RESEARCH ARTICLE

Prenatal exposure to pesticide residues in the diet in association with child autism-related traits: Results from the EARLI study

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Abstract

Prior work has suggested associations between prenatal exposure to several classes of pesticides and child autism spectrum disorder (ASD). We examined a previously developed pesticide residue burden score (PRBS) and intake of high pesticide residue foods in association with ASD-related traits. Participants were drawn from the Early Autism Risk Longitudinal Investigation (EARLI) ($n = 256$), a cohort following mothers who previously had a child with ASD through a subsequent pregnancy and that child's development. ASD-related traits were captured according to total Social Responsiveness Scale (SRS) scores at age 3 (mean raw total SRS score = 35.8). Dietary intake was assessed through a food frequency questionnaire collected during pregnancy. We also incorporated organic intake and fatty foods in modified versions of the PRBS. Associations between high-residue fruit and vegetable intake, the overall PRBS and modified versions of it, and SRS scores were assessed using multivariable linear regression. Overall, we did not observe associations between pesticide residues in foods and ASD-related outcomes, and modified versions of the PRBS yielded similar findings. However, reductions in ASD-related traits were observed with higher overall fruit and vegetable intake (adjusted estimates for Q4 vs. Q1: β −12.76, 95%CI −27.8, 2.3). Thus, findings from this high familial probability cohort did not suggest relationships between pesticide residues in the diet according to the PRBS and ASD-related traits. Beneficial effects of fruit and vegetable intake may influence these relationships. Future work should consider fruit and vegetable intake in association with ASD-related outcomes.

Lay Summary: Diet is the main source of exposure to most pesticides in use today. In this study, we examined the relationship between pesticide exposure from residues in the diet during pregnancy and child autism-related traits. We found that these pesticide residues from the diet were not related to child autism-related outcomes at age three. However, higher prenatal fruit and vegetable intake was associated with reductions in child autism-related traits.

KEYWORDS
autism spectrum disorder, autism-related traits, fruit, pesticide residues, prenatal diet, vegetables

INTRODUCTION

Pesticides have the ability to cross the placenta (Bradman et al., 2003; Caspersen et al., 2016; Dewan et al., 2013; Wolff et al., 2005), as well as disrupt hormones involved in neurodevelopment (C. Li et al., 2014; Wang et al., 2017). Although certain classes of pesticides have been banned or limited in Western countries, including organochlorine (OC) pesticides, there remains a need to examine the impact of these chemicals due to their long half-lives of up to 10 years in lipids, and bioaccumulation in the environment and food chain (Fourth National Report on Human Exposure to Environmental Chemicals, 2009; Jayaraj et al., 2016; Y.-F. Li, n.d.). While newer replacement classes of pesticides, such as organophosphate (OP) pesticides and pyrethroids, do not have these lipophilic properties, their widespread use also makes them relevant to public health considerations. Recent biomonitoring studies demonstrate detectable levels of both newer and older classes of pesticides, both in the general population and in pregnant women (Fourth National Report on Human Exposure to Environmental Chemicals, 2009; Lyall, Croen, Sjödin, et al., 2017; Woodruff et al., 2011).

Evidence has suggested a relationship between prenatal pesticide exposure and cognitive and developmental deficits in children (Bouchard et al., 2010; Engel et al., 2016; Eskenazi et al., 2007; Furlong et al., 2017; Korrick & Sagiv, 2008; Rosas & Eskenazi, 2008), and emerging work has also suggested pesticide exposure may be associated with autism spectrum disorder (ASD) (Brown et al., 2018; Lyall, Croen, Sjödin, et al., 2017; Philippat et al., 2018; Sagiv et al., 2018). ASD is a complex neurodevelopmental condition characterized by social communication deficits and challenges manifesting at a young age (Diagnostic and statistical manual of mental disorders: DSM-V, 2013). There is an abundance of evidence that suggests ASD etiology derives from a combination of genetic and environmental factors, with the prenatal stage as a susceptibility period (Hallmayer et al., 2011; Risch et al., 2014).

Only a handful of studies to date have addressed the association between prenatal pesticide exposure and ASD-related outcomes specifically. Early studies examined residential proximity to agricultural exposure to pesticides and reported increased risk of ASD with exposure to certain OC (Roberts et al., 2007) and OP pesticides (Shelton et al., 2014). Two more recent studies examining close proximity to agricultural applications have shown no association with ASD (Sagiv et al., 2018; Schmidt et al., 2017), while the largest study to date using this exposure metric found associations with multiple individual non-persistent pesticides and close proximity to agriculture applications (von Ehrenstein et al., 2019). A few studies using measured prenatal levels to determine exposure have found evidence for associations between higher exposure to certain OC, OP, and pyrethroid pesticides and increased risk for ASD and ASD-related traits (Braun et al., 2014; Brown et al., 2018; Furlong et al., 2017; Millenson et al., 2017; Sagiv et al., 2018; Schmidt et al., 2012), though null results have also been reported (Barkoski et al., 2021; Lyall, Croen, Sjödin, et al., 2017; Philippat et al., 2018). To date, limited work has considered combined effects of pesticides in association with ASD and/or child neurodevelopment, though pesticides are known to co-occur (Fourth National Report on Human Exposure to Environmental Chemicals, 2009; Hamra et al., 2019; Woodruff et al., 2011). In addition, work from animal studies and other fields suggests the potential for mixture effects that are not fully explained by analyses of individual pesticides alone, suggesting that existing work considering individual pesticides or classes could misrepresent actual exposures and associations (European Commission, 2012; Laetz et al., 2009; Moser et al., 2006). Yet, measurement across multiple classes is costly and may not align with sample-sparing requirements of studies with limited prenatal biological specimens, which are unique resources in studies of ASD.

