulsive subtype, or iii) combined subtype. The diagnosis is based on the presence, during the prior 12 months, of symptoms related to inattention, hyperactivity and impulsivity, with significant impairment in two or more settings (e.g., at school and home).²³ The DSM-IV criterion that symptoms must not occur in conjunction with another neuropsychiatric disorder is not assessed by the DISC-IV. We chose not to use the DSM-IV criterion that symptoms must have been present before 7 years of age because our hypothesis was that urinary DAP concentrations are associated with increased odds of concurrent ADHD.

The DISC-IV identified 119 cases of ADHD, but 30 children did not meet diagnostic criteria although the parent reported use of doctor-prescribed ADHD-medication during the last year. Because the diagnosis interview addresses the presence of symptoms, children whose symptoms are well-controlled by medication would not meet the diagnostic criteria. Thus, we also conducted analyses in which ADHD cases were defined as either meeting the DISC-IV diagnostic criteria, or regularly taking ADHD-medication during the last year.

Measurement of Urinary Metabolites of OP Pesticides

During the physical examination, “spot” urine specimens were collected from participants, aliquoted, and stored cold (2–4°C) or frozen until they were shipped on dry ice to the CDC

for analysis. Six urinary DAP metabolites, resulting from the degradation of at least 28 different OPs, were measured in urine to provide an indicator of the body burden of common OPs.³ The urinary DAP metabolites measured are 3 dimethyl alkylphosphate (DMAP) molecules (dimethylphosphate, dimethylthiophosphate, dimethyldithiophosphate) and 3 diethyl alkylphosphate (DEAP) molecules (diethylphosphate, diethylthiophosphate, diethyldithiophosphate). DMAP metabolites are derived from *O, O*-dimethyl-substituted OP pesticides such as malathion; DEAP metabolites result from the degradation of *O, O*-diethyl-substituted OPs such as chlorpyrifos. The measurements were performed by lyophilization and chemical derivatization, followed by analysis by isotope-dilution gas chromatography–tandem mass spectrometry.²⁴ Stable isotope analogues are used as internal standards for each of these metabolites, resulting in a high degree of accuracy and precision, with low analytical limits of detection. Concentrations below the detection limit were imputed a value corresponding to the value of the detection limit divided by 2.²⁵ The concentration of creatinine was measured using a Jaffé rate reaction, in which creatinine reacts with picrate in an alkaline solution to form a red creatinine-picrate complex; the reaction was measured with a CX3 analyzer.²⁶

Other Covariates

The following variables were considered as potential confounders: sex; age (months); child race/ethnicity (non-Hispanic white, African American, Mexican American, and other/multiracial); PIR, the ratio of self-reported family income to the family's appropriate poverty threshold value based on the census (recoded into 4 categories); body mass index (quartiles); blood lead concentration (log-transformed); maternal age at birth; maternal smoking during pregnancy (yes/no); time since last consuming food or drink, recorded at the time of blood and urine sampling (1 [0–2 hours] to 7 [21–24 hours]).

Data Analyses

We used the Complex Samples module of SPSS 17.0 to conduct all analyses, accounting for the multistage probability sampling design of NHANES. Strata, primary sampling units, and sample weights were used to obtain robust linearized standard errors and unbiased point estimates. The threshold for statistical significance was set at $p < .05$. All statistical tests were 2-sided. The DAP metabolite concentrations were divided by their respective molecular weight, before summing them to obtain the concentrations of DEAP, DMAP, and total DAP (in nmol/L). Given that DMAP and DEAP metabolites might have different relations to the outcome,¹² they were examined separately. Because the distributions of total DAP, DMAP, and DEAP concentrations were skewed, log-transformations (base-10) were applied. Correlates of urinary DAP metabolite concentrations were examined with a general linear model. Logistic regression analysis was used to estimate odds ratios (ORs) and 95% confidence intervals (CI) for ADHD (any subtype) and ADHD subtypes, per 10-fold increase in total DAP, DMAP, and DEAP metabolites concentration in nmol/L. Results are presented for crude analyses, as well as adjusted analyses. Sex- and age-related differences were examined in subpopulation analyses, and since there was no difference in effect estimates and no significant interaction, these variables were included as covariates in the models. In addition, race/ethnicity, PIR, fasting time, and log-transformed urinary creatinine (as recommended by Barr. et al to adjust for urine dilution²⁶) were included in models because they are important potential confounders; other covariates were also examined in sensitivity analyses. Since individual urinary DAP metabolites were below the analytical limit of detection for a large proportion of children (Table 1), which could bias effect estimates,²⁷ we conducted further analyses on the metabolite with the highest detection frequency, dimethylthiophosphate. Children were categorized as below the limit of detection, lower, or higher than the median of detectable concentrations adjusted for creatinine.

