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Supplemental Material

Association of Prenatal Exposure to Organophosphate, Pyrethroid, and Neonicotinoid Insecticides with Child Neurodevelopment at 2 Years of Age: A Prospective Cohort Study

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Table S1. Differences on the demographic characteristics of mother-child pairs among the recruited population (N = 5112), the population of their children completing the evaluation of Bayley scales at two years old (N = 2782), and the study population (N = 1041) from Wuhan, China, 2014–2017.

Table S2. China Recommendations for total weight gain during pregnancy, by pre-pregnancy body mass index (BMI).

Table S3. Related information for target analytes (Li et al., 2022; Mahai et al., 2022).

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Table S9. Weighted quantile sum regression (WQSR) analysis for the associations of weighted quantile sum regression index of pesticide biomarkers [based on the concentrations in the 1st trimester (N = 553 participants, n = 553 samples) and the averaged concentrations over the three trimesters (N = 553 participants, n = 1659 samples)] with boy's MDI scores estimated in the repeated holdout validation in participants from a birth cohort study in Wuhan, China, 2014–2017 (Data correspond to Figure 3).

Table S10. Weighted quantile sum regression (WQSR) analysis for the associations of weighted quantile sum regression index of pesticide biomarkers [based on the concentrations in the 1st trimester (N = 553 participants, n = 553 samples) and the averaged concentrations over the three trimesters (N = 553 participants, n = 1659 samples)] with boy's PDI scores (n = 553) estimated in the repeated holdout validation in participants from a birth cohort study in Wuhan, China, 2014–2017.

Table S11. Comparison of the exposure levels and the associations of prenatal exposure to OPPs and PYRs (characterized by biomarkers) with child neurodevelopment observed in our study with other studies.

References

Additional File- Excel Document

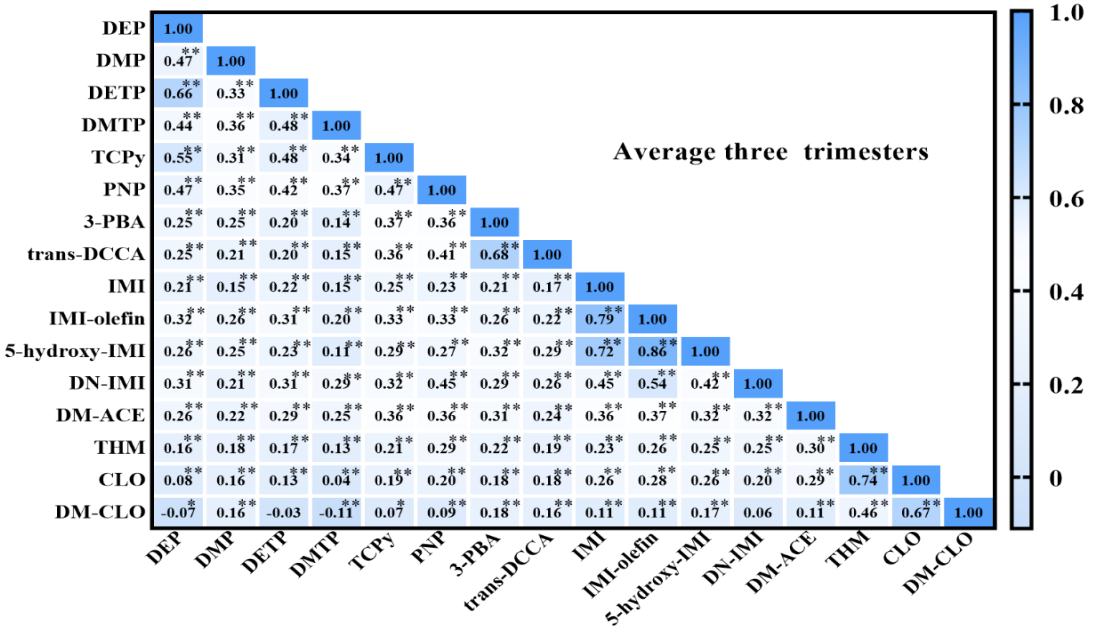

Figure S1. Spearman's rank correlation analysis was conducted to explore the correlation matrix of the urinary specific gravity (SG)-adjusted concentrations of mOPPs, mPYRs, and mNNIs. Correlation matrix of analytes based on the averaged concentrations over the three trimesters among participants from a birth cohort study in Wuhan, China, 2014–2017 (*N* = 1041 participants, *n* = 3123 samples). *p < 0.05; **p < 0.01. The correlation coefficients ≥0.8 were considered to indicate strong correlation, 0.5–0.8 were moderate, 0.3–0.5 were weak, and <0.3 were with no correlation (Rumsey, 2011). Details of chemical abbreviations are provided in Table S3 and the numerical values are listed in Excel Table S2.

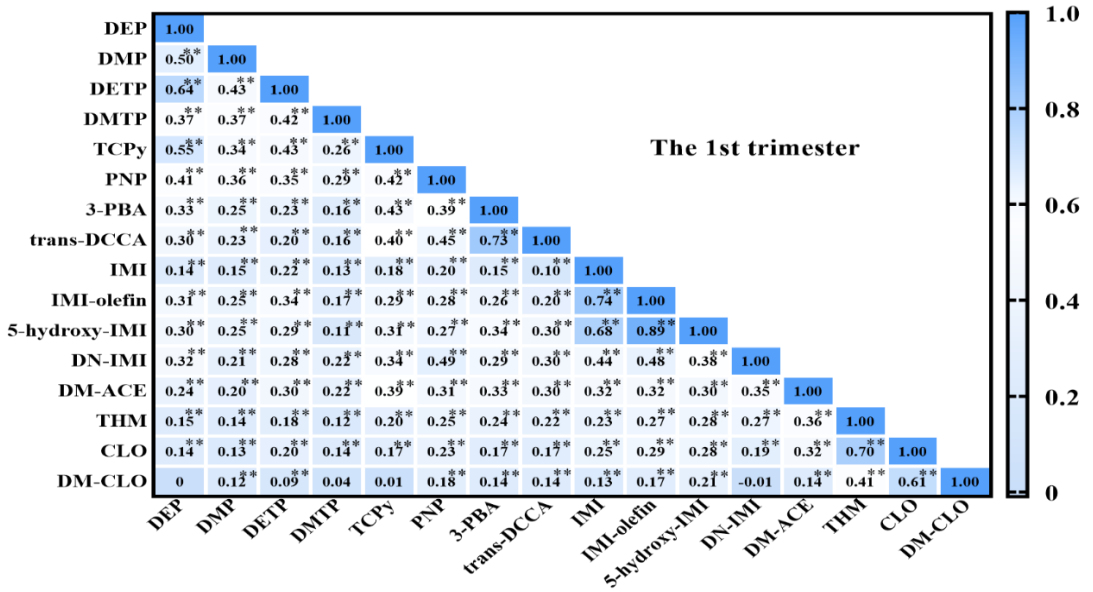

Figure S2. Spearman's rank correlation analysis was conducted to explore the correlation matrix of the urinary specific gravity (SG)-adjusted concentrations of mOPPs, mPYRs, and mNNIs. Correlation matrix of analytes based on the concentrations in the 1st trimester among the participants from a birth cohort study in Wuhan, China, 2014–2017 (*N* = 1041 participants, *n* = 1041 samples). *p < 0.05; **p < 0.01. Details of chemical abbreviations are provided in Table S3 and the numerical values are listed in Excel Table S3.

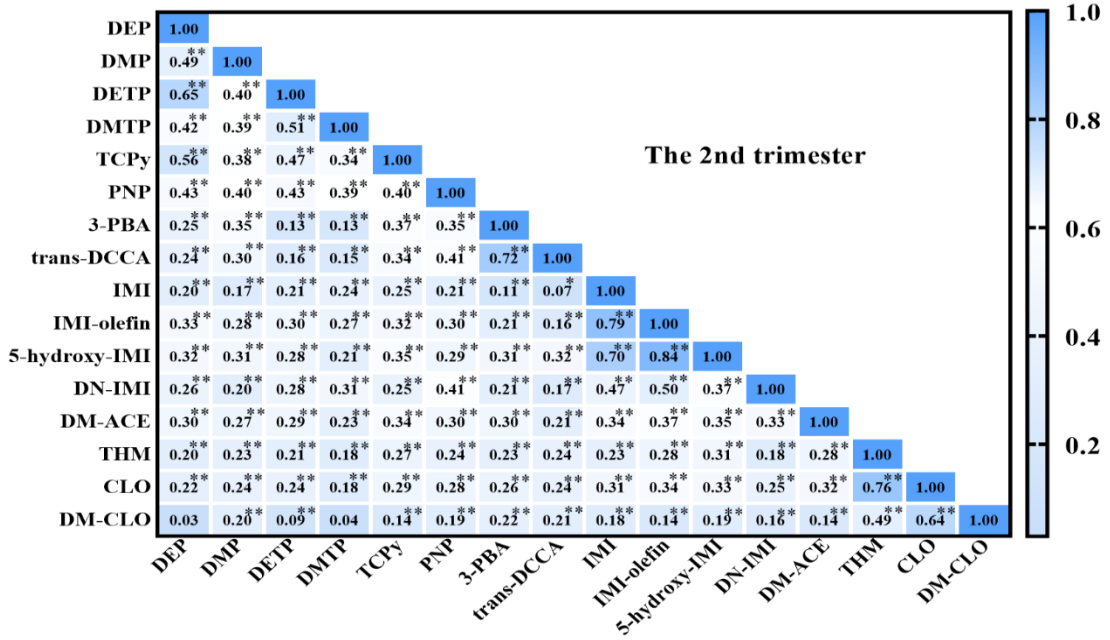

Figure S3. Spearman's rank correlation analysis was conducted to explore the correlation matrix of the urinary specific gravity (SG)-adjusted concentrations of mOPPs, mPYRs, and mNNIs. Correlation matrix of analytes based on the concentrations in the 2nd trimester among the participants from a birth cohort study in Wuhan, China, 2014–2017 (*N* = 1041 participants, *n* = 1041 samples). *p < 0.05; **p < 0.01. Details of chemical abbreviations are provided in Table S3 and the numerical values are listed in Excel Table S4.

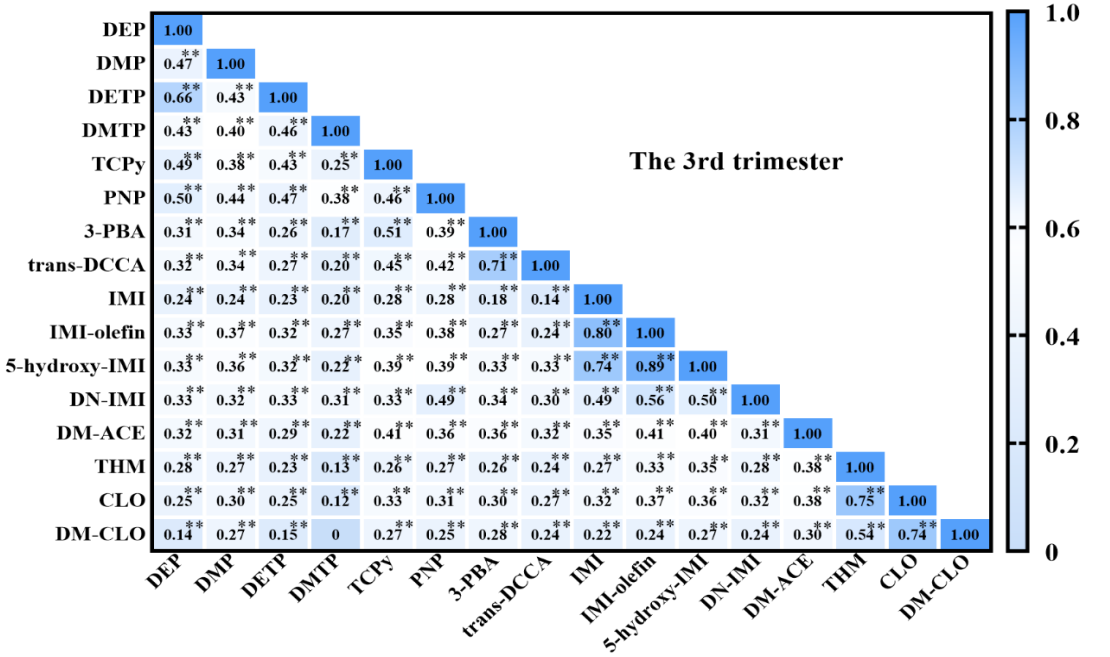

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Table S1. Differences on the demographic characteristics of mother-child pairs among the recruited population (*N* = 5112), the population of their children completing the evaluation of Bayley scales at two years old (*N* = 2782), and the study population (*N* = 1041) from Wuhan, China, 2014–2017.

