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Prenatal and infant exposure to ambient pesticides and autism spe disorder in children: population based case-control study

Ondine S von Ehrenstein, associate professor,[1,2] Chenxiao Ling, research assistant,[2] Xin Cui, researc assistant,[2,3,4] Myles Cockburn, professor,[5] Andrew S Park, research assistant,[2] Fei Yu, researcher,[6] J associate professor,[7] and Beate Ritz, professor[2,8,9]

[1]Department of Community Health Sciences, Fielding School of Public Health, University of California, 951772, Los Angeles, CA 90095-1772, USA
[2]Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, C
[3]Perinatal Epidemiology and Health Outcomes Research Unit, Division of Neonatology, Department of Pediatrics, Stanford University School of Medicine and Lucile Packard Children's Hospital, Palo Alto, C
[4]California Perinatal Quality Care Collaborative, Palo Alto, CA, USA
[5]Preventive Medicine, University of Southern California, Los Angeles, CA, USA
[6]Department of Biostatistics, Fielding School of Public Health, University of California, Los Angeles, CA
[7]Program in Public Health, Susan and Henry Samueli College of Health Sciences, University of Califor Irvine, CA, USA
[8]Department of Environmental Health Sciences, Fielding School of Public Health, University of Californ Angeles, CA, USA
[9]Department of Neurology, Geffen School of Medicine, University of California, Los Angeles, CA, USA
Correspondence to: O von Ehrenstein ovehren@ucla.edu

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Abstract

Objective

To examine associations between early developmental exposure to ambient pesticides and autis spectrum disorder.

Design

Population based case-control study.

Setting

California's main agricultural region, Central Valley, using 1998-2010 birth data from the Offi Vital Statistics.

Population

2961 individuals with a diagnosis of autism spectrum disorder based on the *Diagnostic and Sta Manual of Mental Disorders*, fourth edition, revised (up to 31 December 2013), including 445 intellectual disability comorbidity, were identified through records maintained at the California Department of Developmental Services and linked to their birth records. Controls derived from records were matched to cases 10:1 by sex and birth year.

Exposure

Data from California state mandated Pesticide Use Reporting were integrated into a geographic information system tool to estimate prenatal and infant exposures to pesticides (measured as po pesticides applied per acre/month within 2000 m from the maternal residence). 11 high use pes were selected for examination a priori according to previous evidence of neurodevelopmental t in vivo or in vitro (exposure defined as ever *v* never for each pesticide during specific developr periods).

Main outcome measure

Odds ratios and 95% confidence intervals using multivariable logistic regression were used to associations between pesticide exposure and autism spectrum disorder (with or without intellec disabilities) in offspring, adjusting for confounders.

Results

Risk of autism spectrum disorder was associated with prenatal exposure to glyphosate (odds ra 95% confidence interval 1.06 to 1.27), chlorpyrifos (1.13, 1.05 to 1.23), diazinon (1.11, 1.01 to malathion (1.11, 1.01 to 1.22), avermectin (1.12, 1.04 to 1.22), and permethrin (1.10, 1.01 to 1. autism spectrum disorder with intellectual disability, estimated odds ratios were higher (by abo for prenatal exposure to glyphosate (1.33, 1.05 to 1.69), chlorpyrifos (1.27, 1.04 to 1.56), diazi (1.41, 1.15 to 1.73), permethrin (1.46, 1.20 to 1.78), methyl bromide (1.33, 1.07 to 1.64), and myclobutanil (1.32, 1.09 to 1.60); exposure in the first year of life increased the odds for the di with comorbid intellectual disability by up to 50% for some pesticide substances.

Conclusion

Findings suggest that an offspring's risk of autism spectrum disorder increases following prena exposure to ambient pesticides within 2000 m of their mother's residence during pregnancy, cc with offspring of women from the same agricultural region without such exposure. Infant expo could further increase risks for autism spectrum disorder with comorbid intellectual disability.

Introduction

Autism spectrum disorder comprises severe developmental disorders characterized by atypical socialization, and restricted and repetitive behaviors and interests. Genetics have a role,[1] [2] with heritability estimates of 38%[3] to 83%,[4] but more information is needed about environmental fa operating in early development.[3] Prenatal exposures to several types of pesticides have been as with impaired neurodevelopment,[5] [6] [7] [8] and the few studies that have considered autism spectru disorder have suggested that organophosphates[9] and organochlorines[10] [11] could increase risk.