RESULTS

Descriptive Statistics

Our analytic sample comprised 1,139 children 8 to 15 years, with similar characteristics to children not included in the sample (Table 2). One hundred nineteen children met the diagnostic criteria for any ADHD subtype, which corresponds to a population prevalence of 12.1% (95% CI, 9.6–15.1%). The prevalence estimates were 7.6% (5.5–10.4%) for inattentive subtype, 1.5% (0.8–2.7%) for hyperactive-impulsive subtype, and 3.0% (2.1–4.3%) for combined subtype. When including children taking ADHD-medication in cases, there were 148 cases.

The proportion of children with a urinary DAP concentration below the detection limit was between 35.7% and 80.0% depending on the metabolite (table 1). Most children (93.8%) had at least one detectable metabolite out of the six DAPs measured. In a multivariate analysis, higher DAP concentrations were associated with higher creatinine concentrations ($p < .001$), younger age ($p = .03$), lower blood lead concentrations ($p = .06$), and higher PIR ($p = .10$). DAP concentrations were higher in children examined in 2003–2004 (adjusted mean, 18.15 nmol/L; standard error [SE], 1.15), than in 2000 and 2001–2002 (12.62 nmol/L, SE 1.24, and 11.69 nmol/L, SE 1.18, respectively) although not significantly ($p = .10$). Sex, race/ethnicity, and fasting duration were not significantly associated with DAP metabolite concentrations (all at $p > 0.3$).

Any Subtype of ADHD

The odds of meeting the DISC-IV criteria for ADHD increased with the urinary concentration of total DAP metabolites (table 3). Adjustment for covariates attenuated the estimates (for a 10-fold increase in total DAP, unadjusted OR 1.31, 95% CI [1.06–1.63]; adjusted OR 1.21 [0.97–1.51]). This association was driven by DMAP metabolites, for which the association was statistically significant even after adjustment (OR 1.55 [1.14–2.10]). When children taking ADHD-medication were included as cases, slightly higher effect estimates were obtained for DMAP (adjusted OR 1.72 [1.31–2.28]). A 10-fold difference in DMAP concentration corresponds approximately to the increase from the 25th to 75th percentile of children's concentrations (table 1). DEAP metabolites were not significantly associated with odds of ADHD, whether cases were defined strictly by the DISC-IV criteria, or including children taking ADHD medication (table 3).

The association between DMAP concentrations and ADHD was similar in girls (for cases defined as meeting DISC-IV criteria or taking ADHD-medication, adjusted OR 2.09 [1.39–3.15]) and boys (adjusted OR 1.60 [1.09–2.36]) (p for interaction = .48). Likewise, we examined age-differences in DMAP effect estimates in children ages 8–11 and 12–15 years, but there was no difference (p for interaction = .55).

The metabolite dimethylthiophosphate was the most commonly detected DMAP (64.3% of children) and it accounted for 50% of the total DMAP metabolites. Children with creatinine-adjusted dimethylthiophosphate concentrations above the median of detectable values had double the odds of ADHD compared to those with concentrations below the detection limit (adjusted OR 1.93 [1.23–3.02]) (table 4). The OR was higher when children taking ADHD-medication were included in cases (adjusted OR 2.12 [1.32–3.43]).

Sensitivity Analyses

Urinary creatinine is a potential confounder because higher concentrations were associated both with greater odds of ADHD and with higher DAP concentrations. We examined different analytical approaches to account for creatinine concentration in our analyses. We

used creatinine-adjusted DAP, DMAP and DEAP concentrations (metabolite/creatinine), and results were essentially the same as those obtained with the main analyses where adjustment for creatinine was achieved by including it as an independent variable along with the other covariates.

To evaluate possible cohort effects, we added a term for year of data collection to the models, but this term was not significant and did not appreciably change the effect estimates. The effect estimates were not affected by adjusting for blood lead concentration, maternal age at birth, or maternal smoking during pregnancy. Given that ADHD-medication use could change the metabolism of pesticides and influence their excretion in urine, we excluded the 40 children taking such medication but the results were similar (adjusted OR for a 10-fold increase in DMAP, 1.80 [1.18–2.76]).