Characteristic	Total population recruited (*N* = 5112)	Population completing the evaluation of Bayley scales (*N* = 2782)	Study Population (*N* = 1041)	*p*-value
	N (%) or Mean ± SD	N (%) or Mean ± SD	N (%) or Mean ± SD	
Total	5112	2782	1041	
Maternal characteristics				
Age at delivery (years)	29.1 ± 3.71	29.1 ± 3.67	29.4 ± 3.68	0.14
<25	392 (7.67%)	196 (7.05%)	60 (5.80%)	
25–29	2806 (54.9%)	1538 (55.3%)	548 (52.6%)	
30–34	1465 (28.7%)	802 (28.8%)	330 (31.7%)	
≥35	449 (8.78%)	246 (8.84%)	103 (9.90%)	
Pre-pregnancy BMI (kg/m^2)	20.9 ± 2.88	21.0 ± 2.89	21.1 ± 2.91	0.90
<18.5	999 (19.5%)	556 (19.9%)	195 (18.7%)	
18.5–23.9	3404 (66.6%)	1840 (66.2%)	694 (66.7%)	
≥24	709 (13.9%)	386 (13.9%)	152 (14.6%)	
Maternal education level				0.87
≤High-school degree	1074 (21%)	562 (20.2%)	214 (20.6%)	
Bachelor's degree	3731 (73%)	2061 (74.1%)	763 (73.3%)	
≥Master's degree	307 (6.01%)	159 (5.72%)	64 (6.1%)	
Household income (CNY)				0.22
<50,000	612 (12%)	334 (12.0%)	120 (11.5%)	
50,000–100,000	1725 (33.7%)	992 (35.7%)	384 (36.9%)	
≥100,000	2775 (54.3%)	1456 (52.3%)	537 (51.6%)	
Parity				0.13
Nulliparous	3945 (77.2%)	2220 (79.8%)	806 (77.4%)	
Multiparous	1167 (22.8%)	562 (20.2%)	235 (22.6%)	
Delivery mode				0.32
Vaginal delivery	2447 (47.9%)	1381 (49.6%)	507 (48.7%)	
Cesarean delivery	2665 (52.1%)	1401 (50.4%)	534 (51.3%)	
GWG categories according to NHC				0.22
Inadequate total GWG	734 (14.4%)	422 (15.2%)	165 (15.9%)	
Adequate total GWG	1997 (39.1%)	1110 (39.9%)	428 (41.2%)	
Excessive total GWG	2381 (46.6%)	1250 (44.9%)	447 (42.9%)	
Passive smoking during pregnancy				0.36
Yes	1188 (23.2%)	673 (24.2%)	261 (25.1%)	
No	3924 (76.8%)	2109 (75.8%)	780 (74.9%)	
Folic acid supplement during pregnancy				0.44
Yes	4529 (88.6%)	2478 (89.1%)	912 (87.6%)	
No	583 (11.4%)	304 (10.9%)	129 (12.4%)	
Maternal anemia				0.13
Yes	279 (5.46%)	136 (4.89%)	42 (4.0%)	

Characteristic	Total population recruited (*N* = 5112)	Population completing the evaluation of Bayley scales (*N* = 2782)	Study Population (*N* = 1041)	*p*-value
	N (%) or Mean ± SD	N (%) or Mean ± SD	N (%) or Mean ± SD	
No	4833 (94.5%)	2646 (95.1%)	999 (96.0%)	
Hypertension in pregnancy				0.51
Yes	145 (2.84%)	70 (2.52%)	24 (2.30%)	
No	4967 (97.2%)	2712 (97.5%)	1017 (97.7%)	
Gestational diabetes				0.94
Yes	482 (9.43%)	269 (9.67%)	98 (9.40%)	
No	4630 (90.6%)	2513 (90.3%)	943 (90.6%)	
Paternal education level				0.25
≤High-school degree	1195 (23.4%)	639 (23.0%)	209 (20.1%)	
Bachelor's degree	3682 (72%)	2017 (72.5%)	783 (75.2%)	
≥Master's degree	235 (4.6%)	126 (4.53%)	49 (4.70%)	
Child characteristics				
Child's sex				0.97
Boy	2700 (52.8%)	1466 (52.7%)	553 (53.1%)	
Girl	2412 (47.2%)	1316 (47.3%)	488 (46.9%)	
Birth weight (g)	3337 ± 434	3355 ± 424	3355 ± 424	0.83
<2500 (low birth weight)	128 (2.5%)	68 (2.44%)	21 (2.02%)	
2500–4000	4678 (91.5%)	2558 (92.0%)	956 (91.8%)	
>4000	306 (5.99%)	156 (5.61%)	64 (6.15%)	
Gestational age (wks)	39.3 ± 1.2	39.3 ± 1.16	39.4 ± 1.1	0.73
<37 (preterm birth)	158 (3.09%)	80 (2.88%)	28 (2.70%)	
≥37	4954 (96.9%)	2702 (97.1%)	1013 (97.3%)	
Breastfeeding duration (months)				0.32
<6	2239 (45.2%)	1250 (46.3%)	437 (43.2%)	
≥6	2714 (54.8%)	1449 (53.7%)	574 (56.8%)	
Missing	159	83	30	

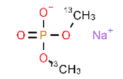
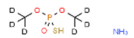
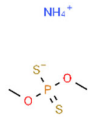
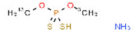
Abbreviations: SD, standard deviation; BMI, body mass index; GWG, gestational weight gain; NHC, National Health Commission of the People's Republic of China. Values are mean ± standard deviation or numbers (percentage). *p*-values were derived from Chi-square test, *p*-values < 0.05 were considered statistically significant.

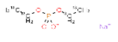
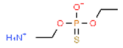
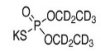
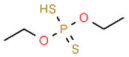
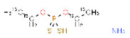
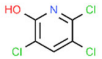
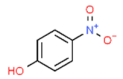
Table S2. China Recommendations for total weight gain during pregnancy, by pre-pregnancy body mass index (BMI).

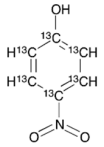
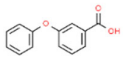
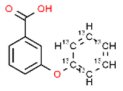
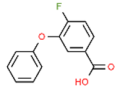
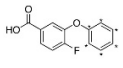
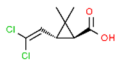
PBMI	GWG (kg)		
	Inadequate	Recommended	Excessive
Underweight (<18.5 kg/m^2)	<12.5	12.5–18	>18
Normal weight (18.5–23.9 kg/m^2)	<11.5	11.5–16	>16
Overweight (24.0–27.9 kg/m^2)	<7	7–11.5	>11.5
Obese (≥28.0 kg/m^2)	<5	5–9	>9

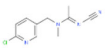
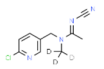
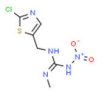
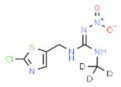
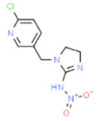
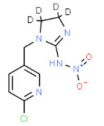
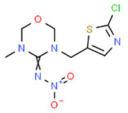
Abbreviations: BMI, body mass index; GWG, gestational weight gain; GWG (kg) for different PBMI (kg/m^2) is divided into three groups based on recommendation of the National Health Commission of the People's Republic of China (NHC, 2022)

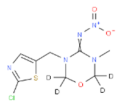
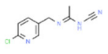
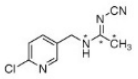
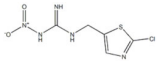
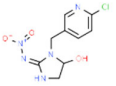
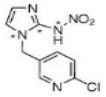
Table S3. Related information for target analytes (Li et al., 2022; Mahai et al., 2022).

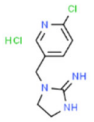
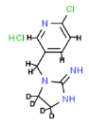
Abbreviation	Full name of the analyte	LOQ; MDL (ng/mL)	Catalog No.	Purity (%)	CAS No.	#LogKow; logP	Formula	Structure	Parent m/z	Product ① m/z	Product ② m/z	DP (V)	CE (eV)	RT
The metabolites of OPPs														
DMP	Dimethyl phosphate	0.05; 0.25	TRC D476995	98.0	813-78-5	-0.66; -0.99	C2H7O4P		125	78.95	63	-30	-33, -22	1.93
DMP-13C2	Dimethyl Phosphate-13C2 Sodium Salt	/	TRC D477603	95%	157487-95-1	/	$^{13}C_2H_6NaO_4P$		127	78.95	63	-35	-33, -22	1.93
DMTP	Dimethyl thiophosphate	0.05; 0.25	TRC D495418	95%	1112-38-5	1.11; -0.38	$C_2H_7O_3PS$		141	125.95	94.9; 95.9	-20	-20, -27	2.66
DMTP-d6	O, O-Dimethyl Phosphorothionate-d6 Ammonium Salt	/	TRC D477622	97%	1330162-95-2	/	$C_2H_4D_6NO_3PS$		147	129	96.9; 94.9; 78.9	-20	-21, -28	2.64
DMDTP	Ammonium O, O-dimethyl phosphorodithioate	0.05; 0.25	TRC D472740	97%	1066-97-3	1.26; 0.65	C2H10NO2PS2		157	141.95	111.9; 78.95	-35	-22, -28	3.58
DMDTP-13C2	O, O-Bis[(13C) methyl] hydrogen phosphorodithioate ammoniate (1:1)	/	TRC D472742	96%	1329610-82-3	/	13C2H10NO2PS2		159	143	112; 78.95	-35	-22, -28	3.58
DEP	Diethyl phosphate	0.05; 0.25	TRC P359430	95%	598-02-7	0.32; 0.08	C4H11O4P		153.05	78.95	125	-20	-26, -15	5.5

Abbreviation	Full name of the analyte	LOQ; MDL (ng/mL)	Catalog No.	Purity (%)	CAS No.	#LogKow; logP	Formula	Structure	Parent m/z	Product ① m/z	Product ② m/z	DP (V)	CE (eV)	RT
DEP-$^{13}C_4$	Diethyl Phosphate-13C4 Sodium Salt	/	TRC D444722	95%	1329613-90-2	/	13C4H10NaO4P		157.1	78.95;	127	-20	-26, -15	5.5
DETP [a]	O, O-Diethyl Thiophosphate Ammonium Salt	0.01; 0.05	TRC D445120	98%	5871-16-9	2.09; 0.68	$C_4H_{14}NO_3PS$		169	94.9	141	-30	-25, -17	7.38
DETP-d10	O, O-Diethyl thiophosphate potassium salt (diethyl-d10,98%) 100 μg/mL in Methanol	/	CIL, DLM-4852-1.2	98.0%	1435934-31-8	/	C4D10KO3PS		179	94.9	147	-30	-27, -20	7.23
DEDTP	O, O-Diethyl dithiophosphate	0.05; 0.25	TRC D444340	>80%	298-06-6	2.24; 1.72	C4H11O2PS2		185	110.9	157	-35	-24, -18	8.28
DEDTP-$^{13}C_4$	O, O-Diethyl Dithiophosphate-13C4 Ammonium Salt		TRC D444267	95.0%	1329641-22-6	/	13C4H14NO2PS2		189	110.9	159	-35	-24, -18	8.28
TCPy	3,5,6-trichloro-2-pyridinol	0.20; 0.10	TRC T773860	98.0%	6515-38-4	1.22; 2.16	C5H2Cl3NO		195.9; 197.9	35	37	-30	-43	8.57
$^{13}C_3$-TCPY	3,5,6-Trichloro-2-pyridinol-13C5	/	TRC T773862	95.0%	1330171-47-5	/	$^{13}C_5H_2Cl_3NO$		199.1; 200.95	34.97	34.97	-40	-40, -15	8.57
PNP	4-Nitrophenol	0.05; 0.25	TRC N496945	98.0	100-02-7	/	$C_6H_5NO_3$		138	108	92;46; 66	-30	-21, -25	7.25

Abbreviation	Full name of the analyte	LOQ; MDL (ng/mL)	Catalog No.	Purity (%)	CAS No.	#LogKow; logP	Formula	Structure	Parent m/z	Product ① m/z	Product ② m/z	DP (V)	CE (eV)	RT
PNP-$^{13}C_6$	4-Nitrophenol-13C6	/	TRC N496909	98.0	/	/	$^{13}C_6H_5NO_3$		144	114	98	-40	-24, -31	7.25
The metabolites of PYRs														
3-PBA	3-Phenoxybenzoic Acid	0.02; 0.01	TRC P228010	98.0	3739-38-6	3.93; 3.91	$C_{13}H_{10}O_3$		213	93	169	-35	-28 -17	8.82
3-PBA-$^{13}C_6$	3-(Phenoxy-13C6) benzoic Acid	/	TRC P228012	97.0	1793055-05-6	/	$C_7{}^{13}C_6H_{10}O_3$		219.15	99	175.1	-35	-22, -15 -28	8.82
4F-3PBA	4-Fluoro-3-phenoxy-benzoic acid	0.02; 0.01	DRE-XA13797500AL	98.4	77279-89-1	3.29; 4.05	$C_{13}H_9FO_3$		231	186.95	92.95	-35	-20; -31	8.84
$^{13}C_6$-4F-3PBA	4-Fluoro-3-phenoxy-benzoic acid-13C6	/	CLM-7389-1.2	98	/	/	C7*C6H9FO3		237.1	193.1	99.05	-35	-20, -31	8.84
trans-DCCA	Trans-3-(2,2-Dichloroethenyl)-2,2-dimethylcyclopropanecarboxylic acid	0.04; 0.02	TRC P287705	98	59042-50-1	3.38; 2.53	$C_8H_{10}Cl_2O_2$		207; 209	35	37	-40	-35	8.85
$^{13}C_2$-trans-DCCA	TRANS-DCCA 100 UG/ML IN ACETONITRILE-D3 (1, CARBOXYL-13C2, 99%;1-D, 97%)	/	CDLM-9206-1.2	97.0	/	/	C6*C2H9DCl2O2		210; 212	35	37	-30	-40; -39; -37	8.85