Experimental in vivo and in vitro studies of autism[12] [13] [14] suggested changes in neuroprotein le altered gene expression, and neurobehavioral abnormalities after exposure to certain pesticides example, when the organophosphate chlorpyrifos was administered prenatally at subtoxic level mouse model that displays several behavioral traits related to the autism spectrum, male offspr showed delayed motor function maturation and enhanced behavioral features associated with a spectrum disorder.[13]

So far, knowledge about pesticide exposure in the real world and risk of autism spectrum disor scarce. In this large population based study, we assess prenatal and infant exposure to high use pesticides, which have been a priori selected on the basis of previous evidence for their experir neurodevelopmental toxicity. Use of these pesticides in an agriculturally intensive region of Ca United States, were recorded in the California state mandated Pesticide Use Reporting (CA-PU program. These records were integrated in our geographic information system tool, which link exposure records to addresses from birth records of the study population.

Methods

Study design and population

Records of autism spectrum disorder cases were retrieved from the registry maintained at the C Department of Developmental Services (DDS), based on diagnostic data collected by contracte regional centers (https://www.dds.ca.gov/RC/RCList.cfm). We included all individuals with a diagnosis of autistic disorder (code 299.00) reported on the DDS client development evaluatior which implements criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourt revised (DSM-IV-R)[15] up to 31 December 2013 ("autistic disorder" is the most severe diagnos autism spectrum disorder under DSM-IV criteria).[16] Validation studies have established the rel and validity of the DDS client development evaluation report in California.[17] Eligibility for DI services does not depend on citizenship or financial status, and services are available to all chil

used California birth records data from the Office of Vital Statistics to create a statewide case-c sample of 1998-2010 births. We matched DDS case records to birth records using a probabilist linkage[18] based on child and parental identifiers including first and last name, birth date, and se estimated the probability that two records were for the same person by assigning total linkage s generated for matches with the National Program of Cancer Registries Link Plus software (link 86.3%).[19] We manually checked cases with borderline scores; the main reason for non-linkage missing information on birth or DDS records.

Randomly selected controls from birth records were matched to each case 10:1 by birth year ar From the statewide sample (n=33 921 cases, n=339 210 controls), we excluded 3401 (10%) cas records and 42 519 (12.5%) control records with missing, implausible, or non-viable gestationa (included range 147-322 days) or birth weights (included range 500-6800 g), and non-singleto We also excluded 1296 (0.4%) controls who died before age 6 (identified by linkage to the Cal death registry).[18] We restricted our sample to the eight major agricultural counties (San Joaqui Stanislaus, Merced, Madera, Fresno, Kings, Tulare, and Kern); 38 331 participants (2961 cases 370 controls) resided here at the time of birth and diagnosis. Although the CA-PUR covers the California, the mandatory reporting reflects agricultural use pesticides (see supplemental eMet which has a different spatial resolution from other pesticide use recorded in the Pesticide Use F system. In urban areas (such as on structures and right of way applications or near roadway applications), non-agricultural pesticide use is most common but this is only reportable to the F Use Reporting at the county level (low spatial resolution); thus variables that estimate pesticide exposure for urban areas would be expected to result in markedly higher exposure misclassific

We distinguished cases according to comorbid intellectual disability (in our study period recor "mental retardation" and diagnosed according to DSM-IV criteria corresponding to ICD-9 (international classification of diseases, 9th revision)). Information on pregnancy characteristic including gestational age, birth weight, pregnancy complications, and sociodemographics (maternal/paternal age, race/ethnicity, education) was retrieved from birth records.

Pesticide exposure

Residential birth addresses, as listed on birth certificates, were geocoded by our open source ge (historical address information was not available).[20] CA-PUR[21] includes information on all agr pesticide applications with the date, location, and amount of active ingredient applied (see supp eMethods). CA-PUR reports were combined with land use survey information from the Califor Department of Water Resources, which provides the location of specific crops, in a geographic information system-based computer model to estimate pesticide exposure from agricultural app (technical details published elsewhere[22]). Briefly, for each pesticide, we summed pounds appli acre (1 acre=4046.9 m^2) per month within a 2000 m radius of each residential address. Our geo information system tool generated calendar month averages, which we then used to generate developmental period-specific averages (for the three months before gestation, each month of gestation/gestation, and the first year of life) using weights according to the developmental period/gestational days covered by a calendar month. For sensitivity analyses, we also used a 2

radius in the same manner. The length of the gestational period for controls was truncated to th of the matched cases to ensure comparable exposure periods. We defined exposure as any vers to a specific substance during a specific developmental period; we chose this method to avoid assumptions about the relative toxicity of agents, shape of the association, or the exposure pote to presence at the time of application. It is, however, possible that this approach generates non-differential exposure error and underestimates effects.