Subtypes of ADHD

The odds of meeting the diagnostic criteria for hyperactive-impulsive ADHD subtype increased significantly with higher DEAP, DMAP, and total DAP (adjusted OR for a 10-fold increase in concentration 2.15 [1.06–4.40], 2.13 [1.08–4.20], and 1.85 [1.04–3.27], respectively) (table 5). The odds of inattentive subtype increased with higher concentrations of DMAP metabolites although this did not reach significance level (adjusted OR 1.47 [0.99–2.19]). Concentrations of DAP metabolites were not significantly associated with odds of combined subtype.

COMMENT

We report an association between urinary DMAP metabolite concentrations -- indicators of exposure to dimethyl-containing OP pesticides -- and increased odds of ADHD in children 8 to 15 years. There was a 55 to 72% increase in the odds of ADHD for a 10-fold increase in DMAP concentration, depending on criteria used for case identification. This association was not explained by sex, age, poverty-income ratio, race/ethnicity, fasting duration, or creatinine concentration. Whether DAP metabolite concentrations are more strongly associated with a specific subtype of ADHD is uncertain due to the small numbers of cases, though the association was stronger for the predominantly hyperactive-impulsive subtype. This study should be generalizable to the U.S. population since the NHANES sample is nationally representative, unlike previous studies in groups with higher exposure levels.^{11–15} Adding to the importance of these findings, OPs are among the most widely used pesticides and the concentrations of DAP metabolites did not decrease from 2000 to 2003–2004 in children.

The most important limitation of the present study is the assessment of OP exposure by measurement of DAP metabolites in only one spot urine sample. Given that long-term exposure to OPs would likely be necessary to produce neurochemical changes causing ADHD-like behaviors, serial measurements of urinary metabolites of OPs over a longer time period would provide a better assessment of average exposure, but NHANES does not include longitudinal follow-up. For OPs coming from the diet, the measure of OP metabolites in a single urine sample may reflect average exposure levels reasonably well, to the extent that diet is consistent. Given that OPs are eliminated from the body after 3–6 days,²⁸ the detection of DAPs in the urine of most children indicates continuing exposure. An additional consideration is that urinary DAP levels might reflect not only exposure to OPs, but also direct exposure to DAPs present in the environment resulting from degradation of OPs by hydrolysis or photolysis. Significant amounts of DAPs have been found on several fruits and vegetables.²⁹ In any case, misclassification of exposure based on measurements of urinary DAPs should be non-differential, and would bias effect estimates towards the null.

Given the cross-sectional nature of our analysis, we cannot rule out that children with ADHD engage in behaviors that expose them to higher levels of OPs. However, if this was the case, we would have expected to see higher levels of urinary DEAP metabolites as well, which was not the case. Another limitation is measurement error in that the concentration for the individual DMAP metabolites was below the analytical limit of detection for a large proportion of children. This problem, however, does not apply to the analysis showing that children with levels higher than the median of detectable dimethylthiophosphate concentrations were twice as likely to be diagnosed with ADHD as those with non-detectable concentrations.

The present study uses a larger sample size than previous investigations on neurodevelopmental effects of OP exposure, as well as a DSM-IV based diagnostic outcome. Comparisons are difficult across studies because of differences in exposure levels, timing of exposure, choice of outcomes assessed, and age at assessment. Higher concentrations of blood chlorpyrifos during pregnancy were found to be associated with poorer mental and motor development at 3 years,¹¹ and higher postnatal exposure to OPs have been associated with difficulties with memory, attention, motor tasks, behavioral problems,¹⁴ and reaction time.¹³ Prenatal exposure to OPs was also associated with poorer mental development at 2 years of age, and, as in our study, the association was with DMAP rather than DEAP metabolites.¹² The stronger association with DMAP metabolites could be explained by higher exposure to OPs metabolized into DMAP metabolites, or it could indicate greater toxicity of these OPs.