Abbreviation	Full name of the analyte	LOQ; MDL (ng/mL)	Catalog No.	Purity (%)	CAS No.	#LogKow; logP	Formula	Structure	Parent m/z	Product ① m/z	Product ② m/z	DP (V)	CE (eV)	RT
NNIs and their metabolites														
ACE	Acetamiprid	0.02; 0.01	TRC A150800	99.7	135410-20-7	2.55; 0.62	C10H11ClN4		223.05	126.05	56.1	40	27, 19	6.89
ACE-d3	Acetamiprid-d3	/	TRC A150802	99.5	1353869-35-8	/	$C_{10}H_8D_3ClN_4$		226.1	125.9	/	40	27	6.88
CLO	Clothianidin	0.10; 0.05	TRC C588500	99.8	210880-92-5	0.64; 0.4	C6H8ClN5O2S		250.02	169.1	132	20	18, 20	6.49
CLO-d3	Clothianidin-d3	/	Sigma 56816	97	1262776-24-8	0.64; -0.15	C6H5D3ClN5O2S		253.1	172.1	132	25	16, 19	6.49
IMI	Imidacloprid	0.05; 0.025	TRC I274990	98	138261-41-3	-0.41; -0.86	C9H10ClN5O2		256.05	209.1	175.1	30	21, 27	6.7
IMI-d4	Imidacloprid-d4	/	TRC I274992	99.8	1015855-75-0	-0.43; /	$C_9H_6D_4ClN_5O_2$		260.1	213.1	179.05	40	23, 27	6.68
THM	Thiamethoxam	0.05; 0.025	TRC T344180	98	153719-23-4	0.8; -1.16	$C_8H_{10}ClN_5O_3S$		292	211.1	132.05	25	17, 30	6.04

Abbreviation	Full name of the analyte	LOQ; MDL (ng/mL)	Catalog No.	Purity (%)	CAS No.	#LogKow; logP	Formula	Structure	Parent m/z	Product ① m/z	Product ② m/z	DP (V)	CE (eV)	RT
THM-d4	Thiamethoxam-d_4	/	TRC T344182	99.5	1331642-98-8	/; -1.16	$C_8H_6D_4ClN_5O_3S$		296.15	215.1	183.1	40	18, 31	6.03
DM-ACE	Desmethyl-acetamiprid	0.02; 0.01	Sigma 32979	99.4	190604-92-3	2.34; /	$C_9H_9ClN_4$		209.05	126.05	90.05	40	23, 44	6.49
DM-ACE-$^{13}C_2{}^{15}N$	Desmethyl-acetamiprid-$^{13}C_2{}^{15}N$	/	CNLM-10862-1.2	98	/	/	$C_7{}^{13}C_2H_9ClN_3{}^{15}N$		212.1	126.1	99	40	22, 46	6.48
DM-CLO	Desmethyl-clothianidin*	0.02; 0.01	TRC C597070	98	135018-15-4	/	$C_5H_6ClN_5O_2S$		234	57.95	152	-40	-20, -14	6.12
5-hydroxy-IMI	5-Hydroxy-imidacloprid$^{\Phi}$	0.10; 0.05	CFW-PN356900U	99.6	155802-61-2	-0.98; /	$C_9H_{10}ClN_5O_3$		272.1	191.1	225.1	35	23, 25	6.13
IMI-olefin	Imidacloprid-olefin	0.05; 0.025	TRC I274995	96	115086-54-9	1.4; /	$C_9H_8ClN_5O_2$		251.97	205	81	-30	-17, -15	5.95
IMI-olefin-$^{15}N_2{}^{13}C$	Imidacloprid-olefin-$^{15}N_2{}^{13}C$	/	CNLM-10866-1.2	97	/	/	$C_8{}^{13}CH_8ClN_3{}^{15}N_2O_2$		255.2	208	84	-20	-17, -15	5.94

Abbreviation	Full name of the analyte	LOQ; MDL (ng/mL)	Catalog No.	Purity (%)	CAS No.	#LogKow; logP	Formula	Structure	Parent m/z	Product ① m/z	Product ② m/z	DP (V)	CE (eV)	RT
DN-IMI	Desnitro-imidacloprid	0.005; 0.025	Sigma 37052	98	127202-53-3	/	$C_9H_{12}Cl_2N_4$		211.07	126.05	90.05	50	31, 47	7.44
DN-IMI-d4	Desnitro-imidacloprid-d4	/	QCC QI591805	98	/	/	$C_9H_8D_4Cl_2N_4$		215.16	126.1	90.1	70	31, 48	7.42

QCC means it was purchased from QUALITY CONTROL CHEMICALS INC., Newark, DE, USA. DRE means it was purchased from Dr. Ehrenstorfer GmbH, Augsburg, Gerany. Sigma means it was purchased from Sigma (Sigma-Aldrich Corp. St. Louis, MO, USA); CFW means it was purchased from CFW LABORATORIES, INC., Newark, DE, USA. CLM/CNLM means it was purchased from Cambridge Isotope Laboratories, Inc (Andover, MA); Cayman means it was purchased from Cayman Chemical (Ann Arbor, Michigan, USA); Other standards and the isotope labeled internal standards were all obtained from Toronto Research Chemical (North York, Ontario, Canada).

#The log Kow values for the analytes were from ChemSpider (http://www.chemspider.com/).

[a] Standards of DETP was of salt form, and the corresponding urinary free acid form concentration was calculated using the following formula: $UC_f=UCs*MW_f/MWs$, where UC_f was urinary free acid form concentration, UCs was urinary salt form concentration, MW_f was molecular weight of free acid form, and MWs was molecular weight of salt form.

※Φ* means that for target analytes with no their corresponding internal standard, they share the internal standards of $^{13}C_2$-trans-DCCA, imidacloprid-d4, and Imidacloprid-olefin-$^{15}N_2{}^{13}C$, respectively.

Product① was used for quantification, and Product② for confirmation.

DP: declustering potential. CE: collision energy. RT: retention time. LOQ: limit of quantification. MDL: method detection limit.

The MDLs of DAPs, DN-IMI, and PNP were calculated based on the LOQs and the dilution factor (1: 5) while the MDLs of other analytes were calculated based on the LOQs and the dilution factor (2: 1).

Table S4. The gradient of mobile phase (flow rate = 0.30 mL/min) for the analysis of target analytes (**except for** DAPs, PNP, and DN-IMI).

Time (min)	0.05% formic acid in water (%, A)	acetonitrile (%, B)
0	98	2
1	96	4
9	1	99
11.4	1	99
11.5	98	2
14.5	98	2

Table S5. The gradient of mobile phase (flow rate = 0.25 mL/min) for the analysis of DAPs, PNP, and DN-IMI.

Time (min)	0.05% formic acid in water (%, A)	methanol (%, B)
0	99	1
1	97	3
6	70	30
8.5	1	99
11.0	1	99
11.1	99	1
14.5	99	1

Table S6. The distribution of the Bayley scores (means ± SD) at two years of age based on the average urinary concentrations (ng/mL) of insecticide biomarkers throughout pregnancy for participants from a birth cohort study in Wuhan, China, 2014–2017 (*N* = 1041 participants, *n* = 3123 samples).

Compound (ng/mL)	**MDI score, mean ± SD**	**PDI score, mean ± SD**
mOPPs		
DEP		
Quartile1 (≤2.53)	110 ± 21.3	110 ± 16.7
Quartile2 (2.53-3.97)	111 ± 21.7	110 ± 17.5
Quartile3 (3.97-6.32)	110 ± 22.7	111 ± 16.6
Quartile4 (≥6.32)	109 ± 21.5	112 ± 17.5
DMP		
Quartile1 (≤2.97)	109 ± 21.4	109 ± 16.3
Quartile2 (2.97-4.79)	111 ± 21.0	110 ± 17.2
Quartile3 (4.79-7.78)	109 ± 23.1	111 ± 16.5
Quartile4 (≥7.78)	111 ± 21.5	114 ± 18.0
DETP		
Quartile1 (≤1.11)	110 ± 22.6	112 ± 17.0
Quartile2 (1.11-1.88)	111 ± 20.5	110 ± 17.3
Quartile3 (1.88-3.29)	109 ± 22.3	110 ± 16.4
Quartile4 (≥3.29)	110 ± 21.7	112 ± 17.6
DMTP		
Quartile1 (≤0.34)	109 ± 21.9	110 ± 15.3
Quartile2 (0.34-0.57)	110 ± 21.6	112 ± 18.3
Quartile3 (0.57-1.07)	110 ± 22.7	110 ± 17.1
Quartile4 (≥1.07)	109 ± 21.0	112 ± 17.4
TCPy		
Quartile1 (≤1.29)	111 ± 21.1	111 ± 17.4
Quartile2 (1.29-1.87)	111 ± 22.9	111 ± 16.0
Quartile3 (1.87-2.67)	111 ± 20.7	111 ± 17.7
Quartile4 (≥2.67)	108 ± 22.2	111 ± 17.2
PNP		
Quartile1 (≤1.53)	110 ± 20.6	112 ± 17.2
Quartile2 (1.53-2.35)	112 ± 21.2	109 ± 16.3
Quartile3 (2.35-3.49)	110 ± 22.1	110 ± 17.4
Quartile4 (≥3.49)	107 ± 22.9	113 ± 17.2
mPYRs		
3-PBA		
Quartile1 (≤0.11)	110 ± 21.9	110 ± 17.0
Quartile2 (0.11-0.19)	111 ± 22.0	111 ± 15.7
Quartile3 (0.19-0.38)	112 ± 21.3	112 ± 16.7
Quartile4 (≥0.38)	107 ± 21.6	111 ± 18.7
trans-DCCA		
Quartile1 (≤0.14)	111 ± 20.5	111 ± 16.1
Quartile2 (0.14-0.24)	111 ± 22.3	111 ± 16.6
Quartile3 (0.24-0.43)	109 ± 22.3	110 ± 17.5
Quartile4 (≥0.43)	108 ± 21.9	111 ± 18.0
mNNIs		
IMI		
Quartile1 (≤0.03)	109 ± 21.7	110 ± 16.8

Compound (ng/mL)	**MDI score, mean ± SD**	**PDI score, mean ± SD**
Quartile2 (0.03-0.05)	109 ± 23.4	110 ± 17.8
Quartile3 (0.05-0.09)	111 ± 21.4	112 ± 16.9
Quartile4 (≥0.09)	111 ± 20.4	112 ± 16.8
IMI-olefin		
Quartile1 (≤0.31)	110 ± 22.3	109 ± 16.9
Quartile2 (0.31-0.53)	109 ± 22.0	111 ± 16.8
Quartile3 (0.53-1.01)	110 ± 22.9	111 ± 17.8
Quartile4 (≥1.01)	112 ± 19.8	112 ± 16.7
5-hydroxy-IMI		
Quartile1 (≤0.48)	109 ± 22.2	110 ± 17.1
Quartile2 (0.48-0.93)	109 ± 22.7	111 ± 17.2
Quartile3 (0.93-1.79)	111 ± 22.2	111 ± 17.3
Quartile4 (≥1.79)	110 ± 20.0	112 ± 16.6
DN-IMI		
Quartile1 (≤0.06)	110 ± 21.3	110 ± 17.0
Quartile2 (0.06-0.11)	110 ± 21.5	110 ± 17.1
Quartile3 (0.11-0.22)	110 ± 22.3	113 ± 16.5
Quartile4 (≥0.22)	109 ± 22.0	111 ± 17.5
DM-ACE		
Quartile1 (≤0.70)	109 ± 21.9	111 ± 16.7
Quartile2 (0.70-1.13)	112 ± 20.7	110 ± 17.2
Quartile3 (1.13-0.23)	108 ± 22.4	111 ± 16.8
Quartile4 (≥0.23)	111 ± 21.9	112 ± 17.5
THM		
Quartile1 (≤0.06)	107 ± 23.3	110 ± 16.4
Quartile2 (0.06-0.11)	111 ± 21.5	110 ± 17.8
Quartile3 (0.11-0.23)	111 ± 21.2	111 ± 17.5
Quartile4 (≥0.23)	111 ± 20.9	113 ± 16.4
CLO		
Quartile1 (≤0.09)	107 ± 23.3	108 ± 16.9
Quartile2 (0.09-0.15)	110 ± 21.8	111 ± 17.4
Quartile3 (0.15-0.27)	109 ± 22.4	110 ± 16.9
Quartile4 (≥0.27)	113 ± 18.9	114 ± 16.7
DM-CLO		
Quartile1 (≤0.17)	106 ± 22.6	109 ± 17.7
Quartile2 (0.17-0.34)	108 ± 23.0	110 ± 18.6
Quartile3 (0.34-0.58)	114 ± 19.9	113 ± 15.5
Quartile4 (≥0.58)	112 ± 20.6	113 ± 15.9

Abbreviation: SD, standard deviation; MDI, mental development index; PDI, psychomotor development index. Details of chemical abbreviations are provided in Table S3.