We a priori decided to select from among 25 most used pesticide substances with peer reviewe published reports of neurodevelopmental interference, leaving 11 pesticides for analysis (classi shown in eTable 1). These substances included glyphosate,[23] [24] [25] [26] chlorpyrifos,[9] [27] diazinon, acephate,[31] [32] [33] malathion,[33] [34] [35] permethrin,[6] [9] bifenthrin,[9] [33] [36] methyl bromide,[37] [38] imidacl [40] avermectin,[41] [42] and myclobutanil.[14] [43]

Statistical analysis

Tetrachoric/Spearman correlations (binary/continuous) of pesticide exposures were examined and between developmental periods. Pesticide use over time was plotted; maps were drawn usi ArcGIS 10.4 (ESRI). Odds ratios and 95% confidence intervals were estimated for associations between developmental period-specific pesticide exposures and autism spectrum disorder with unconditional logistic regression. We adjusted all models for the matching variables sex and ye birth, and selected potential confounders on the basis of previous knowledge.[10] [44] These potent confounders included maternal age, indicators of socioeconomic status (that is, maternal race/e and education), and nitrogen oxides[44] (NOx; pregnancy average) as a marker of traffic related pollution. For air pollution assessment, we used the California Line Source (CALINE4) emissi model, a modified Gaussian dispersion model of local gasoline and diesel vehicles emissions e for 1500 m distance from the residential address based on traffic volume, roadway geometry, v emission rates, and meteorological conditions (wind speed/direction, temperature, atmospheric and mixing heights).[45] [46] [47]

While we estimated parameters for each pesticide in separate models because of collinearities, explored multi-pesticide models for two or three selected pesticides for substances that showed associations with autism spectrum disorder in single pesticide models and belonged to differen chemical classes. For those pesticides with more than one substance per class (organophosphat pyrethroids), we selected a representative chemical (eg, chlorpyrifos for organophosphates) bas the strongest previous evidence for neurodevelopmental toxicity.[48] To further adjust for coexpo adjusted for 11 pesticides in logistic models; in sensitivity analyses, a semi-Bayesian approach used as described elsewhere.[49] There was little difference in effect estimates between the fully conventional logistic and the hierarchical modeling approach, so we present the logistic model results only.[49] [50] [51]

We also stratified analyses by autism spectrum disorder with or without comorbid intellectual to assess risk in more severely impaired individuals separately. We conducted sensitivity analy adjusting for additional variables including maternal birth place (US *v* non-US); residence in u

rural areas[52]; socioeconomic status categories based on census data related to income, educatio occupation[53]; source of payment for delivery (indicator of socioeconomic status); and preterm None of these variables changed the estimates of interest by more than 5%, thus they were not in final models.[54] Sensitivity analyses also included restricting to term births, and stratifying by Analyses were conducted with SAS 9.3.

Patient and public involvement

No patients were directly involved in setting the research question or the outcome measures, nc they involved in developing plans for design or implementation of the study. However, the stuc responds to concerns by the families of patients with autism that environmental toxic exposure life are suspected to contribute to risks for autism spectrum disorder. There are plans to dissem results of the research to the relevant patient community. Affected families are thanked in the acknowledgments.

Results

Baseline characteristics and exposure

In our sample, individuals with autism spectrum disorder were mainly male (>80%), had older and had mothers who had completed more years of education than control mothers (table 1). Correlations between several pesticides in the same or across developmental periods were mod high (r_t=0.45-0.85; eTable 2). In figure 1, we present a map of the study area showing pesticide applications for the most used substance glyphosate as an example.

Table 1

Study population characteristics by autism spectrum disorder status and population controls the Central Valley, CA*

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ASD=autism spectrum disorder; ID=intellectual disability. Data are number (%) or individuals.

*Central Valley counties include San Joaquin, Stanislaus, Merced, Madera, Fresno, Kings, Tulare, and Kern.