Several biological mechanisms could underlie an association between OP pesticides and ADHD. A primary action of OPs, particularly with respect to acute poisoning, is inhibition of acetylcholinesterase,³⁰ and disruptions in cholinergic signaling are thought to occur in ADHD.³¹ At doses lower than those needed to inhibit acetylcholinesterase, certain OPs affect different neurochemical targets, including growth factors, several neurotransmitter systems, and second messenger systems.^{32, 33} Exposure to some of these OP compounds have been shown to cause hyperactivity and cognitive deficits in animal studies.^{34, 35} Developmental exposure to OPs could have persistent effects on multiple neural systems that may underlie ADHD behaviors, such as inattention and cognitive deficits, similar to effects of developmental nicotine exposure.^{36, 37}

CONCLUSION

The present study adds to the accumulating evidence linking higher level of pesticide exposure to adverse developmental outcomes. Our findings support the hypothesis that current levels of OP pesticides exposure might contribute to the childhood burden of ADHD. Future studies should employ a prospective design, with multiple urine samples collected over time to better assess chronic exposure and critical windows of exposure, and establish appropriate temporality.

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Abbreviations

OP	organophosphate
DAP	dialkyl phosphate
DMAP	dimethyl alkylphosphates
DEAP	diethyl alkylphosphate
OR	odds ratio
CI	confidence intervals
ADHD	attention deficit/hyperactivity disorder
NHANES	National Health and Nutrition Examination Survey
NCHS	Center for Health Statistics
CDC	Centers for Disease Control and Prevention
DISC	Diagnostic Interview Schedule for Children
PIR	poverty-income ratio
EPA	Environmental Protection Agency
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition

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Table 1

Concentrations of urinary DAP metabolites (nmol/L) (n=1,139)

	No.	No. below detection limit (%)	Geometric mean	Interquartile Range	Min	Max
Diethylphosphate	1,133	534 (46.9)	4.78	0.92–28.10	0.46	5,902.94
Diethylthiophosphate	1,121	487 (42.8)	2.05	0.41–7.63	0.36	650.89
Diethyldithiophosphate	1,139	911 (80.0)	0.51	0.38–0.38	0.22	36.32
Dimethylphosphate	1,139	581 (51.0)	10.74	2.80–39.00	2.80	1,324.48
Dimethylthiophosphate	1,139	407 (35.7)	13.70	1.99–58.87	0.92	9,929.08
Dimethyldithiophosphate	1,133	664 (58.3)	1.72	0.45–7.36	0.38	7,006.37
DEAP	1,139	253 (22.2)	11.00	2.16–35.05	0.84	5,905.45
DMAP	1,139	209 (18.3)	41.36	10.15–130.75	4.58	10,068.75
Total DAP	1,139	71 (6.2)	68.33	24.45–186.03	6.07	10,195.28

Abbreviations: DEAP, diethyl alkylphosphate; DMAP, dimethyl alkylphosphate; DAP, dialkyl phosphate.

Table 2

Comparison of characteristics between children 8 to 15 years not included and included in the analytic sample

	<u>Not included</u>		<u>Included</u>	
	Total no.	No. (weighted %)	Total no.	No. (weighted %)
Sex (males)	4,578	2,247 (51.2%)	1,139	570 (53.2%)
Race/ethnicity	4,578		1,139	
Non Hispanic white		1,138 (59.6%)		325 (63.3%)
African American		1,533 (16.0%)		342 (13.2%)
Mexican American		1,555 (11.7%)		382 (11.6%)
Other/multiracial		352 (12.7%)		90 (12.0%)
Poverty-income ratio	4,145		1,139	
<1.0		1,390 (23.4%)		363 (21.4%)
1.0–1.84		1,009 (20.7%)		274 (21.3%)
1.85–3.0		730 (20.6%)		214 (21.6%)
>3.0		1,016 (35.3%)		288 (35.8%)
Maternal smoking during pregnancy	4,509	697 (19.8%)	1,125	152 (17.7%)
ADHD cases any subtype	2,859	295 (12.2%)	1,139	119 (12.1%)
ADHD cases Inattentive subtype	2,865	133 (5.9%)	1,139	69 (7.6%)
ADHD cases Hyperactive subtype	2,860	81 (3.2%)	1,139	21 (1.5%)
ADHD cases Combined subtype	2,865	81 (3.1%)	1,139	29 (3.0%)
	Total no.	Weighted mean (SE)	Total no.	Weighted mean (SE)
Age (months)	4,578	144 (0.6)	1,139	143 (1.0)
Body mass index	4,502	20.8 (0.1)	1,139	20.6 (0.2)
Blood lead (ug/dL)	4,036	1.4 (0.04)	1,093	1.4 (0.04)
Maternal age at birth	4,432	26.3 (0.2)	1,107	26.4 (0.3)

Abbreviations: ADHD, attention deficit/hyperactivity disorder; SE, standard error.