Table S7. Multivariate linear regression model evaluating associations between the average SG-adjusted maternal urinary analytes concentrations (ln-transformed, ng/mL) over three trimesters and children's MDI and PDI at two years of age in participants from a birth cohort study in Wuhan, China, 2014–2017 (*N* = 1041 participants, *n* = 3123 samples, data correspond to Figure 1).

Compounds (ng/mL)	MDI										PDI									
	All (*n* = 1041)			Male (*n* = 553)			Female (*n* = 488)			$P_{sex\text{-}int}$	All (*n* = 1041)			Male (*n* = 553)			Female (*n* = 488)			$P_{sex\text{-}int}$
	β (95% CI) [a]	*P*	*P-FDR*	β (95% CI) [b]	*P*	*P-FDR*	β (95% CI) [b]	*P*	*P-FDR*		β (95% CI) [a]	*P*	*P-FDR*	β (95% CI) [b]	*P*	*P-FDR*	β (95% CI) [b]	*P*	*P-FDR*	
mOPPs																				
DEP	-1.78 (-3.83, 0.27)	0.09	0.24	**-3.79 (-6.77, -0.81)**	0.01	0.04	0.60 (-2.21, 3.41)	0.68	0.78	0.04	-0.82 (-2.48, 0.83)	0.33	0.58	**-2.41 (-4.69, -0.13)**	0.04	0.20	1.56 (-0.89, 4.01)	0.21	0.40	0.02
DMP	1.11 (-0.81, 3.04)	0.26	0.41	0.25 (-2.56, 3.06)	0.86	0.86	1.98 (-0.63, 4.58)	0.14	0.77	0.40	**1.97 (0.43, 3.52)**	0.01	0.20	1.51 (-0.64, 3.65)	0.17	0.39	**2.64 (0.37, 4.91)**	0.02	0.35	0.42
DETP	-1.06 (-2.83, 0.70)	0.24	0.41	**-2.94 (-5.58, -0.29)**	0.03	0.08	0.92 (-1.40, 3.24)	0.44	0.77	0.04	-0.92 (-2.34, 0.50)	0.21	0.47	-2.01 (-4.03, 0.01)	0.05	0.20	0.51 (-1.52, 2.53)	0.62	0.77	0.13
DMTP	-0.54 (-2.15, 1.06)	0.51	0.67	-1.25 (-3.64, 1.13)	0.30	0.44	0.37 (-1.76, 2.50)	0.73	0.78	0.28	0.24 (-1.06, 1.53)	0.72	0.77	-0.79 (-2.61, 1.03)	0.40	0.59	1.60 (-0.25, 3.46)	0.09	0.35	0.10
TCPy	**-2.82 (-5.28, -0.35)**	0.03	0.19	**-5.51 (-9.13, -1.90)**	0.003	0.02	0.69 (-2.64, 4.02)	0.68	0.78	0.01	-0.76 (-2.75, 1.23)	0.46	0.66	-2.46 (-5.24, 0.32)	0.08	0.26	1.97 (-0.94, 4.87)	0.18	0.40	0.03
PNP	-2.21 (-4.51, 0.09)	0.06	0.19	**-4.50 (-7.97, -1.02)**	0.01	0.04	-0.03 (-3.05, 2.99)	0.99	0.99	0.05	0.14 (-1.71, 2.00)	0.88	0.88	-1.82 (-4.49, 0.85)	0.18	0.39	2.57 (-0.05, 5.20)	0.05	0.35	0.03
mPYRs																				
3-PBA	-0.97 (-2.46, 0.52)	0.20	0.40	-2.22 (-4.46, 0.01)	0.05	0.12	0.48 (-1.47, 2.44)	0.63	0.78	0.07	-0.30 (-1.50, 0.90)	0.62	0.73	-1.12 (-2.84, 0.59)	0.20	0.39	0.81 (-0.90, 2.52)	0.35	0.51	0.09
trans-DCCA	**-1.63 (-3.16, -0.11)**	0.04	0.19	**-3.50 (-5.78, -1.22)**	0.003	0.02	0.43 (-1.59, 2.45)	0.68	0.78	0.01	-1.15 (-2.38, 0.08)	0.07	0.44	**-2.18 (-3.93, -0.44)**	0.01	0.20	0.08 (-1.68, 1.84)	0.93	0.96	0.05
mNNIs																				
IMI	0.33 (-1.04, 1.70)	0.64	0.73	-0.59 (-2.65, 1.47)	0.58	0.71	1.13 (-0.66, 2.92)	0.22	0.77	0.21	0.27 (-0.83, 1.38)	0.63	0.73	-0.35 (-1.93, 1.22)	0.66	0.77	0.97 (-0.60, 2.53)	0.22	0.40	0.29
IMI-olefin	0.48 (-1.09, 2.05)	0.55	0.67	-0.56 (-2.88, 1.75)	0.63	0.72	1.43 (-0.66, 3.52)	0.18	0.77	0.21	0.30 (-0.96, 1.56)	0.64	0.73	-0.32 (-2.09, 1.45)	0.72	0.77	1.07 (-0.76, 2.90)	0.25	0.40	0.29
5-hydroxy-IMI	0.01 (-1.46, 1.49)	0.98	0.98	-0.99 (-3.19, 1.21)	0.38	0.50	0.93 (-1.02, 2.88)	0.35	0.77	0.20	0.47 (-0.72, 1.65)	0.44	0.66	0.35 (-1.33, 2.03)	0.68	0.77	0.62 (-1.08, 2.32)	0.48	0.63	0.81
DN-IMI	-0.88 (-2.22, 0.46)	0.20	0.40	-1.47 (-3.54, 0.60)	0.16	0.33	-0.68 (-2.38, 1.03)	0.44	0.77	0.49	0.70 (-0.38, 1.78)	0.20	0.47	0.01 (-1.58, 1.59)	0.99	0.99	1.27 (-0.21, 2.76)	0.09	0.35	0.24
DM-ACE	-0.71 (-2.37, 0.95)	0.40	0.58	-1.28 (-3.72, 1.17)	0.30	0.44	0.41 (-1.81, 2.63)	0.72	0.78	0.40	-0.67 (-2.00, 0.67)	0.33	0.58	-1.06 (-2.92, 0.81)	0.27	0.47	0.05 (-1.89, 1.99)	0.96	0.96	0.53
THM	0.12 (-1.10, 1.33)	0.85	0.91	-0.33 (-2.17, 1.51)	0.72	0.77	0.66 (-0.92, 2.25)	0.41	0.77	0.48	0.65 (-0.33, 1.63)	0.19	0.47	0.28 (-1.13, 1.68)	0.70	0.77	1.13 (-0.26, 2.51)	0.11	0.35	0.49
CLO	**1.54 (0.01, 3.07)**	0.05	0.19	1.27 (-1.08, 3.63)	0.29	0.44	1.90 (-0.06, 3.86)	0.06	0.77	0.82	1.01 (-0.23, 2.24)	0.11	0.44	0.76 (-1.04, 2.56)	0.40	0.59	1.24 (-0.47, 2.96)	0.16	0.40	0.80
DM-CLO	**1.77 (0.54, 3.01)**	0.005	0.08	**2.47 (0.67, 4.28)**	0.01	0.04	0.95 (-0.71, 2.62)	0.26	0.77	0.12	0.87 (-0.13, 1.87)	0.09	0.44	1.43 (-0.01, 2.82)	0.06	0.20	0.17 (-1.29, 1.62)	0.82	0.94	0.18

Abbreviation: DMP, dimethyl phosphate; DMTP, dimethyl thiophosphate; DEP, diethyl phosphate; DETP, diethyl thiophopshate; TCPy, 3,5,6-trichloro-2-pyridinol; PNP, para-nitrophenol; 3-PBA, 3-phenoxybenzoic acid; trans-DCCA, trans-3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid; IMI, imidacloprid; IMI-olefin, imidacloprid-olefin; 5-hydroxy-IMI, 5-Hydroxy-imidacloprid; DN-IMI, desnitro-imidacloprid; DM-ACE, desmethyl-acetamiprid; THM, thiamethoxam; CLO, clothianidin; DM-CLO, desmethyl-clothianidin.

[a] Multivariate linear regression (MLR) models, adjusted for maternal age (categorical), pre-pregnancy BMI (categorical), maternal education (categorical), passive smoking (categorical), folic acid supplement during pregnancy (categorical), parity (categorical), child sex (categorical), breastfeeding duration (categorical), and delivery mode (categorical). [b] Stratified analyses were adjusted for all the mentioned confounders except infant sex. *P*: *P* values before performing multiple comparison corrections, which were derived from MLR models (including the major analyses and sex-stratified analyses). *P-FDR*: false discovery rate (FDR)-corrected *P* values for multiple comparisons. $P_{sex\text{-}int}$ for the interaction term between prenatal insecticide exposures and child sex, which were derived from sex-interaction analyses. $P < 0.05$, $P\text{-}FDR < 0.05$, $P_{sex\text{-}int} < 0.05$ were considered statistically significant.

Table S8. Generalized estimating equation model evaluating trimester-specific associations between SG-adjusted maternal urinary analytes concentrations (ln-transformed, ng/mL) with children's MDI and PDI scores at two years of age in participants from a birth cohort study in Wuhan, China, 2014–2017 (*N* = 1041 participants, *n* = 1041 samples for 1st trimester, *n* = 1041 samples for 2nd trimester, *n* = 1041 samples for 3rd trimester, data correspond to Figure 2).

