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Abstract

Influences of pesticide exposures on the clinical expression of children with ASD not known. The aim of this study was to analyze the associations between early residential proximity to agricultural crops, proxy of exposure to pesticides, and adaptive behaviors in children with ASD. Children with ASD were recruited within the Etude Longitudinale de l'Enfant avec Autisme (ELENA) French cohort. Adaptive behaviors were assessed with the second edition of the Vineland Adaptive Behavior Scales (VABS-II). Baseline subscores in communication, daily living skills and socialization were considered. Residential exposure to agricultural crops was estimated by crops acreage within a 1000m radius around homes. We ran multiple linear regression models to investigate the associations between exposures to agricultural crops during the pregnancy (n=183), the first two years of life (n=193) and adaptive behaviors in children with ASD. The mean (SD) age of children at the inclusion in the ELENA cohort was 6.1 (3.5) years, 39% of them presented an intellectual disability (ID). The mean communication score was 73.0 (15.8). On average, the crop acreage covered 29(27)% of the acreage formed by the 1000m radius around homes. Each increase of 20% in the crop acreage was associated with a significant decrease in communication score of the VABS-II in children without ID for the pregnancy (β= -2.21, 95%CI: -4.16 to -0.27) and the first two years of life (β= -1.90, 95%CI: -3.68 to -0.11) periods. No association was found in children with ID. This study opens perspectives for future wors to better understand ASD phenotypes.

Key words: Environmental exposure; Pesticides; Autism spectrum disorder; Adaptive behaviors; Vineland; Children**.**

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1. Introduction

Autism spectrum disorder (ASD) is an early onset neurodevelopmental disorder defined by the association of impairment in social communication and patterns of restricted interests and repetitive behaviors (American Psychiatric Association, 2013). In addition to being a major source of disability, ASD represents an important burden for the individuals, their families, and society in terms of the cost of educational support and loss of productive years (Baxter et al., 2015; Buescher et al., 2014). The clinical expression of ASD is characterized by a wide heterogeneity in adaptive behaviors mainly link to level of cognitive abilities (Chatham *et al.*, 2018; Farmer *et al.*, 2018).

Adaptive behaviors refer to how well a person meets the community standards of personal independence and social responsibility relative to others of a similar age and socio-cultural background (American Psychiatric Association, 2013). Impairments in adaptive behaviors predict the real-world adaptation of individuals with ASD, such as educational attainment and the likelihood of independent living (Farley *et al.*, 2009). A meta-analysis conducted on 828 children with autistic disorders showed that just under 20% presented a normal or near-normal social life and satisfactory functioning at school or work in adulthood (Steinhausen et al., 2016). So, identifying the factors that hinder the well-acquisition of adaptive behaviors in children with ASD is therefore of great importance in planning more effective interventions. Currents findings suggest that lower intellectual quotient (IQ), older age, and higher social-communication impairments are associated with lower adaptive functioning in children with ASD (Tillmann et al., 2019). However, these demographic and clinical characteristics alone, do not seem to explain the frequency and intensity of adaptive behaviors impairments in these children.

A growing body of evidence, mainly case-control studies, suggest that perinatal exposure to environmental toxicants like pesticides were associated to ASD risk (Ongono et al., 2020; Roberts et al., 2019). Investigating whether these exposures might also affect adaptive behaviors of children with ASD could be of great importance to understand its clinical expression in children. Pesticides are chemicals used to fight against pests. The developing human brain could be particularly vulnerable to these chemicals (Grandjean and Landrigan, 2006; Lyall et al., 2017). The main routes of exposure to pesticides are oral (Zartarian et al., 2012) and respiratory (Amaral, 2014). Exposures to pesticides face the challenge of their

retrospectively estimations in studies where ASD cases are recruited a long time after the windows of exposure. In this context, indirect assessments of exposure to pesticides, either via questionnaires or measurements of crops acreages around residences, remain the only possibilities. Indeed, higher levels of pesticides in both biological and environmental matrices were found in people living near agricultural crops than those far away (Dereumeaux et al., 2020). Moreover, acreages of arable crops (cereals, fodder crops, root crops, etc.), vineyards and/or orchards within 500 to 1000-m from homes were also associated with higher levels of pesticides in house dust (Béranger et al., 2019; Glorennec et al., 2017).

In a well-characterized population of children with diagnosed ASD, the French ELENA (Etude Longitudinale chez l'Enfant avec Autisme) cohort, we analyzed associations between residential proximity to agricultural crops, estimated by crop acreage in a 1000-m radius around residential addresses, during the prenatal period and the first two years of life and adaptive behaviors. We hypothesized that crop acreages, proxy of exposure to pesticides, could impair adaptive behaviors in children with ASD.

