Prenatal Imidacloprid Exposure and Subsequent Diagnosis of Autism Spectrum Disorder in a California Case-Control Study

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Introduction and Methods

Imidacloprid, a pesticide present in flea and tick applications for pets, has been identified in animal studies as important in prenatal brain development. The current study uses data from the Childhood Autism Risks from Genetics and the Environment (CHARGE) study to examine the hypothesis of association between imidacloprid and ASD.

- We compared maternally reported, prenatal exposure to imidacloprid, a common flea and tick treatments applied to pets, among children with ASD to children with other developmental delay (DD) and typically developing (TD) controls.
- Diagnoses of ASD and DD confirmed by trained clinicians using standardized diagnostic tools. Participants initially frequency matched on age, region of birth (not shown), and sex.
- Children with ASD classified as either early-onset or regressive based on parent report.
- Multivariable logistic regression and hierarchical Bayesian models with prior information from similar studies to examine association between imidacloprid and ASD. Separate models used for ASD subtypes (early onset vs. regressive).
- Covariates: matching factors, maternal education, age, ethnicity, parity and preterm smoking status, and preterm birth.
- Accounted for misclassification of prenatal imidacloprid exposure using Bayesian hierarchical models according to the methods of Gustafson et al.[1] These methods allow for sensitivity (Se) and false positive rates (FPR, 1-specificity) for exposure classification to differ by individual characteristics and inclusion of additional uncertainty around Se and FPR estimates. We used three Bayesian models with varying assumptions about exposure misclassification.
- We performed a sensitivity analysis to assess changes in posterior odds ratios and 95% credible intervals based on exposure misclassification estimates and to examine possible scenarios under which the observed association could be solely due to exposure misclassification.

Results

- Demographic characteristics were similar across the three participant groups (Table 1).
- Frequentist logistic regression models indicated that prenatal imidacloprid exposure was weakly associated with ASD versus TD and DD controls, but measurement was imprecise (table 2) TD controls: aOR (95%CI) 1.3 (0.77, 2.2); DD controls: 2.0 (0.85, 4.8).
- Bayesian models yielded aORs with similar magnitude but lower precision after accounting for estimated misclassification (table 3), TD controls 1.7 (0.70, 5.5); DD controls 1.9 (0.79, 6.2).
- The association between imidacloprid and ASD appeared stronger among participants with early onset ASD [aOR (95%CI) 2.0 (1.1, 3.6)] than among those with regressive ASD [0.74 (0.37, 1.4)] (table 3).
- This difference appeared to shrink following the prenatal period (figure 1).
- Results from the sensitivity analysis shown in figure 2 show that the estimated association is consistently stronger for early onset ASD participants over a range of sensitivities and false positive rates but apparent associations were null under plausible scenarios of misclassification.
- A sensitivity analysis for the overall ASD model with TD controls indicated that the posterior OR was robust to regression coefficient prior specification, but variations in sensitivity and false positive rate estimates within plausible ranges yielded ORs between 0.6 and 2.0 (not shown).

Table 1 - Demographic Characteristics

	N (%)		
	ASD	**TD**	**DD**
Imidacloprid usage (ever)			
No	399 (79)	217 (81)	139 (88)
Yes	102 (20)	51 (19)	19 (12)
Missing	5 (1)	1 (0)	0 (0)
Maternal education			
College Degree	201 (40)	85 (32)	61 (39)
High School	75 (15)	43 (16)	51 (32)
Some College	230 (45)	141 (52)	46 (29)
Missing	0 (0)	0 (0)	0 (0)
Maternal age			
Mean	31	31	30
Median	31	31	30
Missing	1	0	0
Child's age at interview			
Mean	3.8	3.5	3.8
Median	3.8	3.5	3.9
Missing	2	0	0
Preterm birth			
Born Term	437 (86)	239 (89)	130 (82)
Born Preterm	63 (12)	27 (10)	27 (17)
Missing	6 (1)	3 (1)	1 (1)
Maternal race/ethnicity			
Asian/Pacific Islander	40 (8)	21 (8)	5 (3)
Black	17 (3)	8 (3)	14 (9)
Multiracial	20 (4)	10 (4)	7 (4)
Native American/Alaskan	2 (0)	1 (0)	0 (0)
Other Race	0 (0)	1 (0)	0 (0)
White/Hispanic	120 (24)	57 (21)	57 (36)
White/non-Hispanic	292 (58)	164 (61)	71 (45)
Missing	0 (0)	0 (0)	0 (0)
Maternal smoking			
Non-Smoker	420 (83)	228 (85)	138 (87)
Smoker	57 (11)	19 (7)	11 (7)
Missing	29 (6)	22 (8)	9 (6)
Sex			
Male	437 (86)	218 (81)	111 (70)
Female	68 (13)	51 (19)	47 (30)
Missing	1 (0)	0 (0)	0 (0)
Parity			
Primiparous	143 (28)	76 (28)	35 (22)
2	165 (33)	74 (28)	49 (31)
3	107 (21)	53 (20)	27 (17)
4	48 (9)	36 (13)	25 (16)
>4	38 (8)	27 (10)	21 (13)
Missing	5 (1)	3 (1)	1 (1)

Table 1 - Demographics of CHARGE study population. Participants include all eligible persons recruited into the study who completed the environmental exposure questionnaire and clinical visit to confirm diagnosis.