Diet, particularly fruit and vegetable intake, is the primary source of exposure to major pesticide classes in the general population (Cequier et al., 2017; Fourth National Report on Human Exposure to Environmental Chemicals, 2009; Morgan, 2012). The US Pesticide Monitoring Program has reported that fruits and vegetables contain the highest proportion of detected pesticide levels across all foods annually tested (Pesticide Data Program Annual Summary, Calendar Year *2013*, 2014). Organic foods also contain detected pesticide residues, although at a lesser amount compared to conventional produce (Mie et al., 2017). Recently, a questionnaire-based measure that captures approximately 450 pesticide residues in the diet has been developed and validated against urinary pesticide levels in two independent populations (Chiu, Williams, Mínguez-Alarcón, Gillman, et al., 2018; Hu et al., 2016). In this way, the measure is an efficient metric of combined exposure to pesticides. This pesticide residue burden score (PRBS) has been used in studies examining associations with pregnancy, fetal growth, and live birth outcomes (Chiu, Williams, Gillman, Gaskins, et al., 2018; Chiu, Williams, Gillman, Hauser, et al., 2018). Yet, no prior study has examined whether pesticide residues in the diet may be associated with ASD and related child outcomes. Given challenges with collecting biospecimens in key suspected critical time periods for ASD, cost considerations, and specimen volume requirements associated with pesticide measurement across multiple classes, a questionnaire-based exposure assessment represents an efficient and accessible way to capture pesticide exposure across many classes and address this relationship in ASD research.

In this study, we sought to examine the relationship between diet-based pesticide exposure and ASD-related outcomes, including quantitative ASD-related traits and

cognitive scores, using prospectively collected dietary data from a high-familial probability cohort. We also sought to test modifications to the PRBS to account for other food sources of pesticides, as well as organic food status. Based on prior work suggesting links between prenatal pesticide exposure and ASD diagnosis and/or poorer neurodevelopmental outcomes, we hypothesized that higher prenatal pesticide exposure in the diet would be associated with increases in ASD-related traits and decreases in cognitive scores.

METHODS

Study population

Participants in this study were from the Early Autism Risk Longitudinal Investigation (EARLI) (Newschaffer et al., 2012). EARLI is a high-familial probability cohort study that enrolled women who already had a child with a confirmed ASD diagnosis and followed participants through a subsequent pregnancy and the first 3 years of the child's life. This design capitalizes on the approximately 10-fold increased chance of recurrence of ASD to siblings, in order to enable prospective investigation of ASD and its potential associated factors (Newschaffer et al., 2012). Women were recruited from four sites: Drexel/CHOP, Johns Hopkins University, UC Davis, and Northern CA Kaiser Permanente. To be included in EARLI, women had to be 18 years or older, less than 29 weeks pregnant, English or Spanish speaking, and living no farther than 2 h away from recruitment sites. Overall, 256 women were enrolled in EARLI and children of EARLI participants were enrolled between 2009 and 2012. The EARLI Study was reviewed and approved by the Drexel University Institutional Review Board, and all EARLI Study sites obtained local IRB approvals. Furthermore, all participants in the EARLI Study provided consent prior to study participation.

Participants were excluded from this study if they did not have outcome information available (either Social Responsiveness Scale (SRS) or diagnostic evaluation, both conducted at the 36-month visit) ($n = 51$) and if they did not have information on prenatal diet ($n = 43$). Twins ($n = 4$ pairs) were excluded due to the small number and correlation in exposures. Following these exclusions (Figure S1), 154 women were included in our analytic sample.

Dietary information

Dietary information was collected through a modified version of the National Cancer Institute's Dietary History Questionnaire (DHQ), which focused on diet since becoming pregnant and included additional questions from the validated version in order to capture contaminant exposure. This questionnaire was administered to EARLI participants twice during their pregnancy, at approximately 20 and 36 weeks gestation, and covered diet during the first and second half of pregnancy respectively. DHQ data from the first half of pregnancy were used for analyses here as a greater proportion of participants completed this questionnaire. The DHQ has been validated in previous work (Subar et al., 2001). The DHQ is comparable to the Willett/Harvard Food Frequency Questionnaire (FFQ) for which the PRBS was initially developed, as both questionnaires assess the main components of the diet, and notably, capture the same fruit and vegetable intake required to estimate the PRBS (Fawzi et al., 2004; Subar et al., 2001; W. C. Willett et al., 1985). In the DHQ administered to EARLI participants, organic consumption of individual fruits and vegetables was also assessed via ordinal response options ranging from almost always or always (approximately 90% of the time) to rarely or never (<10% of the time).