Table 3

Odds ratios for any ADHD subtype for a 10-fold increase in urinary DAP metabolites (n=1,139)

	<u>Cases identified with the DISC-IV (n=119)</u>		<u>Cases identified with the DISC-IV or ADHD-medicated (n=148)</u>	
	Crude OR [95% CI]	Adjusted OR ^I [95% CI]	Crude OR [95% CI]	Adjusted OR ^I [95% CI]
DEAP	1.02 [0.74–1.41]	0.94 [0.69–1.28]	0.88 [0.66–1.18]	0.80 [0.60–1.05]
DMAP	1.66 [1.24–2.22]	1.55 [1.14–2.10]	1.87 [1.42–2.47]	1.72 [1.31–2.28]
Total DAP	1.31 [1.06–1.63]	1.21 [0.97–1.51]	1.48 [1.20–1.82]	1.35 [1.10–1.67]

Abbreviations: ADHD, attention deficit/hyperactivity disorder; CI, confidence interval; OR, odds ratio; DEAP, diethyl alkylphosphate; DMAP, dimethyl alkylphosphate; DAP, dialkyl phosphate.

^I Sex, age, race/ethnicity, poverty-income ratio, fasting duration, and log-transformed urinary creatinine concentration

Table 4

Odds ratio for any ADHD subtype by level of creatinine-adjusted urinary dimethylthiophosphate concentration (n=1,139)

Dimethylthiophosphate concentration	Cases identified with the DISC-IV (n=119)		Cases identified with the DISC-IV or ADHD-medicated (n=148)	
	Crude OR [95% CI]	Adjusted OR ¹ [95% CI]	Crude OR [95% CI]	Adjusted OR ¹ [95% CI]
Below detection limit (n=407)	1.0 (reference)			
Lower median ² (n=366)	1.11 [0.63–1.97]	1.05 [0.57–1.95]	1.36 [0.76–2.44]	1.22 [0.65–2.27]
Higher median ³ (n=366)	1.83 [1.18–2.82]	1.93 [1.23–3.02]	2.04 [1.30–3.22]	2.12 [1.32–3.41]

Abbreviations: ADHD, attention deficit/hyperactivity disorder; CI, confidence interval; OR, odds ratio

¹ Adjusted for sex, age, race/ethnicity, poverty-income ratio, and fasting duration

² Range 0.96–30.46 nmol×g of creatinine/L, median 11.26 nmol×g of creatinine/L

³ Range 30.47–7932.06 nmol×g of creatinine/L, median 97.63 nmol×g of creatinine/L

Table 5

Odds ratio [95% CI] for subtypes of ADHD for a 10-fold increase in urinary DAP metabolites (n=1,139)

	Hyperactive-impulsive subtype (n=21)			Inattentive subtype (n=69)			Combined subtype (n=29)		
	Crude OR	[95% CI]	AdjustedOR ^I [95% CI]	Crude OR	[95% CI]	AdjustedOR ^I [95% CI]	Crude OR	[95% CI]	AdjustedOR ^I [95% CI]
DEAP	2.29	[1.25–4.21]	2.15 [1.06–4.40]	0.77	[0.52–1.14]	0.70[0.49–1.01]	1.29	[0.68–2.43]	1.22 [0.59–2.50]
DMAP	2.26	[1.33–3.86]	2.13 [1.08–4.20]	1.61	[1.10–2.37]	1.47[0.99–2.19]	1.30	[0.56–2.99]	1.30 [0.48–3.48]
Total DAP	1.95	[1.18–3.22]	1.85 [1.04–3.27]	1.26	[0.91–1.75]	1.14[0.81–1.61]	1.09	[0.59–2.01]	1.05 [0.51–2.16]

Abbreviations: ADHD, attention deficit/hyperactivity disorder; CI, confidence interval; OR, odds ratio; DEAP, diethyl alkylphosphate; DMAP, dimethyl alkylphosphate; DAP, dialkyl phosphate.

^I Adjusted for sex, age, race/ethnicity, poverty-income ratio, fasting duration, and log-transformed urinary creatinine concentration