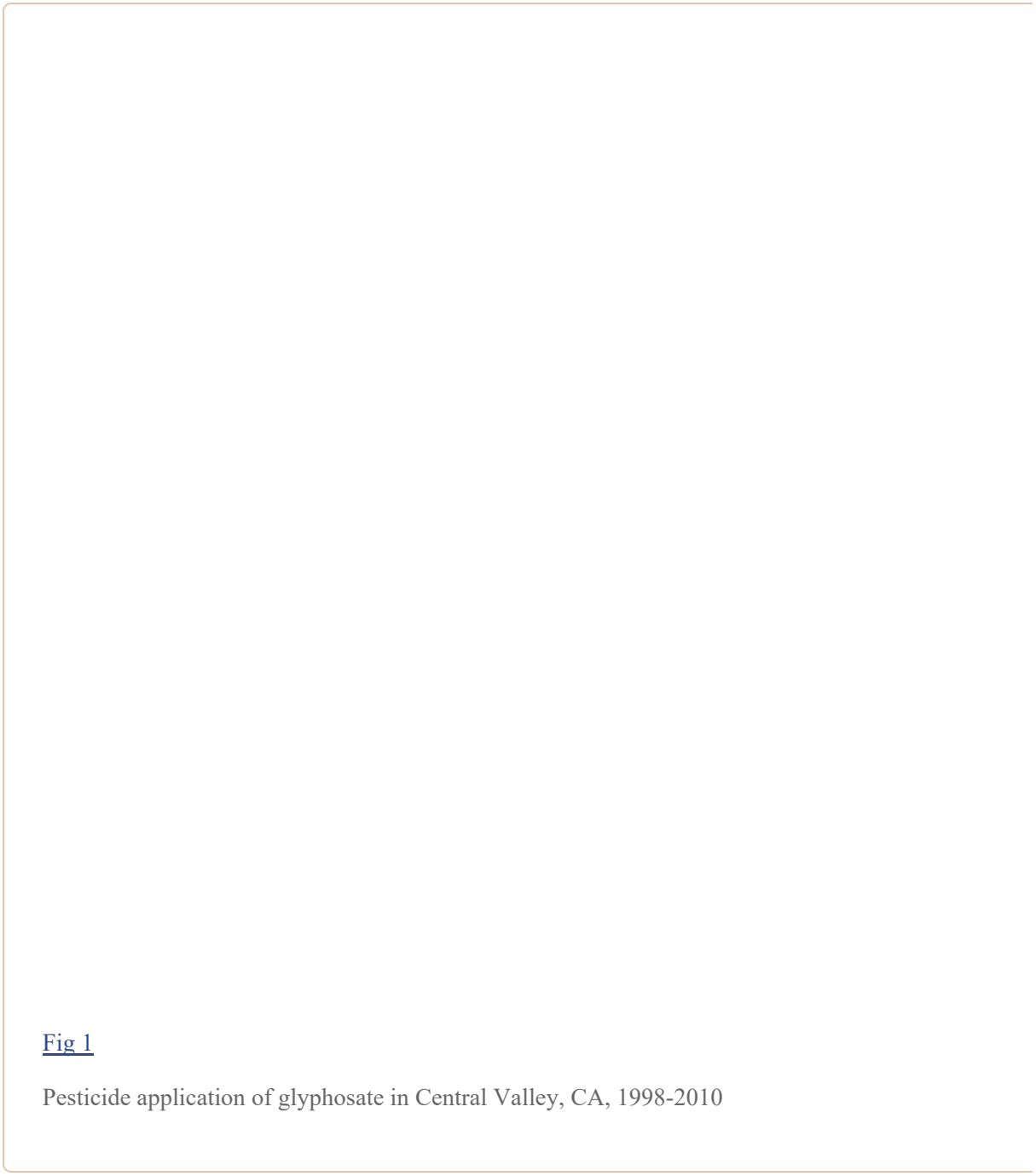

Fig 1

Pesticide application of glyphosate in Central Valley, CA, 1998-2010

Association between autism spectrum disorder and exposure to pesticides, coadjuste developmental period exposures

For all cases of autism spectrum disorder combined, coadjusted for developmental period-spec exposures (three months before pregnancy, during pregnancy, and during the first year of life), ratios were increased for pregnancy exposure to most substances. Associations were strongest chlorpyrifos (1.15; 95% confidence interval 1.02 to 1.29), diazinon (1.14; 1.02 to 1.28), and av (1.14; 1.03 to 1.26). Related to first year of life exposure, most odds ratios were close to one, a the odds ratios for bifenthrin, malathion, and glyphosates were slightly raised (table 2). For aut spectrum disorder with intellectual disability comorbidity, coadjustment for the exposures in al periods resulted in attenuated effect estimates during and before pregnancy, while odds ratios b more pronounced for exposures in the first year of life, particularly for glyphosate (1.60; 1.09 t diazinon (1.45; 1.11 to 1.89), malathion (1.29; 1.00 to 1.65), and bifenthrin (1.33; 1.03 to 1.72; Exposure in the three months before pregnancy (indicating exposure just before or around conc had weaker associations with autism spectrum disorder than exposure during pregnancy or the of life, after exposure period coadjustment (table 2, eTable 3). We saw variation in exposure be developmental periods to each pesticide considered, likely due to annual and seasonal changes application rates (eg, for permethrin, among the controls, 1.5% were solely exposed in the thre before pregnancy, 4.8% were exposed only during pregnancy, 7.6% were exposed only in the f of life, and 12.1% were exposed in all three periods; eTable 4). For exposures by trimester, no patterns were identified (data not shown).