PRBS development and derivations

Previous studies have developed the PRBS as a novel approach to estimate dietary pesticide exposure based on FFQ data (Chiu et al., 2016; Chiu, Williams, Mínguez-Alarcón, Gillman, et al., 2018; Hu et al., 2016). This score aims to rank individual's pesticide exposure through fruit and vegetable intake, using data from the USDA's Pesticide Data Program (PDP). The PDP annually tests US agricultural commodities, following washing and peeling to mimic consumer behavior, for approximately 450 different pesticide residues (Pesticide Data Program Annual Summary, Calendar Year 2013, 2014). Data from the PDP was used to classify fruits and vegetables as high or low residue, according to three indexes assessing percent of samples with: 1) detectable pesticides, 2) above pesticide tolerances, and 3) >3 types of detectable pesticides. Across each of the indexes, foods were ranked into tertiles and assigned a score ranging from 0 (bottom tertile) to 2 (top tertile). Scores were summed to produce a pesticide rank score (PRBS) ranging from 0 (least contaminated) to 6 (most contaminated) (Table S1). Fruits and vegetables with scores ≥4 were considered high residue (HR), while those below 4 were considered low residue (LR). We calculated residue scores for foods tested by the PDP in the years covering EARLI study enrollment (2008–2013; flanking years were included to capture foods not tested during enrollment years). Since not all commodities are tested each year, foods not tested by the PDP during EARLI study enrollment were given a residue score from a previous study that used PDP data between 2006 and 2015 (13% of foods included in the PRBS) (Chiu, Williams, Gillman, Gaskins, et al., 2018). Several residue scores were examined in this study.

High and low pesticide residues and fruit and vegetable intake

For primary analyses, following prior work (Chiu et al., 2016; Chiu, Williams, Gillman, Gaskins, et al., 2018), we stratified foods according to high (residue score as defined ≥4) or low (score <4) residues, and examined associations with consumption of these high-residue fruits and vegetables (HR-FV) and low-residue fruits and vegetables (LR-FV) respectively. Stratification by high and low residues will aim to categorize the presence of pesticides on fruits and vegetables. In addition to examining the pesticide residues in fruits and vegetables (as our primary question of interest), we also examined associations between overall fruit and vegetable (FV) intake with ASD outcomes.

Weighted pesticide residue scores and modifications of the PRBS

Weighted residue scores were also calculated following published methods (Hu et al., 2016), by multiplying each fruit and vegetable's residue score by the individual's consumption frequency (servings/day) of that food reported in the DHQ, and then summing across all fruit and vegetables. Thus, this score aims to describe overall pesticide exposure in the diet. Class-specific organochlorine and organophosphate (OC-PRBS and OP-PRBS) scores were developed using methods discussed previously, including only OC or OP specific residues measured by the PDP (Hu et al., 2016). In addition to these scores following published strategies, we tested several modifications to the PRBS. Given fatty foods are a known source of OC pesticides due to their lipophilic nature (Fourth National Report on Human Exposure to Environmental Chemicals, 2009), we created a modified PRBS that incorporated available fatty foods from the PDP for 2008–2013 (meat, fish, milk, eggs) (PRBS-F). Next, we also incorporated organic food status into the PRBS by multiplying consumption frequency of each food item by the proportion of reported non-organic intake for that food (thereby reducing the estimated pesticide residue exposure; PRBS-organic). Across all residue scores examined, we parameterized the scores in quartiles to examine associations with outcomes under study; such categorization has also been shown to reduce potential misclassification of reported dietary data (W. Willett, 2013).

Outcome assessments

ASD-related traits (primary outcome)

Quantitative ASD phenotype in the child was captured by the original preschool version of the SRS (Constantino & Gruber, 2005, 2012), administered to mother participants when the child was 36 months (Miller et al., 2021; Sacrey et al., 2021; Wetherby et al., 2021; Zwaigenbaum et al., 2015; Zwaigenbaum et al., 2019). The SRS generates a total raw score ranging from 0 to 195, where higher values indicate greater expression of the ASD-related phenotype. The SRS has been previously validated against the Autism Diagnostic Interview-Revised (ADI-R) (Constantino et al., 2003; Constantino et al., 2009), with coefficients ranging between 0.65 and 0.91. The SRS has previously shown strong psychometric properties, including high internal validity, reliability, reproducibility, and score stability over time (Constantino et al., 2003; Constantino et al., 2009), including in the general population (Constantino & Todd, 2003), and in ASD groups (Constantino et al., 2006). SRS scores are continuously distributed and have previously demonstrated evidence for heritability (Constantino & Todd, 2000, 2005).

Cognitive development (secondary outcome)

Due to prior evidence for associations between pesticides and cognitive outcomes (Bouchard et al., 2010; Engel et al., 2016; Eskenazi et al., 2007; Furlong et al., 2017; Korrick & Sagiv, 2008; Rosas & Eskenazi, 2008), (Engel et al., 2016; Eskenazi et al., 2007; Furlong et al., 2017; Korrick & Sagiv, 2008), and the common co-occurrence of intellectual disability and ASD (with approximately 30% of those with an ASD diagnosis also meeting criteria for intellectual disability) (Christensen et al., 2018; Lyall, Croen, Daniels, et al., 2017), we also examined associations with cognitive scores for comparison to associations with ASD-related traits. Cognitive development was assessed at 36 months using the Mullen Scales of Early Learning (MSEL) early learning composite (ELC) score (Mullen, 1995). This score is a standard cognitive tool that captures overall development, incorporating fine motor skills, visual reception, and both receptive and expressive language (Farmer et al., 2016), with prior evidence supporting internal reliability and validity against other scores that measure cognitive ability in children (Bishop et al., 2011; Farmer et al., 2016). Lower scores (mean ELC = 100; SD = 10) are indicative of poorer intellectual functioning (Bishop et al., 2011; Maski et al., 2011).