Compounds (ng/mL)	MDI										PDI									
	All (*n* = 1041)			Male (*n* = 553)			Female (*n* = 488)			$P_{sex\text{-}int}$	All (*n* = 1041)			Male (*n* = 553)			Female (*n* = 488)			$P_{sex\text{-}int}$
	β (95% CI) [a]	*P*	*P-FDR*	β (95% CI) [b]	*P*	*P-FDR*	β (95% CI) [b]	*P*	*P-FDR*		β (95% CI) [a]	*P*	*P-FDR*	β (95% CI) [b]	*P*	*P-FDR*	β (95% CI) [b]	*P*	*P-FDR*	
mOPPs																				
DEP																				
1st trimester	-1.00 (-2.52, 0.52)	0.20	0.39	-2.05 (-4.23, 0.14)	0.07	0.15	0.51 (-1.55, 2.58)	0.63	0.98	0.06	-0.26 (-1.48, 0.96)	0.68	0.90	-0.67 (-2.34, 1.01)	0.43	0.61	0.83 (-0.97, 2.63)	0.37	0.67	0.07
2nd trimester	-0.98 (-2.57, 0.61)	0.23	0.69	-2.29 (-4.59, 0.01)	0.05	0.35	0.16 (-1.98, 2.30)	0.88	0.98	0.06	0.24 (-1.04, 1.52)	0.71	0.90	-1.17 (-2.93, 0.58)	0.19	0.61	1.87 (-0.001, 3.74)	0.05	0.51	0.02
3rd trimester	-0.23 (-1.75, 1.30)	0.77	0.99	-0.47 (-2.69, 1.75)	0.68	0.74	0.27 (-1.76, 2.30)	0.79	0.90	0.18	-0.39 (-1.61, 0.84)	0.54	0.57	-0.82 (-2.52, 0.88)	0.34	0.68	0.34 (-1.43, 2.11)	0.71	0.71	0.09
DMP																				
1st trimester	-0.03 (-1.47, 1.41)	0.97	0.97	-0.77 (-2.92, 1.38)	0.48	0.64	0.79 (-1.09, 2.67)	0.41	0.95	0.28	0.61 (-0.55, 1.77)	0.31	0.56	0.24 (-1.40, 1.89)	0.77	0.82	1.19 (-0.44, 2.82)	0.15	0.49	0.16
2nd trimester	1.31 (-0.14, 2.77)	0.08	0.41	0.85 (-1.25, 2.96)	0.43	0.51	1.73 (-0.22, 3.68)	0.08	0.76	0.34	0.71 (-0.46, 1.88)	0.24	0.90	0.24 (-1.37, 1.85)	0.77	0.96	1.45 (-0.25, 3.14)	0.09	0.51	0.12
3rd trimester	0.56 (-0.82, 1.95)	0.43	0.85	0.34 (-1.63, 2.32)	0.73	0.74	0.92 (-0.98, 2.83)	0.34	0.51	0.42	**1.72 (0.60, 2.83)**	0.003	**0.04**	1.03 (-0.48, 2.54)	0.18	0.68	**2.56 (0.91, 4.22)**	0.002	**0.04**	0.09
DETP																				
1st trimester	-1.00 (-2.30, 0.30)	0.13	0.35	-1.66 (-3.57, 0.26)	0.09	0.16	0.02 (-1.69, 1.73)	0.98	0.98	0.22	-0.57 (-1.61, 0.48)	0.29	0.56	-1.32 (-2.79, 0.14)	0.08	0.24	0.60 (-0.89, 2.09)	0.43	0.68	0.12
2nd trimester	-0.29 (-1.56, 0.99)	0.66	0.99	-0.77 (-2.66, 1.12)	0.42	0.51	-0.01 (-1.67, 1.66)	1.00	1.00	0.48	-0.41 (-1.44, 0.61)	0.43	0.90	-1.45 (-2.89, 0.00)	0.05	0.39	0.74 (-0.71, 2.20)	0.32	0.65	0.04
3rd trimester	0.05 (-1.17, 1.27)	0.93	0.99	-0.87 (-2.72, 0.99)	0.36	0.66	0.69 (-0.86, 2.25)	0.38	0.51	0.24	0.21 (-0.77, 1.19)	0.68	0.68	-0.39 (-1.80, 1.02)	0.59	0.68	0.76 (-0.60, 2.12)	0.27	0.43	0.30
DMTP																				
1st trimester	-0.63 (-1.84, 0.58)	0.30	0.44	-0.67 (-2.49, 1.15)	0.47	0.64	-0.50 (-2.06, 1.07)	0.53	0.95	0.57	-0.13 (-1.10, 0.84)	0.79	0.91	-0.65 (-2.04, 0.73)	0.36	0.57	0.61 (-0.75, 1.98)	0.38	0.67	0.12
2nd trimester	0.04 (-1.12, 1.21)	0.94	0.99	-0.98 (-2.78, 0.83)	0.29	0.51	0.79 (-0.66, 2.24)	0.29	0.76	0.10	-0.42 (-1.35, 0.52)	0.38	0.90	**-1.49 (-2.86, -0.11)**	0.03	0.39	0.54 (-0.72, 1.80)	0.40	0.71	0.03
3rd trimester	0.00 (-1.21, 1.21)	0.99	0.99	-0.64 (-2.44, 1.16)	0.48	0.66	0.81 (-0.77, 2.38)	0.31	0.51	0.22	0.50 (-0.48, 1.47)	0.32	0.40	-0.37 (-1.74, 1.00)	0.60	0.68	**1.44 (0.07, 2.82)**	0.04	0.29	0.07
TCPy																				
1st trimester	**-1.96 (-3.66, -0.26)**	0.02	0.13	**-3.16 (-5.59, -0.74)**	0.01	**0.04**	-0.06 (-2.39, 2.27)	0.96	0.98	0.07	-0.71 (-2.08, 0.66)	0.31	0.56	-1.69 (-3.54, 0.17)	0.07	0.24	1.10 (-0.93, 3.14)	0.29	0.66	0.07
2nd trimester	0.01 (-1.64, 1.66)	0.99	0.99	-1.09 (-3.49, 1.30)	0.37	0.51	1.33 (-0.88, 3.54)	0.24	0.76	0.14	0.49 (-0.84, 1.82)	0.47	0.90	-0.43 (-2.26, 1.40)	0.65	0.94	1.76 (-0.17, 3.69)	0.07	0.51	0.09
3rd trimester	0.06 (-1.27, 1.38)	0.93	0.99	-0.46 (-2.42, 1.50)	0.65	0.74	0.84 (-0.90, 2.58)	0.34	0.51	0.50	0.54 (-0.53, 1.60)	0.33	0.40	0.49 (-1.01, 1.99)	0.52	0.68	0.77 (-0.75, 2.28)	0.32	0.43	0.95
PNP																				
1st trimester	-1.61 (-3.23, 0.01)	0.05	0.18	**-3.06 (-5.45, -0.68)**	0.01	**0.04**	0.10 (-2.05, 2.24)	0.93	0.98	**0.05**	-0.20 (-1.51, 1.11)	0.77	0.91	-1.55 (-3.37, 0.27)	0.10	0.25	1.66 (-0.20, 3.53)	0.08	0.49	0.02
2nd trimester	-0.54 (-2.20, 1.11)	0.52	0.99	-1.39 (-3.92, 1.13)	0.28	0.51	0.11 (-2.00, 2.22)	0.92	0.98	0.21	0.10 (-1.24, 1.43)	0.89	0.90	-1.11 (-3.04, 0.82)	0.26	0.65	1.40 (-0.44, 3.24)	0.14	0.54	0.03
3rd trimester	-1.65 (-3.29, 0.00)	0.05	0.23	-2.19 (-4.58, 0.20)	0.07	0.58	-1.10 (-3.21, 1.02)	0.31	0.51	0.41	1.03 (-0.27, 2.34)	0.12	0.27	0.85 (-0.98, 2.68)	0.36	0.68	1.40 (-0.44, 3.24)	0.14	0.31	0.45

Compounds (ng/mL)	MDI										PDI									
	All (*n* = 1041)			Male (*n* = 553)			Female (*n* = 488)			$P_{sex\text{-}int}$	All (*n* = 1041)			Male (*n* = 553)			Female (*n* = 488)			$P_{sex\text{-}int}$
	β (95% CI) [a]	*P*	*P-FDR*	β (95% CI) [b]	*P*	*P-FDR*	β (95% CI) [b]	*P*	*P-FDR*		β (95% CI) [a]	*P*	*P-FDR*	β (95% CI) [b]	*P*	*P-FDR*	β (95% CI) [b]	*P*	*P-FDR*	
mPYR																				
3-PBA																				
1st trimester	-0.82 (-2.05, 0.41)	0.19	0.39	-1.70 (-3.47, 0.07)	0.06	0.15	0.57 (-1.09, 2.23)	0.50	0.95	0.13	-0.50 (-1.49, 0.49)	0.32	0.56	**-1.55 (-2.90, -0.20)**	0.02	0.20	1.11 (-0.34, 2.56)	0.13	0.49	0.06
2nd trimester	-0.12 (-1.31, 1.06)	0.84	0.99	0.06 (-1.75, 1.87)	0.95	0.95	-0.33 (-1.82, 1.17)	0.67	0.92	0.49	-0.17 (-1.12, 0.78)	0.72	0.90	-0.12 (-1.50, 1.26)	0.86	0.96	-0.11 (-1.42, 1.20)	0.87	0.98	0.38
3rd trimester	0.24 (-0.75, 1.22)	0.64	0.99	-0.25 (-1.72, 1.22)	0.74	0.74	0.82 (-0.45, 2.10)	0.20	0.51	0.29	**0.97 (0.18, 1.76)**	0.02	0.13	1.18 (0.00, 2.36)	0.05	0.63	0.77 (-0.34, 1.88)	0.17	0.31	0.52
trans-DCCA																				
1st trimester	**-1.43 (-2.57, -0.30)**	0.01	0.11	**-2.24 (-3.89, -0.58)**	0.008	**0.04**	-0.30 (-1.81, 1.22)	0.70	0.98	0.04	**-1.11 (-2.03, -0.20)**	0.02	0.28	**-1.90 (-3.16, -0.64)**	0.003	**0.05**	0.00 (-1.33, 1.32)	1.00	1.00	0.02
2nd trimester	-0.67 (-1.83, 0.49)	0.26	0.69	-1.66 (-3.43, 0.10)	0.06	0.35	0.30 (-1.17, 1.78)	0.69	0.92	0.06	-0.56 (-1.50, 0.37)	0.24	0.90	-1.20 (-2.55, 0.15)	0.08	0.44	0.13 (-1.16, 1.42)	0.85	0.98	0.06
3rd trimester	-0.64 (-1.73, 0.44)	0.25	0.56	-1.11 (-2.66, 0.45)	0.16	0.58	-0.03 (-1.51, 1.46)	0.97	0.99	0.13	0.53 (-0.35, 1.40)	0.24	0.35	0.42 (-0.77, 1.61)	0.49	0.68	0.67 (-0.62, 1.97)	0.31	0.43	0.18
mNNIs																				
IMI																				
1st trimester	0.30 (-0.72, 1.32)	0.56	0.6	0.43 (-1.11, 1.97)	0.58	0.72	0.11 (-1.19, 1.40)	0.87	0.98	0.33	0.00 (-0.81, 0.82)	0.99	0.99	-0.28 (-1.45, 0.90)	0.64	0.73	0.27 (-0.86, 1.40)	0.64	0.74	0.28
2nd trimester	-0.03 (-1.11, 1.05)	0.95	0.99	-0.64 (-2.22, 0.94)	0.43	0.51	0.62 (-0.81, 2.05)	0.40	0.76	0.22	0.18 (-0.69, 1.05)	0.68	0.90	0.03 (-1.17, 1.24)	0.96	0.96	0.45 (-0.80, 1.70)	0.48	0.77	0.32
3rd trimester	0.10 (-0.94, 1.15)	0.84	0.99	-0.83 (-2.40, 0.75)	0.30	0.66	0.89 (-0.46, 2.24)	0.20	0.51	0.21	0.40 (-0.45, 1.24)	0.36	0.41	-0.21 (-1.41, 0.99)	0.73	0.78	1.02 (-0.16, 2.20)	0.09	0.29	0.23
IMI-olefin																				
1st trimester	0.44 (-0.75, 1.63)	0.47	0.54	0.17 (-1.61, 1.94)	0.86	0.91	0.66 (-0.88, 2.20)	0.40	0.95	0.49	0.42 (-0.54, 1.38)	0.39	0.56	0.07 (-1.28, 1.43)	0.91	0.91	0.88 (-0.47, 2.22)	0.20	0.54	0.36
2nd trimester	0.18 (-1.01, 1.37)	0.77	0.99	-0.69 (-2.48, 1.09)	0.45	0.51	1.01 (-0.54, 2.55)	0.20	0.76	0.18	0.06 (-0.90, 1.02)	0.90	0.90	-0.43 (-1.79, 0.93)	0.54	0.94	0.68 (-0.67, 2.03)	0.32	0.65	0.27
3rd trimester	0.04 (-1.05, 1.12)	0.95	0.99	-0.55 (-2.12, 1.03)	0.50	0.66	0.53 (-0.93, 1.99)	0.47	0.58	0.41	0.74 (-0.13, 1.62)	0.10	0.27	0.42 (-0.78, 1.62)	0.49	0.68	1.11 (-0.16, 2.38)	0.09	0.29	0.43
5-hydroxy-IMI																				
1st trimester	0.43 (-0.66, 1.52)	0.44	0.54	0.29 (-1.30, 1.88)	0.72	0.82	0.57 (-0.88, 2.03)	0.44	0.95	0.81	0.40 (-0.48, 1.28)	0.37	0.56	0.42 (-0.79, 1.63)	0.50	0.61	0.47 (-0.80, 1.74)	0.47	0.68	0.97
2nd trimester	0.17 (-0.94, 1.29)	0.76	0.99	-0.90 (-2.58, 0.78)	0.29	0.51	1.20 (-0.24, 2.64)	0.10	0.76	0.06	0.11 (-0.78, 1.01)	0.80	0.90	-0.38 (-1.67, 0.90)	0.56	0.94	0.72 (-0.54, 1.98)	0.26	0.65	0.20
3rd trimester	-0.24 (-1.30, 0.81)	0.65	0.99	-0.67 (-2.21, 0.87)	0.39	0.66	0.01 (-1.39, 1.42)	0.99	0.99	0.64	0.76 (-0.09, 1.61)	0.08	0.27	0.64 (-0.53, 1.82)	0.28	0.68	0.86 (-0.37, 2.08)	0.17	0.31	0.88
DN-IMI																				
1st trimester	-0.66 (-1.81, 0.48)	0.26	0.41	-1.51 (-3.21, 0.19)	0.08	0.16	0.08 (-1.42, 1.57)	0.92	0.98	0.13	0.07 (-0.85, 0.99)	0.88	0.94	-0.77 (-2.07, 0.53)	0.24	0.56	0.96 (-0.35, 2.26)	0.15	0.49	0.07
2nd trimester	-0.33 (-1.50, 0.84)	0.58	0.99	-1.21 (-3.02, 0.59)	0.19	0.51	0.35 (-1.11, 1.82)	0.64	0.92	0.17	0.07 (-0.88, 1.01)	0.89	0.90	0.16 (-1.22, 1.54)	0.82	0.96	-0.02 (-1.30, 1.26)	0.98	0.98	0.26
3rd trimester	-0.70 (-1.86, 0.45)	0.23	0.56	-0.63 (-2.40, 1.14)	0.49	0.66	-1.00 (-2.46, 0.46)	0.18	0.51	0.40	0.69 (-0.25, 1.62)	0.15	0.27	0.04 (-1.32, 1.39)	0.96	0.96	1.22 (-0.06, 2.49)	0.06	0.29	0.13