Table 2

Odds ratios and 95% confidence intervals* for association between pesticide exposure and cases of autism spectrum disorder (ASD) combined and those with intellectual disability comorbidity, coadjusted for developmental period of pesticide exposure, by pesticide subst

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*Logistic regression; adjusted for year of birth, sex, maternal race or ethnicity, maternal age, maternal educa and NOx (CALINE4) as a marker of traffic related air pollution, and simultaneously for exposures three mo before pregnancy (just before or around conception), during pregnancy, and during the first year of life; pest exposure defined as ever versus never to specific substance in considered developmental period.
†Glyphosate compounds include glyphosate isopropylamine salt, glyphosate potassium salt, glyphosate monoammonium salt, glyphosate diammonium salt, glyphosate trimesium, and glyphosate dimethylamine sa

Association between prenatal or infant exposure to pesticides and autism spectrum di

For all cases of autism spectrum disorder, considering the pregnancy and infant exposures sepa exposure during pregnancy was associated with about a 10% increase in adjusted odds ratios fo glyphosate (1.16; 95% confidence interval 1.06 to 1.27), chlorpyrifos (1.13; 1.05 to 1.23), diaz (1.11; 1.01 to 1.21), malathion (1.11; 1.01 to 1.22), avermectin (1.12; 1.04 to 1.22), and permet (1.10; 1.01 to 1.20). Also adjusting for all 11 pesticides resulted in attenuation of associations. However, odds ratios for glyphosate and avermectin remained elevated for exposure during pre while odds ratios for the remaining pesticides were close to one, and the odds ratio for imidacl below one (table 3).

Table 3

Odds ratios and 95% confidence intervals for association between all cases of autism spectr disorder combined and pesticide exposure during pregnancy and first year of life in logistic regression models, by pesticide substance

Pesticide substance	Pregnancy			First year of life		
	No of exposed cases/controls	Model 1*	Model 2†	No of exposed cases/controls	Model 1*	Moc
Glyphosate‡	2293/26 660	1.16 (1.06 to 1.27)	1.12 (0.99 to 1.27)	2256/26 390	1.15 (1.05 to 1.26)	1.17 to 1
Chlorpyrifos	1799/20 914	1.13 (1.05 to 1.23)	1.07 (0.96 to 1.19)	1876/22 125	1.10 (1.02 to 1.20)	1.04 to 1
Diazinon	764/9176	1.11 (1.01 to 1.21)	1.09 (0.98 to 1.20)	787/9890	1.04 (0.95 to 1.14)	1.00 to 1
Acephate	341/4047	1.09 (0.97 to 1.23)	1.06 (0.93 to 1.19)	381/4783	1.00 (0.90 to 1.13)	0.96 to 1
Malathion	642/7277	1.11 (1.01 to 1.22)	1.05 (0.95 to 1.16)	784/8911	1.11 (1.02 to 1.21)	1.07 to 1
Permethrin	930/10 773	1.10 (1.01 to 1.20)	1.04 (0.94 to 1.14)	1047/12 129	1.10 (1.01 to 1.19)	1.05 to 1
Bifenthrin	638/7300	1.03 (0.94 to 1.13)	0.96 (0.87 to 1.07)	886/9671	1.09 (1.00 to 1.19)	1.05 to 1
Methyl bromide	657/8085	1.03 (0.94 to 1.13)	0.95 (0.86 to 1.05)	761/8986	1.08 (0.99 to 1.18)	1.04 to 1
Imidacloprid	1123/14 490	0.93 (0.86 to 1.00)	0.81 (0.74 to 0.89)	1323/16 771	0.95 (0.88 to 1.02)	0.86 to (
Avermectin	1513/17 212	1.12 (1.04 to 1.22)	1.10 (1.00 to 1.22)	1719/20 100	1.07 (0.99 to 1.15)	1.01 to 1
Myclobutanil	1254/15 222	1.04 (0.96 to 1.12)	0.99 (0.90 to 1.09)	1375/16 871	1.01 (0.93 to 1.09)	0.95 to 1

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*Logistic regression; adjusted for year of birth, sex, maternal race or ethnicity, maternal age, maternal educa
and NOx (CALINE4) as a marker of traffic related air pollution; pesticide exposure defined as ever versus n
specific substance in considered developmental period.
†Logistic regression; adjusted as model 1; pesticide exposure defined as ever versus never to specific substar
considered developmental period with all considered pesticides in the model.
‡Glyphosate compounds include glyphosate isopropylamine salt, glyphosate potassium salt, glyphosate
monoammonium salt, glyphosate diammonium salt, glyphosate trimesium, and glyphosate dimethylamine sa

Association between prenatal or infant exposure to pesticide and autism spectrum dis with intellectual disability

Among cases of autism spectrum disorder with intellectual disability, odds ratios had greater ir
(by 30-40%) in pregnancy and infancy for glyphosate, chlorpyrifos, diazinon, permethrin, metl
bromide, and myclobutanil when considering the pregnancy and infant periods separately (tabl
Among cases without intellectual disability (about 85% of cases), estimated odds ratios were si
those reported for the models analyzing all cases of autism spectrum disorder (eTable 5).