Statistical analysis

Descriptive statistics of baseline characteristics were examined across the study sample and by quartiles of the PRBS. We qualitatively compared differences in baseline characteristics by examining the variance for continuous variables (via SD) and frequency of response for categorical variables across highest and lowest quartiles of exposure categories (Q1 HR-FV and Q4 HR-FV. Correlation between our exposure measurements was assessed using Spearman

correlation coefficients. Due to minor differences between our FFQ used in EARLI and the FFQ used in the original PRBS development, we compared foods identified as high residue according to the published PRBS and our PRBS based on PDP data from 2008 to 2013.

For analyses examining diet-based pesticide exposure in association with SRS scores, we ranked individuals into quartiles based on their PRBS, with the lowest quartile as the referent. Linear regression was used to assess the relationship between quartiles of HR/LR-FV intake, FV intake, and weighted-PRBS. Adjusted models included the following covariates, selected based on *a priori* associations between exposures and outcomes: maternal age, pre-pregnancy BMI (weight in kg/height in m²), sex of the child, and total calorie intake (as a continuous variable in models examining dietary exposures) (Getz et al., 2016; Lyall, Croen, Daniels, et al., 2017; Shelton et al., 2010). In order to consider the role of healthy diet overall, we additionally adjusted for a modified version of the Alternative Healthy Eating Index (AHEI) dietary pattern (McCullough et al., 2002). This dietary pattern emphasizes a diet high in produce, whole grains, nuts, and polyunsaturated fatty acids, moderate consumption of alcohol, and low in red meat, trans fats, and saturated fatty acids. We excluded fruit and vegetable intake in the AHEI so FVs were not included twice in the model, and alcohol consumption was excluded due to contraindication in pregnancy (and near non-use in our population). Finally, as performed in prior work, HR-FV and LR-FV intake were adjusted for one another (Chiu et al., 2016; Chiu, Williams, Gillman, Gaskins, et al., 2018). Several other covariates tested for adjustment on the basis of potential or known a priori associations were: maternal prenatal vitamin use, a binary indicator for organic food consumption based on reported intake from the DHQ (as a complement to the PRBS-organic measure described above), study site, maternal education, race/ethnicity, household income, as well as folate and vitamin D intake. These additional factors were not included in final models as they did not change estimates by >10% (and given inclusion of the latter two nutrients may ultimately complicate the interpretation of FV effects). Covariate missingness was low (5 individuals or fewer, or roughly 3% or less), and simple imputation was used for individuals missing covariate information. Analyses of secondary outcome measure (MSEL ELC scores) followed the approach outlined for SRS scores. Across analyses, estimates with 95% confidence intervals not including the null value of 0 (consistent with $p < 0.05$) were interpreted as statistically significant. All analyses were conducted using SAS 9.4 software.

RESULTS

Characteristics of the 154 EARLI participants included in primary analyses are shown in Table 1. East coast participants, Hispanic, Black and multi-racial mothers and those with less than a college degree were more likely to consume more high pesticide residue fruit and vegetables (HR-FV) than non-Hispanic or white mothers. Individuals who were ranked in the top quartile of HR-FV had a lower mean pre-pregnancy BMI compared to those in the bottom quartile of HR-FV (Table 1).

Dietary characteristics of those in the top and bottom quartile of HR-FV intake are shown in Table S2. As expected, those in the highest quartile of the HR-FV had higher fruit and vegetable intake. Overall, fruit and vegetable intake were highly correlated with one another ($\rho = 0.67$), as were HR and LR-FV intake ($\rho = 0.65$). Those in the top quartile of HR-FV intake reported higher intake of organic foods (18.4% vs. 2.6%) and had higher intake of several nutrients of relevance to (and with prior evidence for inverse associations with) ASD compared to those in the bottom quartile of HR-FV (Table S2).

Pesticide residue scores derived over EARLI study years (2008–2013) were comparable (the same or within 1 rank) across 88% of foods in the previously published PRBS based on PDP data covering 2006–2015 (Chiu, Williams, Gillman, Gaskins, et al., 2018). In addition, there was 85% similarity of foods identified as high residue between our score and the published PRBS, providing support for comparability and reliability of our PRBS. In testing modifications to the PRBS, fatty foods available from the PDP (beef, fish, milk & eggs, which were incorporated in our PRBS-fatty foods) were all low residue (residue scores <4). Consistent intake of organic foods was relatively low in our study population ($n = 17$ classified as regular organic consumers, defined according to report of eating organic foods ≥50% of the time). Though we did not examine FV intake based on dietary data from the second half of pregnancy, among the subset with DHQ data across two time points (approximately 50% of the eligible participants), the correlation of food intake that contributed to the PRBS was high ($\rho = 0.75$).

Associations with pesticide residues

In analyses of HR/LR-FV intake with ASD-related traits, overall, we did not observe strong or statistically significant associations (Table 2; beta estimates consistent with approximately a 2-point increase and 5-point decrease in SRS scores, with 95% CIs including the null, were found for Q4 vs. Q1 of HR-FV and LR-FV, respectively). After adjustment, increased HR/LR-FV intake was not associated with changes in SRS scores (Table 2). When examining associations of fruit and vegetable intake, vegetable intake, as well as combined fruit/vegetable intake, were associated with decreases in SRS scores of approximately 8 to 12 points, which did not reach statistical significance (Q4 vs. Q1 adjusted $\beta = -8.70$, 95% CI −23.9, 6.5 for vegetable intake which

TABLE 1 Basic characteristics of the study population overall and by lowest and highest high-residue fruit and vegetable intake (HR-FV) quartile