Methods

1.1.Study population

The study population came from the ELENA cohort, a French ongoing prospective and multicentric cohort of children with a confirmed ASD diagnosis, initiated in 2012 (Baghdadli et al., 2019). The ELENA cohort was set up to study ASD developmental trajectories. Between 2012 and 2019, 889 children aged 2 to 16 years were recruited at the time of diagnosis in 15 French autism research centers covering six regions: Occitanie, Auvergne-Rhône-Alpes, Ile-de-France, Provence-Alpes-Côte d'Azur, Nouvelle Aquitaine, and Grand-Est. In the ELENA cohort, ASD diagnosis, ascertained by a trained multidisciplinary team on the basis of DSM-5 criteria (American Psychiatric Association, 2013), relied on the second edition of the Autism Diagnostic Observation Schedule™ (ADOS-2, Lord et al., 2012), the revised version of the Autism Diagnostic Interview (ADI-R, Le Couteur *et al.*, 2003), the Vineland Adaptive Behavior Scales (VABS-II, Sparrow *et al.*, 2005), and a valid psychometric test of intelligence to have the best estimate of the intellectual quotient (IQ). The IQ, based on an age-appropriate test, was derived from the Wechsler Intelligence Scales (Wechsler, 2014a, 2014b, 2003, 1974, 1967, 1949) and Kaufman Assessment Battery for Children (Kaufman and Kaufman, 1983) according to the Howlin approach (Howlin et al., 2014); The detailed process is presented elsewhere (Baghdadli et al., 2019).

In early 2020, parents of the 889 children originally included were asked to answer a questionnaire covering sociodemographic characteristics, the residential history of the mother and child from pregnancy to two years after the child's birth, and the mother's lifestyle during the pregnancy. Between February 1 and May 31, 2020, 373 (42%) parents completed this questionnaire.

We included all children who had exhaustive data on outcome and covariates (n=295). We excluded children whose mother's pregnancies took place outside of mainland France (n=19), adopted children (n=2), and extremely premature children (n=3). In addition, 47 children were excluded because of incomplete addresses. The remaining study population consisted of 224 children (Figure 1). The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The study design was reviewed and approved by the French National Commission for Computerized Data and Individual (CNIL) and the Personal Protection Committees (PPC). Informed consent of the parent's participants was obtained after the nature of the procedures had been fully explained.

1.2.Residential proximity to agricultural crops

Crop acreage near residential addresses during pregnancy and the first two years of life

We considered the whole pregnancy and early postnatal periods as exposure periods to crops because they are critical windows during brain development (Grandjean and Landrigan, 2006; Lyall et al., 2017; Shelton et al., 2012).

Exposure to crops was estimated at the geocoded addresses of each child for the pregnancy and the first two years of life. We used the "MonGeocodeur" database from the French National Geographic Institute to geocode addresses. During the whole pregnancy period, an average of 73% of the addresses was geocoded to the street number, 24% to the street, 1% to the hamlet, and 2% to the municipality. For the first two years of life of the children, an average of 70% of addresses was geocoded to the street number, 26% to the street, 1% to the hamlet, and 3% to the municipality.

We used the CORINE Land Cover data (CLC; French Ministry of Environment, Statistics and Observation Department, scale 1:100 000), a biophysical inventory of the earth surface in 38 European states derived from satellite imagery, to characterize the residential environment of each child. Because children of the study population were born between 1996 and 2017, we used CLC data close to the year of birth of each child, thus CLC data produced in 2000, 2006, 2012 and 2018.

Before estimating the agricultural crop acreage around residential addresses, we additionally excluded the "strictly urban" subpopulation from the study population to minimize the risk of comparing rural versus urban populations in analyses. The "strictly urban" status was defined by more than 99% of urbanized area within a 500-m radius around each address and accounted for 18% (n=41) of the residences during the pregnancy and 14% (n=31) during the first two years of life of the children. The remaining study population consisted then of children from rural and moderately urban areas for the exposure periods covering the whole pregnancy (n=183) and the first two years of life (n=193) (Figure 1).

From the CLC, we considered five crops subcategories: (1) non-irrigated arable land (cereals, fodder crops, root crops and fallow land, flower and tree cultivation, and vegetables); (2) vineyards, (3) fruit trees and berry plantations, (4) annual crops associated with permanent crops (woody crops, olives in combination with either non-permanent crops like fodder roots, fodder maize, etc., or permanent grass surfaces) and (5) land principally occupied by agriculture with significant areas of natural vegetation. The acreages of every crop subcategory were summed within a 1000-m radius around addresses using a geographical information system (QGIS 3.8.0 software).

Exposure score to agricultural crops

We considered a 1000-m radius around residential addresses to estimate exposure to agricultural crops. We then built a quantitative exposure score for agricultural crops with (1) the percentage of crop acreage within a 1000-m radius around the addresses weighted by (2) the duration of residence at each address. We assumed that a 1000-m radius captured the intensity and diversity of exposure to agricultural crops.

$$\textbf{Exposure score}^{i} = \sum_{j=1}^{n} (\textbf{\% of crop surface}^{i}_{j} \ \textbf{X \% of duration at the address}^{i}_{j})$$

i is the participant, **n** is the total number of addresses of the participant i for the time windows of exposure considered (n is ≥1) and **j** is one of the n addresses during the window of exposure considered.