Table 4

Odds ratios and 95% confidence intervals for association between autism spectrum disorde intellectual disability comorbidity and exposure to pesticides during pregnancy and first ye life in logistic regression models

Pesticide substance	Pregnancy			First year of life		
	No of exposed cases/controls	Model 1*	Model 2†	No of exposed cases/controls	Model 1*	Mod
Glyphosate‡	351/26 660	1.33 (1.05 to 1.69)	1.12 (0.82 to 1.53)	360/26 390	1.51 (1.18 to 1.92)	1.37 to 1
Chlorpyrifos	284/20 914	1.27 (1.04 to 1.56)	1.07 (0.82 to 1.41)	301/22 125	1.31 (1.07 to 1.61)	1.00 to 1
Diazinon	152/9176	1.41 (1.15 to 1.73)	1.24 (0.97 to 1.58)	169/9890	1.51 (1.23 to 1.85)	1.37 to 1
Acephate	65/4047	1.26 (0.95 to 1.65)	1.17 (0.88 to 1.56)	74/4783	1.25 (0.96 to 1.62)	1.12 to 1
Malathion	99/7277	1.12 (0.89 to 1.41)	0.94 (0.74 to 1.21)	125/8911	1.23 (0.99 to 1.52)	1.02 to 1
Permethrin	175/10 773	1.46 (1.20 to 1.78)	1.36 (1.08 to 1.71)	191/12 129	1.44 (1.19 to 1.75)	1.27 to 1
Bifenthrin	91/7300	1.13 (0.89 to 1.43)	1.05 (0.81 to 1.35)	134/9671	1.33 (1.08 to 1.64)	1.22 to 1
Methyl bromide	133/8085	1.33 (1.07 to 1.64)	1.12 (0.88 to 1.42)	148/8986	1.33 (1.08 to 1.63)	1.09 to 1
Imidacloprid	163/14 490	0.93 (0.76 to 1.13)	0.73 (0.58 to 0.92)	198/16 771	1.01 (0.83 to 1.22)	0.78 to (
Avermectin	209/17 212	1.05 (0.87 to 1.28)	0.84 (0.66 to 1.07)	247/20 100	1.09 (0.90 to 1.33)	0.78 to 1
Myclobutanil	217/15 222	1.32 (1.09 to 1.60)	1.20 (0.94 to 1.53)	232/16 871	1.27 (1.05 to 1.54)	1.04 to 1

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*Logistic regression; adjusted for year of birth, sex, maternal race or ethnicity, maternal age, maternal educa and NOx (CALINE4) as a marker of traffic related air pollution; pesticide exposure defined as ever versus n specific substance in considered developmental period.
†Logistic regression; adjusted as model 1; pesticide exposure defined as ever versus never to specific substar considered developmental period with all considered pesticides in the model.
‡Glyphosate compounds include glyphosate isopropylamine salt, glyphosate potassium salt, glyphosate monoammonium salt, glyphosate diammonium salt, glyphosate trimesium, and glyphosate dimethylamine sa

Multi-pesticide models

In multi-pesticide models with two or three pesticides, most odds ratios were above one for all autism spectrum disorder combined even though several confidence intervals widened (table 5) autism spectrum disorder with intellectual disability and pesticide exposure during the first yea estimated associations were pronounced for glyphosate (odds ratio 1.34; 95% confidence inter to 1.74) and permethrin (1.31; 1.07 to 1.62); also including chlorpyrifos or myclobutanil chang in the associations for glyphosate and permethrin, whereas the estimated odds ratios for chlorp myclobutanil were null (table 5).

Table 5

Multi-pesticide models of association among all cases of autism spectrum disorder combine and those with intellectual disability comorbidity, and exposure of selected pesticides from different chemical classes during pregnancy and the first year of life*

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*Adjusted for year of birth, sex, maternal race or ethnicity, maternal age, maternal education, and NOx (CAI as a marker of traffic related air pollution; pesticide exposure defined as ever versus never to specific substa considered developmental period.

†Glyphosate compounds include glyphosate isopropylamine salt, glyphosate potassium salt, glyphosate monoammonium salt, glyphosate diammonium salt, glyphosate trimesium, and glyphosate dimethylamine sa

Sensitivity analyses: buffer size, sex stratification, area type, and term birth restriction

In sensitivity analyses, we examined associations between autism spectrum disorder and pestic exposure within a 2500 m distance from home; findings were similar or slightly stronger than t the 2000 m distance (eTable 6). Stratifying by sex, associations among male individuals were s seen for the entire sample, with increased odds ratios for glyphosate, chlorpyrifos, diazinon, pe and avermectin. Among female individuals, the findings were similar but the 95% confidence i were wider due to the smaller number of cases (eTable 7). Restricting to term births only or ad for area type (urban, rural) did not change our findings appreciably (data not shown).