	Overall (*n* = 154)	HR-FV Q1 (*n* = 38)	HR-FV Q4 (*n* = 38)
	n (%)		
Study sites[a]			
West Coast	77 (50%)	22 (57.9%)	17 (44.7%)
East Coast	77 (50%)	16 (42.1%)	21 (55.3%)
Child sex			
Male	83 (53.9%)	25 (65.8%)	20 (52.6%)
Female	71 (46.1%)	13 (34.2%)	18 (47.4%)
Maternal ethnicity			
Hispanic/Latino	30 (19.5%)	5 (13.2%)	9 (23.7%)
Not Hispanic/Latino	124 (80.5%)	33 (86.8%)	29 (76.3%)
Maternal race			
White	104 (67.5%)	25 (65.8%)	20 (52.6%)
Black/African American	9 (5.8%)	2 (5.3%)	5 (13.2%)
Asian & Pacific Islander	20 (13.0%)	7 (18.4%)	6 (15.8%)
Multiple/Other Race	16 (10.4%)	3 (7.9%)	5 (13.2%)
Missing	5 (3.3%)	1 (2.6%)	2 (5.3%)
Household income			
$0–50,000	36 (23.4%)	10 (26.3%)	9 (23.7%)
$50,001-100,000	58 (37.7%)	15 (39.5%)	15 (39.5%)
$100,001+	60 (38.9%)	13 (34.2%)	14 (36.8%)
Maternal education level			
High School Diploma or Less	20 (13.0%)	5 (13.2%)	6 (15.8%)
Some College	43 (27.9%)	10 (26.3%)	13 (34.2%)
Bachelor's degree	46 (29.9%)	10 (26.3%)	9 (23.7%)
Graduate degree	44 (28.6%)	13 (34.2%)	9 (23.7%)
Missing	1 (0.6%)		1 (2.6%)
Prenatal smoking			
Active smoking	5 (3.3%)	3 (7.9%)	0 (0%)
Secondhand, not active smoking	2 (1.3%)	1 (2.6%)	0 (0%)
No smoking exposure	120 (77.9%)	26 (68.4%)	31 (81.6%)
Missing	27 (17.5%)	8 (21.1%)	7 (18.4%)
Maternal weight			
Obese	47 (30.5%)	14 (36.8%)	7 (18.4%)
Overweight	40 (26.0%)	8 (21.1%)	12 (31.6%)
Normal	61 (39.6%)	16 (42.1%)	17 (44.7%)
Underweight	2 (1.3%)	0 (0%)	1 (2.6%)
Missing	4 (2.6%)		1 (2.6%)
Parity			
1	68 (44.2%)	16 (42.1%)	15 (29.5%)
2	62 (40.3%)	15 (39.5%)	19 (50.0%)
3+	23 (14.9%)	7 (18.4%)	3 (7.9%)
Missing	1 (0.6%)		1 (2.6%)
Prenatal vitamin use			
Yes	145 (94.2%)	36 (94.7%)	37 (97.4%)
No	8 (5.2%)	2 (5.3%)	0 (0%)
Missing	1 (0.6%)		1 (2.6%)

(Continues)

T A B L E 1   (Continued)

	Overall (*n* = 154)	HR-FV Q1 (*n* = 38)	HR-FV Q4 (*n* = 38)
	n (%)		
Autism diagnosis			
Yes	32 (20.8%)	13 (34.2%)	8 (21.1%)
No	120 (77.9%)	25 (65.8%)	30 (78.9%)
Missing	2 (1.3%)		
	Mean (*std*)		
Maternal age (years)	33.9 (4.6)	33.6 (3.8)	33.7 (5.1)
Pre-pregnancy BMI (kg/m²)[b]	28.0 (7.1)	28.8 (7.2)	26.1 (5.1)
Total SRS raw score[b]	35.8 (26.2)	38.0 (27.5)	33.5 (29.2)
Total SRS T score[b]	47.7 (10.1)	48.6 (10.7)	46.9 (11.3)
Mullen ELC score[b]	99.1 (20.9)	96.0 (20.8)	99.1 (23.3)

[a]EARLI recruited participants at four sites; West coast study sites include UC Davis and Kaiser Permanente Northern CA; East coast study sites include Drexel/CHOP and Johns Hopkins University.
[b]Four were missing information on BMI. Twenty-three individuals in EARLI did not have SRS scores and 9 did not have Mullen Scores (none overlapping).

is consistent with roughly a 1/3 SD unit decrease in raw SRS scores; Q4 vs. Q1 adjusted $\beta = -12.76$, 95% CI: -27.8, 2.3 for combined fruit and vegetable intake) (Table 2). Fruit intake on its own did not suggest the same association (Q4 vs. Q1 adjusted β for SRS = -0.11, 95% CI -14.1, 13.8 for fruit intake) (Table 2).

When examining associations with weighted residue scores, as for HR/LV-FV intake, we did not find evidence for associations with ASD-related traits (Table 3). However, a reduction in SRS scores was observed for the PRBS incorporating reported organic intake (PRBS-organic) (Q4 vs. Q1 adjusted $\beta = -16.86$, 95% CI -31.9, -1.8) (Table 3). Additional adjustment for a range of other factors, including maternal folate intake and additional maternal dietary and demographic characteristics, did not materially alter these findings for SRS scores (Table S3).

In secondary analyses, pesticide residue scores were not associated with MSEL ELC scores (Tables S4 and S5). However, consistent with associations with SRS scores, combined fruit and vegetable intake was associated with higher MSEL ELC scores (indicative of improved cognitive development), driven primarily by vegetable intake (Table S4).