Compounds (ng/mL)	MDI										PDI									
	All (*n* = 1041)			Male (*n* = 553)			Female (*n* = 488)			$P_{sex\text{-}int}$	All (*n* = 1041)			Male (*n* = 553)			Female (*n* = 488)			$P_{sex\text{-}int}$
	β (95% CI) [a]	*P*	*P-FDR*	β (95% CI) [b]	*P*	*P-FDR*	β (95% CI) [b]	*P*	*P-FDR*		β (95% CI) [a]	*P*	*P-FDR*	β (95% CI) [b]	*P*	*P-FDR*	β (95% CI) [b]	*P*	*P-FDR*	
DM-ACE																				
1st trimester	-1.20 (-2.44, 0.03)	0.06	0.18	-1.37 (-3.18, 0.44)	0.14	0.22	-0.69 (-2.32, 0.95)	0.41	0.95	0.64	-0.53 (-1.53, 0.46)	0.29	0.56	-0.51 (-1.89, 0.88)	0.47	0.61	-0.34 (-1.77, 1.09)	0.64	0.74	0.99
2nd trimester	-0.48 (-1.70, 0.74)	0.44	0.99	-0.30 (-2.10, 1.50)	0.74	0.79	-0.65 (-2.24, 0.95)	0.43	0.76	0.91	-0.54 (-1.52, 0.44)	0.28	0.90	-0.75 (-2.13, 0.62)	0.28	0.65	-0.16 (-1.55, 1.24)	0.83	0.98	0.52
3rd trimester	1.14 (-0.04, 2.31)	0.06	0.23	1.04 (-0.67, 2.76)	0.23	0.62	1.42 (-0.15, 2.98)	0.08	0.51	0.86	0.73 (-0.21, 1.68)	0.13	0.27	0.45 (-0.86, 1.77)	0.50	0.68	1.09 (-0.28, 2.45)	0.12	0.31	0.58
THM																				
1st trimester	-0.58 (-1.51, 0.36)	0.23	0.41	**-1.53 (-2.92, -0.13)**	0.03	0.10	0.45 (-0.78, 1.67)	0.47	0.95	0.29	0.33 (-0.42, 1.09)	0.39	0.56	0.50 (-0.57, 1.57)	0.36	0.57	0.25 (-0.82, 1.32)	0.65	0.74	0.96
2nd trimester	0.81 (-0.20, 1.82)	0.12	0.47	0.98 (-0.54, 2.50)	0.21	0.51	0.55 (-0.75, 1.85)	0.41	0.76	0.80	0.19 (-0.63, 1.00)	0.65	0.90	-0.31 (-1.47, 0.85)	0.60	0.94	0.69 (-0.44, 1.83)	0.23	0.65	0.62
3rd trimester	0.76 (-0.19, 1.71)	0.12	0.37	1.03 (-0.45, 2.51)	0.17	0.58	0.55 (-0.64, 1.75)	0.37	0.51	0.80	0.48 (-0.28, 1.25)	0.22	0.35	0.54 (-0.59, 1.68)	0.35	0.68	0.44 (-0.60, 1.49)	0.41	0.47	0.90
CLO																				
1st trimester	0.55 (-0.60, 1.71)	0.35	0.46	-0.02 (-1.73, 1.69)	0.98	0.98	1.29 (-0.22, 2.79)	0.09	0.95	0.62	0.88 (-0.05, 1.81)	0.06	0.38	0.64 (-0.67, 1.95)	0.34	0.57	1.14 (-0.18, 2.45)	0.09	0.49	0.80
2nd trimester	**1.20 (0.02, 2.38)**	0.05	0.39	1.21 (-0.55, 2.97)	0.18	0.51	1.02 (-0.52, 2.55)	0.19	0.76	0.94	0.14 (-0.81, 1.09)	0.77	0.90	-0.05 (-1.39, 1.30)	0.95	0.96	0.20 (-1.14, 1.54)	0.77	0.98	0.91
3rd trimester	**1.29 (0.18, 2.41)**	0.02	0.23	1.54 (-0.21, 3.29)	0.08	0.58	1.12 (-0.28, 2.51)	0.12	0.51	0.99	0.66 (-0.24, 1.56)	0.15	0.27	0.95 (-0.39, 2.29)	0.16	0.68	0.46 (-0.75, 1.68)	0.45	0.48	0.98
DM-CLO																				
1st trimester	**1.22 (0.32, 2.12)**	0.01	0.11	**1.70 (0.40, 3.00)**	0.01	**0.04**	0.52 (-0.69, 1.74)	0.40	0.95	0.10	0.67 (-0.06, 1.40)	0.07	0.38	**1.05 (0.06, 2.05)**	0.04	0.20	0.11 (-0.95, 1.17)	0.85	0.90	0.19
2nd trimester	0.83 (-0.001, 1.66)	0.05	0.39	**1.57 (0.33, 2.80)**	0.01	0.21	0.05 (-1.01, 1.12)	0.92	0.98	0.06	0.35 (-0.32, 1.01)	0.31	0.90	0.67 (-0.28, 1.62)	0.17	0.61	0.01 (-0.92, 0.95)	0.98	0.98	0.28
3rd trimester	**1.01 (0.10, 1.92)**	0.03	0.23	0.89 (-0.41, 2.20)	0.18	0.58	1.17 (-0.06, 2.41)	0.06	0.51	0.53	0.56 (-0.17, 1.29)	0.13	0.27	0.64 (-0.36, 1.64)	0.21	0.68	0.49 (-0.59, 1.57)	0.38	0.46	0.58

Abbreviation: DMP, dimethyl phosphate; DMTP, dimethyl thiophosphate; DEP, diethyl phosphate; DETP, diethyl thiophopshate; TCPy, 3,5,6-trichloro-2-pyridinol; PNP, para-nitrophenol; 3-PBA, 3-phenoxybenzoic acid; trans-DCCA, trans-3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid; IMI, imidacloprid; IMI-olefin, imidacloprid-olefin; 5-hydroxy-IMI, 5-Hydroxy-imidacloprid; DN-IMI, desnitro-imidacloprid; DM-ACE, desmethyl-acetamiprid; THM, thiamethoxam; CLO, clothianidin; DM-CLO, desmethyl-clothianidin.

[a] Generalized estimating equation (GEE) models were adjusted for maternal age (categorical), pre-pregnancy BMI (categorical), maternal education (categorical), passive smoking (categorical), folic acid supplement during pregnancy (categorical), parity (categorical), child sex (categorical), breastfeeding duration (categorical), delivery mode (categorical), and sampling seasons (categorical).

[b] sex-stratified analyses were adjusted for all the mentioned confounders except child sex.

p: *p* values before performing multiple comparison corrections, which were derived from GEE models (including the major analyses and sex-stratified analyses).

p_{FDR}: false discovery rate (FDR)-corrected *p* values for multiple comparisons.

$p_{sex\text{-}int}$ for the interaction term between prenatal insecticide exposures and child sex, which were derived from sex-interaction analyses.

$p < 0.05$, $p_{FDR} < 0.05$, $p_{sex\text{-}int} < 0.05$ were considered statistically significant.

Table S9. Weighted quantile sum regression (WQSR) analysis[a] for the associations of weighted quantile sum regression index of pesticide biomarkers [based on the concentrations in the 1st trimester (*N* = 553 participants, *n* = 553 samples) and the averaged concentrations over the three trimesters (*N* = 553 participants, *n* = 1659 samples)] with boy's MDI scores estimated in the repeated holdout validation[b] in participants from a birth cohort study in Wuhan, China, 2014–2017 (Data correspond to Figure 3).

Compounds (ng/mL)	**Average trimester**	**Compounds (ng/mL)**	**1st trimester**
	Negative association with WQS index		Negative association with WQS index
WQS unit β (95% CI)	**−2.80 (−4.96, −0.64)**	**WQS unit β (95% CI)**	**−3.02 (−5.47, −0.57)**
***p*-value**	0.006	***p*-value**	0.01
	Average weight		Average weight
TCPy	0.282	trans-DCCA	0.182
trans-DCCA	0.120	THM	0.165
PNP	0.117	TCPy	0.126
DEP	0.101	DN-IMI	0.121
3-PBA	0.094	PNP	0.096
DMTP	0.064	DEP	0.070
THM	0.046	3-PBA	0.065
DN-IMI	0.040	DMTP	0.057
DETP	0.037	DETP	0.051
IMI	0.035	DM-ACE	0.040
DM-ACE	0.030	CLO	0.017
IMI-olefin	0.016	DMP	0.012
5-hydroxy-IMI	0.016		

[a] WQSR analysis was counducted in negative direction according to the results from MLR and GEE models. Models were adjusted for maternal age (categorical), pre-pregnancy BMI (categorical), maternal education (categorical), passive smoking (categorical), folic acid supplement during pregnancy (categorical), parity (categorical), and breastfeeding duration (categorical), delivery mode (categorical), and sampling seasons (except for average trimesters, categorical).[b] The repeated holdout validation was used, basing on the mean of 100 repeated holdouts on 40/60% training/testing splits. *p*-value < 0.05 was considered statistically significant, which were derived from WQSR analysis.

Table S10. Weighted quantile sum regression (WQSR) analysis[a] for the associations of weighted quantile sum regression index of pesticide biomarkers [based on the concentrations in the 1st trimester (*N* = 553 participants, *n* = 553 samples) and the averaged concentrations over the three trimesters (*N* = 553 participants, *n* = 1659 samples)] with boy's PDI scores (*n* = 553) estimated in the repeated holdout validation[b] in participants from a birth cohort study in Wuhan, China, 2014–2017.

Compounds (ng/mL)	**Average trimester**	**Compounds (ng/mL)**	**1st trimester**
	Inverse association with WQS index		Inverse association with WQS index
WQS unit β (95% CI)	−1.56 (−3.39, 0.28)	**WQS unit β (95% CI)**	−0.96 (−2.76, 0.84)
***p*-value**	0.15	***p*-value**	0.46
	Average weight		Average weight
trans-DCCA	0.217	trans-DCCA	0.211
DETP	0.130	DMTP	0.199
DEP	0.126	DETP	0.165
DMTP	0.113	IMI	0.116
PNP	0.109	TCPy	0.083
DM-ACE	0.107	DM-ACE	0.068
TCPy	0.068	DN-IMI	0.050
IMI	0.056	PNP	0.037
IMI-olefin	0.042	DEP	0.036
3-PBA	0.032	3-PBA	0.035

[a] WQSR analysis was counducted in negative direction according to the results from MLR and GEE models. Models were adjusted for maternal age (categorical), pre-pregnancy BMI (categorical), maternal education (categorical), passive smoking (categorical), folic acid supplement during pregnancy (categorical), parity (categorical), and breastfeeding duration (categorical), delivery mode (categorical), and sampling seasons (except for average trimesters, categorical). [b] The repeated holdout validation was used, basing on the mean of 100 repeated holdouts on 40%/60% training/testing splits. *p*-value < 0.05 was considered statistically significant which were derived from WQSR analysis.

Table S11. Comparison of the exposure levels and the associations of prenatal exposure to OPPs and PYRs (characterized by biomarkers) with child neurodevelopment observed in our study with other studies.