Discussion

To our knowledge, this study is the largest to investigate pesticide exposure and autism spectru disorder so far, and the first to also consider the disorder with intellectual disability comorbidit results indicate small to moderately increased risks for the disorder in offspring with prenatal e to the organophosphates chlorpyrifos, diazinon, and malathion, the pyrethroids permethrin and bifenthrin, as well as to glyphosate, avermectin, and methyl bromide compared with offspring women without such exposure within 2000 m of their residence. For autism spectrum disorder comorbid intellectual disability, risks were more pronounced for exposures during the first yea Importantly, the pesticides considered for analysis were selected a priori on the basis of experi evidence indicating neurodevelopmental toxicity. Thus, our findings support the hypotheses th prenatal and infant pesticide exposures to these substances increase the risks for autism spectru disorder, and exposures in infancy could contribute to risks for more severely impaired phenot comorbid intellectual disability.

Comparison with other studies

Environmental toxicants have been suspected to increase the risk of autism spectrum disorder, available research suggesting associations between air pollution and the disorder.[44] [55] [56] [57] Stu examining pesticides and the disorder are rare. In a California study of DDS case records (n=4 linked to birth records from 1996-98, researchers assigned exposures during pregnancy using C similar to our approach; findings suggested that grouped organochlorines were strongly associ risks of pregnancy (odds ratio 6.1 (95% confidence interval 2.4 to 15.3)).[10] Another study inclu cases of autism spectrum disorder and assigned pounds per active ingredient in aggregated che

classes (organophosphates, organochlorines, pyrethroids, carbamates), also derived from CA-P for applications within 1250-1750 m from the home address[9]; findings suggested a 60% increa for the disorder related to organophosphate exposures during pregnancy. Children of mothers l near agricultural pyrethroid applications just before conception or during their third trimester a at greater risk for autism spectrum disorder and general developmental disability (odds ratios r from 1.7 to 2.3).[9] In a smaller case-control study measuring organochlorines and polychlorinat biphenyls in banked mid-pregnancy serum (from 2000 to 2003), higher concentrations for seve compounds in cases than in general population controls were seen.[11]

We did not consider organochlorines because many have been banned from use in California f decades. In a high risk, mother-child study of 46 cases of autism spectrum disorder, prenatal u dimethylthiophosphate was associated with the disorder in girls but not in boys[58]; in our study, little evidence of a sex difference in effects. Overall, the few earlier studies corroborate our fin most of the pesticides we examined. While all the 11 pesticides were a priori selected among h substances, based on prior evidence for neurodevelopmental toxicity, odds ratios were increase several but not all substances in our analyses. Possible explanations could include different me related to the development of autism spectrum disorder, bioavailability of the chemical (eg, in resulting from ambient applications and based on chemical properties), and the application pra these real world scenarios. Different combinations of substances or mixture exposures might al in synergistic effects, including those leading to a selective survival of the fetus.[59]

Although environmental exposure studies considering autism spectrum disorder are rare, organophosphates and pyrethroids have been related to neurodevelopmental and cognitive imp in children in previous studies.[5 7 60 61] Decrements in IQ scores at age 7 have been associated v prenatal residential proximity to agricultural use of organophosphates and pyrethroids, acephat chlorpyrifos, and diazinon,[5] in line with our findings. Pyrethroid metabolites in maternal urine pregnancy and in child urine were associated with worse behavioral scores assessed in 6 year c children.[62] Thus, human studies corroborate the adverse effect of early developmental exposur ambient pesticides on child neurodevelopment, consistent with our findings.

Additional evidence is provided by experimental studies. Mice exposed in utero to chlorpyrifos postnatal deficits in social behavior and restricted interests while the behavior of the dams (ma mice) was not affected.[63] Prenatal exposure to chlorpyrifos enhanced brain oxidative stress and prostaglandin E2 synthesis in a mouse model of autism.[64] Oxidative stress and dysregulated im responses are implicated in organophosphate related toxicity and pathogenesis of autism spectr disorder, suggesting a possible mode of action.[13] Coexposing mice shortly after birth to cypern pyrethroid) and endosulfan altered levels of neuroproteins and resulted in neurobehavioral abnormalities.[12] Gene expression of mouse cortical neurons was altered by certain fungicides a resembled transcriptional changes thought to underlie development of autism spectrum disorde Translational research connecting toxicological and animal studies with findings from epidemi studies is needed to identify the specific modes of action of pesticides relevant for the pathoge autism spectrum disorder.[65 66 67 68 69]

Residential proximity to pesticide applications during pregnancy has been shown to be a valid of prenatal exposure.[70] [71] [72] [73] Pesticides, including organophosphates, have been identified in indoor air, and dust in homes in agricultural areas in California.[74] [75] Elevated levels in five of s pesticides applied within 1250 m of homes according to Pesticide Use Reporting records were measured in dust from such homes.[76] Our exposure assessment method using the geographic information system tool has been validated against serum concentrations of organochlorines,[77] specific methylation patterns found among those with organophosphate exposure,[78] and can be considered a valid proxy for prenatal exposures.