DISCUSSION

In this high-familial probability cohort, we examined the relationship between pesticide residues in the diet during pregnancy in association with child ASD-related outcomes at age 3. Overall, we did not find evidence to support associations in the hypothesized positive direction with ASD-related traits, and in some cases, associations with diet-based residue in the opposite direction

(suggesting an inverse relationship) were found. However, decreases in ASD-related traits were observed with overall fruit and vegetable intake, suggesting beneficial nutrients in these foods could outweigh adverse effects of pesticide residues in the diet on these outcomes. Additional considerations may play into these findings, as further discussed below.

The FFQ used in our study, a modified version of the DHQ, was shown to be comparable to the Harvard/Willett FFQ used in original work for assessment of dietary pesticide exposure. Score development using the PDP was reproducible across different study years, and there were consistencies in pesticide residues across foods assessed in these studies. Original work developing the PRBS verified the score's utility in approximating urinary and serum pesticide biomarkers in a large population-based cohort, validating the score is an accurate approximation of total pesticide exposure (Hu et al., 2016).

As noted, we had hypothesized that pesticide residue scores would be associated with increases in ASD-related traits, given prior evidence for adverse effects of prenatal exposure to pesticides on neurodevelopment (Korrick & Sagiv, 2008; Rosas & Eskenazi, 2008). However, null associations and results consistent with a non-significant decrease in ASD-related traits were observed in many analyses. Results for our primary exposure assessment, intake of high and low residue fruits and vegetables, did not suggest strong associations with ASD-related traits. Given the high correlation between high and low residue FV, future work should further consider ways to address the challenge of identifying distinct contributions of these correlated exposure sources, such as in mixtures analyses. Results for associations with ASD-related traits were also similar for the weighted residue scores incorporating FV intake more broadly. We observed an association

TABLE 2 Crude and adjusted associations (β estimates and 95% confidence intervals) between maternal HR/LR-FV intake & overall fruit and vegetable intake during pregnancy and child SRS scores ($n = 131$)

Associations with SRS scores			
	n	Crude (β, 95% CI)	Adjusted (β, 95% CI)[a]
HR-FV			
Q1	34	(Referent)	(Referent)
Q2	33	−2.67 (−15.1, 9.8)	0.10 (−12.2, 12.4)
Q3	34	−2.09 (−14.5, 10.3)	4.34 (−9.9, 18.6)
Q4	30	−4.47 (−17.2, 8.3)	1.37 (−14.6, 17.4)
LR-FV			
Q1	32	(Referent)	(Referent)
Q2	32	−8.53 (−21.1, 4.1)	−4.45 (−17.7, 8.8)
Q3	36	2.22 (−10.0, 14.5)	6.01 (−8.5, 20.5)
Q4	31	−6.40 (−19.1, 6.3)	−5.57 (−22.4, 11.3)
Fruit intake			
Q1	31	(Referent)	(Referent)
Q2	35	−0.46 (−13.1, 12.1)	1.71 (−10.4, 13.8)
Q3	34	−0.65 (−13.3, 12.0)	2.95 (−9.6, 15.5)
Q4	31	−2.90 (−15.9, 10.1)	−0.11 (−14.1, 13.8)
Vegetable intake			
Q1	33	(Referent)	(Referent)
Q2	33	−9.79 (−22.2, 2.7)	−8.56 (−20.8, 3.7)
Q3	33	−5.00 (−17.4, 7.4)	−0.78 (−14.4, 12.9)
Q4	32	−8.79 (−21.3, 3.7)	−8.70 (−23.9, 6.5)
Total fruit and vegetable intake			
Q1	33	(Referent)	(Referent)
Q2	33	−16.58 (−28.7, −4.4)	−11.28 (−23.4, 0.83)
Q3	34	−4.48 (−16.6, 7.6)	−0.45 (−13.3, 12.4)
Q4	31	−13.1 (−25.5, −0.8)	−12.76 (−27.8, 2.3)

[a]Adjusted for maternal age, maternal pre-pregnancy BMI, child sex, total calorie intake, and a modified version of the AHEI (Alternative Healthy Eating Index) dietary pattern score that excluded fruits, vegetables, and alcohol. HR-FV and LR-FV additionally adjusted for one another.

TABLE 3 Crude and adjusted associations (β estimates and 95% confidence intervals) between weighted versions of maternal pesticide residue burden scores during pregnancy and child raw total SRS scores ($n = 131$)

	n	Crude (β, 95% CI)	Adjusted (β, 95% CI)[a]
PRBS			
Q1	34	(Referent)	(Referent)
Q2	32	−1.83 (−14.4, 10.7)	2.66 (−10.4, 15.8)
Q3	35	−3.49 (−15.8, 8.8)	2.98 (−10.4, 16.4)
Q4	30	−4.51 (−17.3, 8.3)	0.28 (−16.0, 16.5)
PRBS-F			
Q1	33	(Referent)	(Referent)
Q2	33	−3.39 (−15.9, 9.2)	1.31 (−11.6, 14.2)
Q3	35	−3.82 (−16.2, 8.5)	2.87 (−10.8, 16.6)
Q4	30	−5.15 (−18.0, 7.7)	−0.28 (−16.7, 16.1)
PRBS–Organic			
Q1	32	(Referent)	(Referent)
Q2	35	−5.38 (−17.7, 7.0)	−5.79 (−17.7, 6.1)
Q3	33	−3.51 (−16.0, 9.0)	−4.11 (−16.9, 8.7)
Q4	31	−11.39 (−24.1, 1.3)	−16.86 (−31.9, −1.8)
OC-PRBS			
Q1	33	(Referent)	(Referent)
Q2	33	−3.43 (−16.0, 9.1)	0.56 (−12.1, 13.3)
Q3	33	−1.15 (−13.7, 11.4)	5.06 (−8.4, 18.5)
Q4	32	−4.28 (−16.9, 8.4)	−0.69 (−16.4, 15.1)
OP-PRBS			
Q1	34	(Referent)	(Referent)
Q2	32	−2.53 (−15.1, 10.0)	2.07 (−10.4, 14.6)
Q3	35	−2.20 (−14.5, 10.1)	3.76 (−10.0, 17.6)
Q4	30	−4.89 (−17.7, 7.9)	0.87 (−15.4, 17.1)