Reference	Area/country	Cohort/study	Sample Year	Sample	N	Trimester/age	Compounds (median concentration if not indicated)	Method	Outcome assessments	Main Results
(NHANES, 2020)	USA	NHANES	2013–2014	Urine sample	790	Adult females (> 19 years)	**TCPy** (0.84 ng/mL); **PNP** (0.56 ng/mL); **3-PBA** (0.62 ng/mL); **Trans-DCCA** (<0.6 ng/mL)	HPLC-MS/MS	/	/
(NHANES, 2022)	USA	NHANES	2017–2018	Urine sample	864	Adult females (> 19 years)	**DEP** (1.84 ng/mL; 11.9 nM); **DETP** (0.13 ng/mL; 0.76 nM); **DMP** (1.15 ng/mL; 9.13 nM); **DMTP** (0.54 ng/mL; 3.80 nM); **DEDTP** (<0.1 ng/mL); **DMDTP** (<0.1 ng/mL);	UHPLC-MS/MS	/	/
(Anai et al., 2021)	Kumamoto, Japan	/	2014–2016	Urine sample	*n* = 109 participants (314 samples)	Pregnant women (3 visits)	**ACE** (<0.26 μg/g creatinine); **DM-ACE** (<1.59 μg/g creatinine); **THM** (7.40 μg/g creatinine); **CLO** (15.3 μg/g creatinine);	LC-MS/MS	/	/
Child neurodevelopment assessed using Bayley scales										
This study	Wuhan, China	/	2014–2017	urine sample	*n*=1041 participants (3123 urine samples)	the 1st trimester (13.0 ± 1.0 wks); 2nd trimester (24.5 ± 3.6 wks); 3rd trimester	*__DEP__ (2.70–3.75 ng/mL; 17.6–24.5 nM); *__DETP__ (1.18–1.72 ng/mL; 6.31–9.20 nM); *__DMP__ (2.99–4.74 ng/mL; 23.7–37.6 nM); *__DMTP__ (0.38–0.46 ng/mL; 2.64–3.24 nM); **TCPy** (1.29–1.90 ng/mL); **PNP** (1.71–2.12 ng/mL); **3-PBA** (0.10–0.17 ng/mL); **trans-DCCA** (0.12–0.21 ng/mL); **IMI** (0.03 ng/mL);	UHPLC-MS/MS	**BSID-CR scales** (MDI and PDI) for children aged **2 years**	Higher urinary concentrations of some insecticide metabolites (i.e., TCPy, PNP, trans-DCCA, THM) at the 1st trimester were significantly associated with lower MDI/PDI scores, and the associations were more prominent among boys. Trans-DCCA and TCPy contributed most to the mixture effect of insecticide mixture exposure

Reference	Area/country	Cohort/study	Sample Year	Sample	N	Trimester/age	Compounds (median concentration if not indicated)	Method	Outcome assessments	Main Results
						(33.9 ± 2.9 wks)	**IMI-olefin** (0.33–0.43 ng/mL); **5-hydroxy-IMI** (0.52–0.73 ng/mL); **DN-IMI** (0.06–0.09 ng/mL); **DM-ACE** (0.75–0.93 ng/mL); **THM** (0.06–0.07 ng/mL); **CLO** (0.09–0.11 ng/mL); **DM-CLO** (0.23–0.32 ng/mL).			
(Qi et al., 2022)	Xuan wei county in Southwest China	/	2016–2018	urine sample	*n* = 419	8–12; 20–23; 32–35 weeks gestation	**3-PBA** (0.21–0.24 μg/g cre.); **4F-3-PBA** (0.14–0.17 μg/g cre.); **cis-DBCA** (median: 0.21-0.81 μg/g cre.)	UHPLC-MS/MS	**BSID-III scales** (MDI and PDI) for children aged **1 year**	In the second trimester, cognition scores were inversely associated with 3-PBA [β = −3.34 (95% CI = −6.11, −0.57)], and language scores were inversely associated with 3-PBA [β = −2.90 (95% CI = −5.20, −0.61)].
(Eskenazi et al., 2007)	Salinas Valley, California	CHAMACOS	2000–2003	urine sample	*n* = 372–396	14.0 and 26.6 weeks gestation (**using average concentrations**)	**DEP** (NA); **DETP** (NA); **DEDTP** (NA); **DMP** (NA); **DMTP** (NA); **DMDTP** (NA); **ΣDEP**[a] (GM: 18.1 nM); **ΣDMP**[a] (GM: 81.5 nM); **ΣDAP**[a] (GM: 114.9 nM), **TCPy** (3.54 ng/mL)	HPLC-MS/MS	**Bayley Scales** (MDI and PDI) for children aged **6** (n=396)**, 12** (n=395)**, 24 months** (n=372); **CBCL** for children aged **24 months** (n=356); **DSM-oriented scales** for children aged **24 months** (n=356)	For every 10-fold increase in pregnancy averaged ΣDEP and ΣDAP concentrations, they found a 3.64 and 3.54-point decrease in the 24-month-olds' MDI scores, respectively.
(Engel et al., 2011)	New York City	the Mount Sinai cohort	1998–2002	urine sample	*n* = 360	3rd-trimester (26-28 weeks gestation)	**DEP** (NA); **DETP** (NA); **DEDTP** (NA); **DMP** (NA); **DMTP** (NA); **DMDTP** (NA); **ΣDEP**[a] (20.2 nM); **ΣDMP**[a] (44.8 nM); **ΣDAP**[a] (81.3 nM)	GC-MS/MS	**BSID-II scales** (MDI and PDI) for children aged **12 months** (n = 200) and **24 months** (n = 276); **WISC** for children aged **6–9 years** (n = 169)	At the 12-month BSID-II exam, each 10-fold increase in maternal ΣDEP and ΣDAP was associated with a 3.35 and 3.29-unit decrease in MDI scores, respectively.

Reference	Area/country	Cohort/study	Sample Year	Sample	N	Trimester/age	Compounds (median concentration if not indicated)	Method	Outcome assessments	Main Results
(Kongtip et al., 2017)	Thailand	/	2011	urine sample	*n* = 50	3rd-trimester (28 weeks gestation)	**DMP** (36.83 nM); **DEP** (15.15 nM); **DETP** (0.07 nM); **DEDTP** (0.15 nM); **ΣDEP**[a] (37.8 nM); **ΣDAP**[b] (85.47 nM)	GC-MS	**BSID-III scales** (MDI and PDI) for children aged **five months**	For each IQR increase in maternal ΣDEP and ΣDAP metabolite levels were associated with a 3.46 and 4.42-unit decrease in MDI scores, respectively. For each IQR increase in maternal ΣDEP level was significantly associated with a 1.77-unit decrease in MDI scores.
(Rauh et al., 2006)	New York City	/	1998–2002	umbilical cord plasma	*n* = 254	/	**Chlorpyrifos** (mean: 7.6 pg/g)	GC–HR-MS	**BSID-II scales** (MDI and PDI) for children aged 12, 24, and 36 months	Children with higher cord blood level of chlorpyrifos (>6.17 pg/g plasma) had 6.5 points lower PDI and 3.3 points lower MDI at 3 years of age compared with those with lower exposure level.
(Lovasi et al., 2011)	New York City	/	1998–2002	umbilical cord plasma	*n* = 266	/	**Chlorpyrifos** (mean: 7.6 pg/g)	GC–HR-MS	**BSID-II scales** (MDI and PDI) for children aged **36 months**	Higher chlorpyrifos exposure (greater than 6.17 pg/g) was associated with an approximately 7.0-point decrease in PDI and an approximately 3.0-point decrease in MDI at age 36 months.
(Eskenazi et al., 2018)	Limpopo, South Africa	The VHEMBE Cohort	2012–2013	urine sample	*n* = 689 *n* = 681	3rd-trimester (prior to delivery)	**trans-DCCA** (SG-median: 0.34 ng/mL); **3-PBA** (SG-median: 0.70 ng/mL); **4F-3PBA** (SG-median: <0.011 ng/mL); **cis-DBCA** (SG-median: 0.223 ng/mL); **cis-DCCA** (SG-median: 0.301 ng/mL);	GC-MS	**BSID-III scales** (MDI and PDI) for children aged **1 year** (n = 689) **and 2 years** (n = 681)	At the 1-y visit, each 10-fold increase in maternal cis-DCCA, trans-DCCA, and 3-PBA was associated with a 0.63, 0.48, and 0.58-unit decrease in social-emotional scores, respectively. At 2 y of age, a 10-fold increase in maternal cis-DBCA concentrations was associated with a 0.40-unit decrease in Expressive Communication scores and a 1.74-unit decrease in Language Composite scores.

Reference	Area/country	Cohort/study	Sample Year	Sample	N	Trimester/age	Compounds (median concentration if not indicated)	Method	Outcome assessments	Main Results
(Fluegge et al., 2016)	Cincinnati, Ohio	/	2002–2005	urine sample	*n* = 118	the 2nd trimester; the 3rd trimester	**3-PBA** (7.28-8.36 ng/kg/day), **trans-DCCA** (5.10-5.97ng/kg/day), **TCPy** (19.62-20.45 ng/kg/day), **cis-DCCA** (0.0019-2.56 ng/kg/day)	GC-MS	**BSID-II scales** (MDI and PDI) for children aged **three months**	Each 1 ng/kg bw/day increase in TCPy at the third trimester was associated with lower PDI score by -0.031; Each 1 ng/kg bw/day increase in the 3-PBA metabolite was associated with approximately 0.10 to 0.12 lower MDI score.
(Donauer et al., 2016)	Cincinnati, Ohio	The HOME Study	2003–2006	urine sample	*n* = 327	16 and 26 weeks gestation (**using average concentrations**)	**DEP** (GM: 0.50 μg/g cre.); **DETP** (GM: 0.11 μg/g cre.); **DEDTP** (GM: 0.02 μg/g cre.); **DMP** (GM: 1.45 μg/g cre.); **DMTP** (GM: 2.11 μg/g cre.); **DMDTP** (GM: 0.08 μg/g cre.); **ΣDEP**[a] (GM: 9.3 nmol/g cre.); **ΣDMP**[a] (GM: 45.9 nmol/g cre.); **ΣDAP**[a] (GM: 73.7 nmol/g cre.)	GC-MS/MS	**BSID-II scales** (MDI and PDI) for children aged **1 year, 2 years, and 3 years.**	No associations between prenatal exposure to organophosphate pesticides and cognition at 1–5 years of age were found.
(Watkins et al., 2016)	Mexico City	The ELEMENT study	1997–2001	urine sample	*n* = 187	the 3rd trimester	**3-PBA** (<0.25 ng/mL; P75: 0.34 ng/mL)	HPLC-MS/MS	**BSID-II scales** (MDI and PDI) for children aged **24 and 36 months**	No associations between in utero 3-PBA concentrations and PDI scores at either 24 or 36 months of age were observed.
Child neurodevelopment assessed using other scales										
(Jusko et al., 2019)	Rotterdam, Netherlands	Generation R Study	2004–2006	urine sample	*n* = 708	<18, 18–25, and >25 weeks of gestation	**DEP** (31–32.7 nmol/g cre); **DETP** (7.0–7.5 nmol/g cre); **DEDTP** (P75: 0.3 nmol/g cre); **DMP** (130–138 nmol/g cre); **DMTP** (103.2–111.1 nmol/g cre); **DMDTP** (3.0–3.3 nmol/g cre);	GC–MS/MS	Mosaics and Categories subtests from the Snijders-Oomen Nonverbal Intelligence Test–Revised (nonverbal	An inverse relation between nonverbal IQ and late pregnancy urinary ΣDAP and ΣDMP concentration was observed.

Reference	Area/country	Cohort/study	Sample Year	Sample	N	Trimester/age	Compounds (median concentration if not indicated)	Method	Outcome assessments	Main Results
							ΣDEP[a] (41.5–43.4 nmol/g cre); **ΣDMP**[a] (249.1–269.1 nmol/g cre); **ΣDAP**[a] (310–316.7 nmol/g cre)		**IQ**) for children aged **6 years**	
(Liu et al., 2016)	Jiangsu Province, China	/	2011–2012	urine sample	*n* = 310	3rd-trimester (prior to delivery)	**DEP** (75.73 nM); **DETP** (21.69 nM); **DEDTP** (6.73 nM); **DMP** (6.80 nM); **DMTP** (62.28 nM); **DMDTP** (27.25 nM); **ΣDEP**[a] (134.88 nM); **ΣDMP**[a] (128.16 nM); **ΣDAP**[a] (295.8 nM)	GC-MS	**GDS** for children aged **2 years**	Adverse associations between prenatal and postnatal OP exposure and neurodevelopment of infants were observed only in boys, not in girls.
(Wang et al., 2017)	Shandong, China	/	2011–2013	urine sample	*n* = 235 *n* = 237	3rd-trimester (prior to delivery)	**DEP** (5.17 ng/mL); **DETP** (0.78 ng/mL); **DMP** (9.85 ng/mL); **DMTP** (0.78 ng/mL); **ΣDEP**[a] (NA); **ΣDMP**[a] (NA); **ΣDAP**[a] (352.67 nmol/g cre.)	GC-MS	**GDS** for children aged **12** (n=235) **and 24 months** (n=237).	Prenatal OP exposure was negatively associated with 24-month-old children's DQs, especially among boys.
(Chiu et al., 2021)	Taiwan, China	Taiwan Birth Panel Study	2004–2005	cord blood	*n* = 425	/	**Chlorpyrifos** (GM: 5.29 ng/mL)	LC-HESI-MS/MS	Comprehensive Developmental Inventory for Infants and Toddlers (**CDIIT**) at **2 years** of age	Prenatal chlorpyrifos exposure affected performance in the cognitive and language domains, especially in boys.
(Rauh et al., 2011)	New York City	/	/	umbilical cord plasma	*n* = 265	/	**Chlorpyrifos** (mean: 3.7 pg/g)	GC-MS	**WISC-IV** for children at **7 years** of age	Prenatal chlorpyrifos exposure was negatively associated 7-year-old children's Working Memory Index and Full-Scale IQ.