Strengths and limitations of our study

A strength of our study was our pesticide exposure assessment tool; it can estimate exposures f multiple substances with short half-lives for which frequent measurements of metabolites woul necessary but not feasible in a population based study of the size needed to investigate the risk autism spectrum disorder. California's mandatory Pesticide Use Reporting program is recogniz most detailed and comprehensive worldwide. Thus, we were able to rely on agricultural applic records of specific pesticides with high spatial and temporal resolution, which we believe is a s that could have reduced exposure misclassification, because we relied on Pesticide Use Report information based on the date of application using a relatively fine spatial scale (a buffer of 20 around the residential address. We also relied on the gestational age and birth date to construct individual exposure estimates corresponding to different developmental periods. We still have assume that individuals were present at their residences around the application dates and that th applications resulted in exposures in the targeted periods only and did not get trapped in or aro homes over extended periods of time. Our registry based design avoided participation bias due selection and recall bias of parents (which is an issue in case-control studies that rely on self re past exposures).

Although our ability to pinpoint one or more specific substances was limited by the collinearity pesticide exposure owing to agricultural practices, we could capture the real life scenario of po living in agricultural areas; typically, a variety of substances are used over several weeks or mo Sensitivity analyses using the 2500 m radius buffer further corroborated and even strengthened results. Simultaneous exposures to frequently used pesticides are likely in residences near agric applications, and some of our findings could reflect adverse effects of typical exposure mixture coexposures. Multi-pesticide models coadjusted for all pesticides or for two or three substances generally consistent with our single pesticide models. We present results from real world expos scenarios while being cognizant of issues of collinearity, sparse data, or overly restrictive mode assumptions.

A limitation was that we only had birth addresses available and that 9-30% of families could ha moved during pregnancy.[79] However, most moves in pregnancy have been found to be local (< and misclassification would be expected to be non-differential because moving residence woul before diagnosis; thus any bias would likely be toward the null. We also lacked exposure infor on pesticides from other sources such as diet or occupation, potentially resulting in underestim

total exposure if these were associated with residential exposures (eg, women who work and li farms); however, this would have been similar for cases and controls and most likely to have re attenuation of risk estimates toward the null.[54] We also lacked information about passive and a smoking. However, pregnancy smoking rates are very low in California (<2%),[80] and smoking places has been banned since the 1990s. Even though we had detailed information on potential confounders, and sensitivity analyses did not change our findings, uncontrolled residual confou always remains a concern.

Conclusions

Our findings suggest that risk of autism spectrum disorder increases with prenatal and infant ex to several common ambient pesticides that have been shown to affect neurodevelopment in experimental studies. Further research should be translational and integrate experimental and epidemiological approaches to further elucidate underlying mechanisms in the development of disorder. However, from a public health and preventive medicine perspective, our findings sup need to avoid prenatal and infant exposure to pesticides to protect early brain development.

What is already known on this topic

- Common pesticides have been previously shown to cause neurodevelopmental impairr experimental research
- Environmental exposures during early brain development are suspected to increase risl autism spectrum disorders in children

What this study adds

- Prenatal or infant exposure to a priori selected pesticides—including glyphosate, chlor diazinon, and permethrin—were associated with increased odds of developing autism spectrum disorder
- Exposure of pregnant women and infants to ambient pesticides with a potential neurodevelopmental toxicity mode of action should be avoided as a preventive measur against autism spectrum disorder

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Web extra.

Extra material supplied by authors

Web appendix: Online materials

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Notes

Contributors: OSvE directed the analysis and drafted the manuscript. OSvE and BR contribute design of the study and interpretation of the results. CL carried out the main statistical analysis contributed to setting up the database and quality control. MC was responsible for the geograpl information system methods. FY contributed to the statistical analyses. CL, MC, and ASP cont to exposure estimation. JW estimated the air pollution exposure. All authors commented on dra read and approved the final manuscript. The corresponding author attests that all listed authors authorship criteria and that no others meeting the criteria have been omitted. OSvE is the guara

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from the National Institute of Environ Health Sciences for the submitted work; no financial relationships with any organizations that have an interest in the submitted work in the previous three years; BR has been acting as an ex witness/consultant in a lawsuit for the plaintiffs against Monsanto in non-Hodgkins lymphoma litigation concerning glyphosate; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This research was approved by the University of California, Los Angeles Off the Human Research Protection Program and the California Committee for the Protection of H Subjects, and was exempt from informed consent requirements as there was no contact with th population.

Data sharing: No additional data are available.

The lead author affirms that the manuscript is an honest, accurate, and transparent account of tl being reported; that no important aspects of the study have been omitted; and that any discrepa from the study as planned (and, if relevant, registered) have been explained.

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