Table 2 - Logistic and Bayesian hierarchical model results - all ASD participants

	TD controls			DD controls		
	OR	95% CI	CLR	OR	95% CI	CLR
Frequentist						
Crude	1.2	(0.74, 1.9)	2.5	2.7	(1.3, 5.8)	4.6
Matching factors	1.4	(0.83, 2.2)	2.6	2.7	(1.2, 5.9)	4.8
Fully adjusted	1.3	(0.77, 2.2)	2.9	2.0	(0.85, 4.8)	5.6
Bayesian models						
Model 1	1.3	(0.79, 2.2)	2.8	2.1	(0.93, 5.3)	5.7
Model 2	1.4	(0.54, 5.8)	11	2.7	(0.91, 9.8)	11
Model 3	1.7	(0.70, 5.5)	7.8	1.9	(0.79, 6.2)	7.9

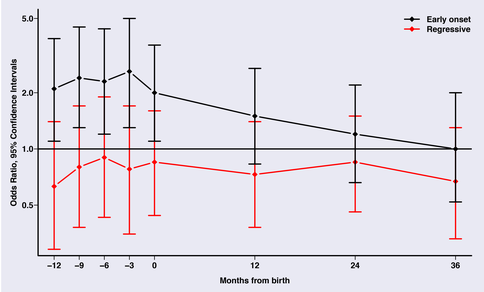
Table 2 - Odds ratios, 95% confidence/credible intervals, and confidence/credible limit ratios from frequentist and Bayesian models with all ASD participants and TD or DD controls. Model 1 assumes no exposure misclassification, while model 2 assumes that exposure misclassification is known with certainty. Model 3 places a distribution around the estimated exposure misclassification based on information from a previous validation study regarding prenatal exposures and early life outcomes. Confidence/credible limit ratios are calculated as (upper 95% limit)/(lower 95 % limit)

Table 3 - Logistic and Bayesian hierarchical model results - by regressive subtype

	Early onset			Regressive		
	OR	95% CI	CLR	OR	95% CI	CLR
Frequentist						
Crude	1.7	(1.0, 2.8)	2.7	0.69	(0.38, 1.3)	3.4
Matching factors	2.2	(1.3, 3.7)	2.9	0.71	(0.38, 1.4)	3.6
Fully adjusted	2.0	(1.1, 3.6)	3.2	0.74	(0.37, 1.4)	3.9
Bayesian models						
Model 1	1.5	(1.0, 2.2)	2.1	1.0	(0.68, 1.5)	2.3

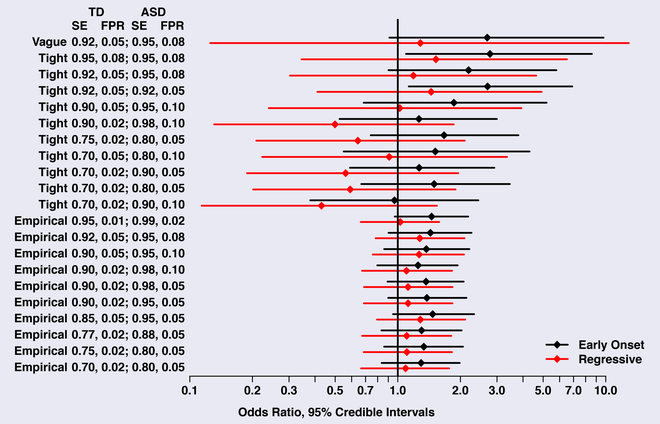
Table 3 - Odds ratios, 95% confidence intervals, and confidence limit ratios from frequentist and Bayesian models for ASD subtypes.

Figure 1 - OR by timing of exposure and regressive subtype



Differential association of imidacloprid with ASD by regressive subtype. Odds ratios with 95% confidence intervals are fully adjusted for all *a priori* potential confounders. Each odds ratio is for maternally reported imidacloprid use between the ASD subtype and TD controls within each trimester of pregnancy or year of child's life.

Figure 2 - Sensitivity analysis odds ratios and 95% confidence intervals by ASD subtype



Odds Ratios and 95% credible intervals for imidacloprid exposure between for Bayesian models assuming known misclassification while varying Sensitivity, false positive rate, and priors on logistic model. Prior estimates for regression coefficients were based on frequentist estimates from the logistic model with all participants (Empirical), N (0,1) coefficients (tight), or N (0,10) coefficients (vague).

Summary

We observed a modest, yet imprecise association between imidacloprid exposure and ASD, and the effect appeared to differ between regressive subtypes. The observed associations could be causal or alternatively, as shown in the sensitivity analysis, could result from measurement error possibly due to recall bias. Evidence from current analysis and animal studies suggests that a causal association is possible, but since this is the first human study, replication is necessary. The sensitivity analysis shows that exposure misclassification cannot be ruled out as the source of the apparent association. Estimates provided here show the degree to which subtle changes in sensitivity and false positive rate can impact the magnitude and precision of the estimates, but without better prior information, it does not provide more certainty about the direction of this association. While case control studies remain the most efficient way to test hypotheses regarding environmental factors in ASD, they are prone to exposure misclassification. The current study highlights the importance of validation studies of prenatal exposures in ASD.

Sources

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