Reference	Area/country	Cohort/study	Sample Year	Sample	N	Trimester/age	Compounds (median concentration if not indicated)	Method	Outcome assessments	Main Results
(Furlong et al., 2017)	New York City	the Mount Sinai cohort	1998–2002	urine sample	*n* = 404	3rd trimester (25-40 weeks of gestation)	**DEP** (0.2 nM); **DETP** (9.9 nM); **DEDTP** (0.1 nM); **DMP** (12.6 nM); **DMTP** (23.5 nM); **DMDTP** (0.3 nM); **ΣDEP**[a] (16.6 nM); **ΣDMP**[a] (37.1 nM)	GC-MS/MS	**BASC** for children aged **4–9 years** (n = 238); **BRIEF** for children aged **4–9 years** (n = 242);**WPPSI-III** for children aged **6 years** (n = 162) ; **WISC-IV** for children aged **7–9 years** (n = 161);	Inverse associations between ∑ DMPs and Internalizing Factor scores, and between ∑ DEPs and the working memory index were observed.
(Ntantu Nkinsa et al., 2020)	10 Canadian cities	the MIREC cohort	2008–2011	urine sample	*n* = 247	1st trimester	**DEP** (NA); **DETP** (NA); **DEDTP** (NA); **DMP** (NA); **DMTP** (NA); **DMDTP** (NA); **ΣDEP**[a] (SG-median: 25.3 nM); **ΣDMP**[a] (SG-median: 62.3 nM); **ΣDAP**[a] (SG-median: 86.1 nM)	GC–MS/MS	**WPPSI-III** for children aged **3-4 years**	Urinary metabolites of organophosphate pesticides were not associated with IQ in girls, but higher maternal urinary DEAPs were associated with poorer Verbal IQ in boys.
(Zhang et al., 2014)	Shenyang, China	/	2011–2012	urine sample	*n* = 708	3rd-trimester (prior to delivery)	**DEP** (5.42 ng/mL); **DETP** (7.04 ng/mL); **DEDTP** (<1.0 ng/mL); **DMP** (24.04 ng/mL); **DMTP** (11.84 ng/mL); **ΣDEP**[a] (GM: 107.39 nM); **ΣDMP**[b] (GM: 283.66 nM); **ΣDAP**[c] (NA)	GC-FPD	Neonatal Behavioral Neurological Assessment **(NBNA)** for Neonates **(3 days old)**	Maternal exposure to OPs during pregnancy strongly associated with adverse neonatal neurobehavioral development.
(Furlong et al., 2014)	New York City	the Mount Sinai cohort	1998–2002	urine sample	*n* = 136	3rd trimester (25-40 weeks of gestation)	**DEP** (NA); **DETP** (NA); **DEDTP** (NA); **DMP** (NA); **DMTP** (NA); **DMDTP** (NA);	GC-MS/MS	Social Responsiveness Scale (**SRS**) for children aged **7-9 years**	The results support an association of prenatal OP exposure with deficits in social functioning among blacks and among boys

Reference	Area/country	Cohort/study	Sample Year	Sample	N	Trimester/age	Compounds (median concentration if not indicated)	Method	Outcome assessments	Main Results
							ΣDEP[a] (GM: 17.4 nM); **ΣDMP**[a] (GM: 41.7 nM); **ΣDAP**[a] (GM: 76.9 nM)			
(Furlong et al., 2014)	New York City	the Mount Sinai cohort	1998–2002	urine sample	*n* = 136	3rd trimester (25-40 weeks of gestation)	**DEP** (NA); **DETP** (NA); **DEDTP** (NA); **DMP** (NA); **DMTP** (NA); **DMDTP** (NA); **ΣDEP**[a] (GM: 17.4 nM); **ΣDMP**[a] (GM: 41.7 nM); **ΣDAP**[a] (GM: 76.9 nM)	GC-MS/MS	Social Responsiveness Scale (**SRS**) for children aged **7-9 years**	The results support an association of prenatal OP exposure with deficits in social functioning among blacks and among boys.
(Lizé et al., 2022)	French	PELAGIE cohort	2002–2006	urine sample	*n* = 185	1st trimester (<19weeks of gestation)	**ΣDEP**[a] (<LOD nM); **ΣDMP**[a] (24.1 nM); **ΣDAP**[a] (33.3 nM); **chlorpyrifos** (<0.01ng/mL), **CPF-oxon** (<0.001 ng/mL); **TCPy** (<0.042 ng/mL)	LC/MS-MS	The Childhood Autism Spectrum Test (**CAST**) parent questionnaire was used to screen for autistic traits in **11-year-old** children	The findings indicated a statistically significant association between prenatal maternal exposure to CPF and an increase in autistic traits for 11-year-old children, especially among boys.
(Dalsager et al., 2019)	Odense, Denmark	Odense Child Cohort	2010–2012	urine sample	*n* = 948	3rd-trimester (28 weeks gestation)	**3-PBA** (0.24 ng/mL); **trans-DCCA** (<0.4 ng/mL); **4-F-3-PBA** (<0.2 ng/mL); **cis-DCCA** (<0.5 ng/mL); **cis-DBCA** (<0.5 ng/mL); **TCPy** (1.61 ng/mL)	LC-MS/MS	ADHD traits in **2-4-year-old** children assessed by **CBCL** for ages 1.5–5 years	Prenatal exposure to pyrethroids was associated with ADHD related traits at 2–4 years of age.

Reference	Area/country	Cohort/study	Sample Year	Sample	N	Trimester/age	Compounds (median concentration if not indicated)	Method	Outcome assessments	Main Results
(Lee et al., 2022)	South Korea	/	2008–2010	urine sample	*n* = 449 *n* = 414	14-27 weeks of gestation	**3-PBA** (0.77 ng/mL)	GC–MS/MS	ADHD symptoms at **ages 6 (**n=449) **and 8 (**n=414) were assessed using the ADHD Rating Scale IV **(ARS)**	Prenatal exposure to 3-PBA was associated with ADHD symptoms.
(Binter et al., 2020)	French	PELAGIE cohort	2002–2006	urine sample	*n* = 95	1st trimester (<19 weeks of gestation)	**DEP** (NA); **DETP** (NA); **DEDTP** (NA); **DMP** (NA); **DMTP** (NA); **DMDTP** (NA); **ΣDEP**[a] (0.8 µmol/L); **ΣDMP**[a] (31.8 µmol/L); **ΣDAP**[a] (44.4 µmol/L)	LC-MS/MS	Motor inhibition function of **10- to 12-year-old** children was evaluated using **Go/No-Go paradigm**	Increasing levels of DM and DE were associated with decreased brain activity in the left inferior and bilateral superior frontal regions.
(Fortenberry et al., 2014)	Mexico City	The ELEMENT study	1997–2000; 2001–2005	urine sample	*n* = 142	3rd trimester	**TCPy** (1.78 ng/mL)	HPLC-MS/MS	Child attention and hyperactivity of children aged **6–11 years** was assessed using **CRS-R, CPT**, and **BASC-2**	No statistically significant associations between maternal TCPY concentrations and ADHD-related outcomes in children were observed.
(Cartier et al., 2016)	French	PELAGIE cohort	2002–2006	urine sample	*n* = 231	1st trimester (<19 weeks of gestation)	**DEP** (NA); **DETP** (NA); **DEDTP** (NA); **DMP** (NA); **DMTP** (NA); **DMDTP** (NA); **ΣDEP**[a] (P75: 13.2 nM); **ΣDMP**[a] (34.3 nM);	LC-MS/MS	**WISC-IV** was administered when the children were **6 years** of age to evaluate cognitive function	No evidence that prenatal OP exposure adversely affecting cognitive function in 6-year-olds was found.

Reference	Area/country	Cohort/study	Sample Year	Sample	N	Trimester/age	Compounds (median concentration if not indicated)	Method	Outcome assessments	Main Results
							ΣDAP[a] (43.9 nM)			
(Guo et al., 2019)	Sheyang, Jiangsu Province	SMBCS Cohort	2009–2010	urine sample	*n* = 377	3rd-trimester (prior to delivery)	**TCPy** (5.39 ng/mL)	GC-MS/MS	**GDS** for children aged **3 years**	The findings suggest that adverse neurodevelopmental effects were associated with early childhood CPF exposure, but not prenatal exposure.
(Viel et al., 2015)	French	PELAGIE cohort	2002–2006	urine sample	*n* = 287	1st trimester (6-19 gestational weeks)	**3-PBA** (<0.008 ng/mL); **trans-DCCA** (0.14 ng/mL); **4-F-3-PBA** (<0.003 ng/mL), **cis-DCCA** (0.09 ng/mL), **cis-DBCA** (0.11 ng/mL);	UPLC/MS–MS	**WISC-IV** was administered when the children were **6 years** of age to evaluate cognitive function	Maternal pyrethroid metabolite concentrations were not consistently associated with any children's cognitive scores
(Viel et al., 2017)	French	PELAGIE cohort	2002–2006	urine sample	*n* = 287	1st trimester (6-19 gestational weeks)	**3-PBA** (<0.008 ng/mL); **trans-DCCA** (0.14 ng/mL); **cis-DBCA** (0.11 ng/mL); **4-F-3-PBA** (<0.003 ng/mL), **cis-DCCA** (0.09 ng/mL)	UPLC/MS–MS	Child behavior at **age 6** was assessed using the Strengths and Difficulties Questionnaire (SDQ)	Higher maternal urinary concentration of cis-DCCA was associated with internalizing difficulties
(Barkoski et al., 2021)	California	MARBLES cohort	2007–2014	urine sample	*n* = 194	14–27; >28 weeks gestation	**3-PBA** (SG-median:1.45-1.46 ng/mL)	HPLC-MS/MS	During the child's **3-year** visit, expert clinicians evaluate children on **ADOS**	Maternal urinary 3-PBA was not associated with a higher risk for ASD at 3-years
(Andersen et al., 2021)	Odense, Denmark	Odense Child Cohort	2010–2012	urine sample	*n* = 755	3rd-trimester (28 weeks gestation)	**3-PBA** (0.24 µg/g cre.); **trans-DCCA** (<0.4µg/g cre.); **TCPy** (1.73 µg/g cre.); **ΣDEP**[a] (23.7 nmol/g cre.); **ΣDMP**[a] (30.9 nmol/g cre.); **ΣDAP**[a] (59.6 nmol/g cre.)	UPLC-MS/MS	Language development at age **20–36 months** was assessed using the validated Danish adaption of **MB-CDI**	No significant association between gestational exposure to organophosphate or pyrethroid insecticides and early language development in the children was found.

Abbreviation: **BSID-II**, The Bayley Scales of Infant Development, 2nd edition; **BSID-III**, Bayley Scales of Infant and Toddler Development-III; **MDI**, Mental Development Index; **PDI**, Psychomotor Development Index; **GDS**, Gesell Developmental Schedules; **WISC**, Wechsler Intelligence Scale for Children; **WPPSI-III**, Wechsler Preschool and Primary Scales of Intelligence-III: **DSM**, Diagnostic and Statistical Manual of Mental Disorders diagnoses; **CRS-R,** Conners' Prental Rating Scales-Revised; **CPT**, Conners' Continuous Performance Test; **BASC**, Behavioral Assessment Scale for Children. **BRIEF,** Behavior Rating Inventory of Executive Functioning; **ADOS,** Autism Diagnostic Observation Scale; **MB-CDI,** MacArthur-Bates Communicative Development Inventories; **CBCL,** The Child Behavior Checklist; **GC-MS/MS,** Gas chromatography-tandem mass spectrometry; **GC-MS,** Gas chromatography-mass spectrometry; **GC–HR-MS,** Gas chromatography–high-resolution mass spectrometry; **UHPLC-MS/MS,** Ultra-High Performance Liquid Chromatography system coupled with a tandem Mass Spectrometry detector; **HPLC-MS/MS,**: High performance liquid chromatography-tandem mass spectrometry; **LC-HESI-MS/MS,** liquid chromatography-heated electrospray ionization tandem mass spectrometry; **GC-FPD,** Gas chromatography with flame photometric detection; **LC/MS-MS,** liquid chromatography-electrospray ionization tandem mass spectrometry; **DMP,** dimethylphosphate, **DMTP,** dimethylthiophosphate, **DMDTP,** dimethyldithiophosphate; **DEP,** diethylphosphate, **DETP,** diethylthiophosphate, and **DEDTP,** diethyldithiophosphate; **CPF,** chlorpyrifos; **CPF-oxon,** chlorpyrifos-oxon; **TCPy,** 3,5,6-trichloro-2-pyridinol; [a]: ΣDEP, the sum concentrations of DEP, DETP, and DEDTP; **ΣDMP,** the sum concentrations of DMP, DMTP, and DMDTP; **ΣDAP**, the sum concentrations of DEP, DETP, DEDTP, DMP, DMTP, and DMDTP; [b]: **ΣDMP**, the sum concentrations of DMP and DMTP; **ΣDAP**, the sum concentrations of DEP, DETP, DEDTP, and DMP; [c]: **ΣDAP**, the sum concentrations of DEP, DETP, DEDTP, DMP and DMTP; **3-PBA**, 3-phenoxybenzoic acid; **4F-3-PBA**, 4-fluoro-3- phenoxybenzoic acid; **cis-DCCA**, cis–(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylicacid; **trans-DCCA**, trans–(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylicacid; **cis-DBCA**, cis-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylicacid; *For ease of comparison with other studies, DAPs were also converted from the untransformed concentration (ng/mL) to their corresponding molar concentrations (nM) (DEP = concentration/0.154 μg/nmol; DETP = concentration/0.170 μg/nmol; DMP = concentration/0.126 μg/nmol; DMTP =concentration/0.142 μg/nmol); **GM**: geometric mean; **Cre.**:creatinine; **NA**: not available.

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