[a]Adjusted for maternal age, maternal pre-pregnancy BMI, child sex, total calorie intake, and a modified version of the AHEI (Alternative Healthy Eating Index) dietary pattern score that excluded fruits, vegetables, and alcohol.

bordering statistical significance of higher fruit and vegetable intake and decreases in ASD-related traits, which appeared to be driven more by vegetable intake. Taken together, these findings may suggest that the potential effects of pesticide residues on ASD-related outcomes may be counterbalanced by the effects of vegetable intake. Further work should examine this hypothesis, address factors that may drive the suggested protective association of vegetable intake based on nutrients or other health-related factors, and replicate this finding in larger samples.

We also did not observe differences in associations with outcomes according to the modified versions of the PRBS we tested, with the potential exception (in the unexpected direction) of the organic PRBS. Although we had a small number of women reporting regular intake of organic foods, incorporating reported organic intake into scores did result in improved relationships between score ranks (PRBS-organic). However, accounting for organic intake in this modified version of the PRBS may have also unintentionally captured other factors related to healthy behaviors, and may have introduced negative bias into this score when examining associations with outcomes.

Though adjustment for additional sociodemographic and dietary factors did not materially alter our results, we cannot rule out potential residual confounding by more challenging-to-capture health-related characteristics. Those who were ranked in the top quartile of HR-FV intake in our study had a lower BMI, ate a generally healthier diet, and more often ate organic foods compared to those in the bottom quartile; factors consistent with characteristics of a previous study that assessed high-residue fruit and vegetable intake in a cohort of women receiving infertility treatment (Chiu, Williams, Gillman, Gaskins, et al., 2018). For ASD, previous

studies have demonstrated decreased risk with maternal folic acid supplementation, as well as (with somewhat less consistency) polyunsaturated fatty acids (DeVilbiss et al., 2015; Julvez et al., 2016; Lyall et al., 2013; Schmidt et al., 2012). Nonetheless, in addition to residual confounding, it is also possible that live birth bias could also play into unexpected null and inverse results (Raz et al., 2018), given that prior work has shown that women who were in the top quartile of high-residue pesticide exposure from fruit and vegetable intake had a greater probability of pregnancy loss and a lower probability of clinical pregnancy compared to women who were in the bottom quartile, representing the lowest exposure to pesticide residues (Chiu, Williams, Gillman, Gaskins, et al., 2018).

The residue score accounts for hundreds of pesticides tested in the PDP across several classes. As such, it represents an efficient way to capture exposure to multiple classes of pesticides and may help address pesticide mixture effects. Few prior studies have considered combined effects of pesticides on ASD-related outcomes, though a number of prior studies have supported associations between prenatal pesticide exposure and ASD outcomes. Braun and colleagues examined the relationship between environmental chemical exposures and ASD-related traits in mixture analyses in the HOME cohort in Ohio, and found measured levels of *trans*-nonachlor (accounting for other pesticides and endocrine-disrupting chemicals) were associated with increases in SRS-T scores (Braun et al., 2014). In a large nested case–control study of births in Finland conducted by Brown et al, children in the top 75th percentile of maternal *p,p′*-DDE levels increased the odds of ASD (Brown et al., 2018). The Early Markers for Autism (EMA) population-based case control study conducted in California reported null results when assessing the relationship between *p,p′*-DDE and ASD diagnoses in California, but showed a non-monotonic association with intellectual disability (Lyall, Croen, Sjödin, et al., 2017).

Though fruits and vegetables are the primary source of exposure to pesticides in use today, intake of these foods may not best capture total dietary exposure to some classes of pesticides including OCs, given OC pesticides are lipophilic chemicals (Fourth National Report on Human Exposure to Environmental Chemicals, 2009). OC pesticides have been largely banned and replaced by the OP and pyrethroid classes. Previous work on sources of pesticide exposures in diet found that parents and children consumed most OC pesticides (including *p,p′*-DDE as well as others) from dairy, and fish (Vogt et al., 2012). Furthermore, prior work examining and developing class-specific PRBS has reported stronger relationships between the OP-PRBS and measured levels of OP metabolites (creatinine-adjusted dimethylphosphate, diethylphosphate, dimethylthiophosphate, diethylthiophosphate, and dimethyldithiophosphate) than between the OC-PRBS and measured levels of OC metabolites (lipid-adjusted

hexachlorobenzene, oxychlordane, *trans*-nonachlor and heptachlor epoxide) (Hu et al., 2016). This could be in part explained by reduced body burden of OCs in the decades following their ban (Hagmar et al., 2006). Though the fatty foods included here were classified as low residue by the PDP, future work addressing pesticide exposure may consider additional food sources.

Different classes of pesticides may have differing associations with ASD, and there is evidence from other studies pesticides such as OPs and pyrethroids may be related to ASD outcomes (Shelton et al., 2014; von Ehrenstein et al., 2019). OPs are known to inhibit acetylcholinesterase in the brain, resulting in neurotoxic effects at high exposure (Fourth National Report on Human Exposure to Environmental Chemicals, 2009; Sagiv et al., 2018). However, neurological and developmental effects of routine low-dose exposure to OPs in humans is not well categorized. A 10-fold increase in prenatal urinary OP levels (specifically DAPs and DMs) was positively associated with child SRS scores for women who live close to agricultural applications during pregnancy (Sagiv et al., 2018). At the same time, other studies have shown null results between OP pesticides and SRS scores (Millenson et al., 2017). Another high familial probability cohort study in California (MARBLES: Markers of Autism Risk in Babies—Learning Early Signs), which enrolled participants at a similar time to EARLI, showed no association between urinary OP markers and ASD diagnosis (Philippat et al., 2018). These mixed findings suggest the need for further work examining associations with measured levels of pesticides across multiple classes and comparing these associations with dietary-based residue exposures to better consider the role of primary sources. In addition, given suggestions that combined exposure can create measurable risk even when the individual toxicant is not associated with adverse outcomes (Chiu, Bellavia, et al., 2018; Kortenkamp, 2007; Rider et al., 2010), studies with the ability to examine multiple classes of pesticides will be useful in further addressing the question of combined effects.

In this study, we had the ability to examine associations with broader cognitive development. Mullen scores were generally reduced with higher PRBS quartiles, although these associations were not statistically significant. Other studies have also examined more general neurodevelopmental outcomes that may be influenced by pesticides (Bradman et al., 2003; Dewan et al., 2013). Several studies have shown that prenatal exposure to OPs are related to cognitive deficits (Bouchard et al., 2011; Engel et al., 2016; Eskenazi et al., 2007; Philippat et al., 2018; Rauh et al., 2012) and ASD-related traits (Eskenazi et al., 2007; Furlong et al., 2014; Sagiv et al., 2018). However, there are inconsistencies regarding associations between OC exposure and child neurodevelopmental outcomes (Eskenazi et al., 2006; Gaspar et al., 2015; Lyall, Croen, Sjödin, et al., 2017; Yamazaki

et al., 2018), and some studies have reported sex differences (Braun et al., 2014; Gaspar et al., 2015; Pan et al., 2009; Sioen et al., 2013), which we did not have sufficient power to address here. Several mechanisms may underlie these potential associations. Thyroid hormone disruption, inflammation, and oxidative stress have the ability to influence neurodevelopment of the fetus (and have been linked with ASD [Garay & McAllister, 2010; Goines & Van de Water, 2010; Lyall, Anderson, Kharrazi, & Windham, 2017; Soldin et al., 2003; Yau et al., 2015]) and have been shown to be influenced by pesticide exposure (De Felice et al., 2016; C. Li et al., 2014; Mense et al., 2006; Starek-⊠wiechowicz et al., 2017; Wang et al., 2017).

This is the first study to address pesticide residues in the diet in association with ASD-related outcomes. Strengths of our work include use of prospectively collected data, notably dietary data during pregnancy, and the consideration of several versions of the weighted-PRBS. These included the incorporation of organic food status and inclusion of fatty foods from the PDP, to help address other sources of dietary exposure to pesticides in addition to conventional produce.

Several limitations should also be noted. Though fruits and vegetables are the main source of pesticide exposure in the diet, we were limited in our ability to address residues from other food sources due to the scope of the PDP database. The majority of foods tested by the PDP were fruits and vegetables (Pesticide Data Program Annual Summary, Calendar Year *2013*, 2014), and consequently there were limited fatty foods, such as fish and dairy, tested by the PDP that were relevant to commodities assessed in the DHQ. Dietary data from EARLI was collected using a slightly modified version of the DHQ, and although the DHQ has been validated and the changes made did not alter calculation of the PRBS, the modified version of the DHQ used here has not itself been examined in validation work. Furthermore, we cannot rule out potential exposure misclassification due to self-report of diet, however our work and prior studies have demonstrated broad validity not only of PRBS but also of self-reported diet through FFQ measurement (Rimm et al., 1992; Subar et al., 2001), and any such misclassification would be expected to be non-differential with respect to the outcome due to prospective collection of data. Finally, we also had a small sample size, limiting our ability to examine autism diagnosis due to an insufficient number of cases in our study, and yielding wide confidence intervals in several analyses, highlighting the need for future larger studies on this topic.

CONCLUSIONS

Diet is not only the primary source of pesticide exposure in the general population (Fourth National Report on Human Exposure to Environmental Chemicals, 2009;

Morgan, 2012; Xue et al., 2014), but it is also a source of micronutrients that can potentially reduce risk of adverse outcomes or interact with pesticide exposure. Additional work is needed to parse the role of diet and pesticides in ASD and related outcomes. We did not find associations indicating an increased probability of ASD-related traits with dietary pesticide residue scores in this high-familial probability cohort. Instead, we found that vegetable intake, or perhaps key nutrients in vegetables or correlates of a diet with high vegetable intake, was inversely associated with ASD-related traits. Future work should follow up on the suggestive findings we observed for this association with vegetable intake, and further consider combined effects of prenatal exposure to pesticides on ASD-related outcomes.

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