1.3.Assessment of the adaptive behaviors

We assessed adaptive behaviors of children using the VABS-II scores obtained at baseline in the ELENA cohort. So, the children age at the administration of the VABS-II was the age at the inclusion in the ELENA cohort. The VABS-II is a standardized semi-structured interview administered to the parent/caregiver measuring how an individual adjusts to daily life activities (Sparrow et al., 2005). The VABS-II provides scores for the domains of communication, socialization, daily living skills, and motor skills. We did not consider "motor skills" domain

as it can only be assessed to children up to 6 years. The VABS-II consists of 297 items, each scored on a 3-point Likert scale for the frequency of behaviors or skills investigated: 0 ("never"), 1 ("sometimes or partly"), and 2 ("usually"). We used population-normed standard scores, standardized for the children's age. Each VABS-II subdomain score ranges from 20 to 160, with higher scores indicating better functioning.

1.4.Covariates

The potential confounders were selected *a priori* based on literature review. They consisted of the child's sex, age at inclusion in the ELENA cohort (≤ median, > median), the highest parental education level in the household (≤ high school, university) and the children's intellectual disability (ID) status using the IQ score, < 70 for ID and ≥ 70 for non-ID (World Health Organization, 1993).

1.5.Statistical analysis

We analyzed associations between early exposure to agricultural crops and VABS-II subdomain scores of children with ASD at the baseline using multiple linear regression models.

Independent models were performed for each VABS-II subdomain score and each window of exposure. The crude associations between the total exposure score to agricultural crops and VABS-II subdomains scores were investigated. Thereafter, we adjusted model for the children's sex, age at inclusion in the ELENA cohort, and the highest parental education level in the household. The potential modification of the effect by sex, age at inclusion in the cohort, parental education, and IQ was assessed by including an interaction term with the total exposure scores to agricultural crops. As a significant interaction was observed between total exposure scores and IQ (Table S1) for each VABS-II subdomain, analyses were stratified by ID status. Total exposure scores to agricultural crops were analyzed as continuous variables and effect estimates for each increase of 20% in the crop acreage within a 1000-m radius around the addresses.

The Statistical Analysis Systems (Enterprise) software package, version 9.5 (SAS Institute, Cary, North Carolina, USA) was used for statistical analyses and *p-values* < 5% were considered for statistical significance. All statistical tests were two-sided.

1.6.Sensitivity analyses

Further analyses were performed after additionally adjusted the final model for birth season (spring, summer, autumn, winter), maternal alcohol consumption during pregnancy (yes/no), maternal smoking during pregnancy (yes/no), folic-acid supplementation during pregnancy

(yes/no), and recruiting center of the ELENA cohort (Occitanie, Auvergne-Rhône-Alpes, Ile-de-France, Provence-Alpes-Côte d'Azur, Nouvelle Aquitaine, Grand Est).

To refine the exposure score to crops and determine whether a particular type of crop could impair adaptive behaviors, we gathered the five subcategories of crops considered into two main groups, group 1 for "vineyards, fruit trees, and berry plantations" and group 2 for the remaining subcategories. We then analyzed them as dichotomous variables (exposure score ≤ median and exposure score > median).

We also analyzed associations between adaptive behaviors and cumulative total exposure score to crops, within a 1000-m radius around addresses, from pregnancy to the first two years of children's life taking into account residential moving (8% between the pregnancy period and the first two years of life).

Finally, to estimate the effects of exposure intensity on the VABS-II subdomains scores, we investigated associations in a 500-m radius around residential addresses.

2. Results

2.1. Baseline characteristics and exposure

Characteristics of the study population are presented in Table 1. Among the 183 children, 39% presented with an ID. The mean age of children at inclusion in the ELENA cohort was 6.1±3.5 years, boys represented 78% of the study population. The mean VABS-II subdomains scores were 73.0±15.8, 74.8±13.6, and 71.8±11.3 for the communication, daily living skills, and socialization domains, respectively. The total exposure score to agricultural crops varied from 0 to 90%, with a mean of 29%±27%, with higher exposure scores indicating the highest exposure levels. Children without ID were older than those with ID at inclusion and presented higher VABS-II scores (Table 1). The characteristics were similar to the study population analyzed for the first two years of life (n=193, data not shown).

Characteristics of the study population were similar to those of children excluded from the initial sample in terms of age at inclusion in the ELENA cohort, sex, and parental education level (Table 2). However, children excluded from the study presented more severe ASD based on the Autism Diagnostic Observation Schedule calibrated severity score (Lord et al., 1999), lower scores in the IQ, communication, and socialization scores than those in the study population (Table 2). Among the excluded population, those "strictly urban" during the pregnancy period were older and presented lower scores in the IQ and VABS-II relative to the study population (Table S2); The findings were similar for the period of the first two years of children (data not shown).

2.2. Exposure to agricultural crops in a 1000-m radius around residential addresses and the VABS-II subdomain scores

There was a decrease of 2.21 points (95% confidence interval (CI): -4.16 to -0.27) in the communication score for children without ID for each 20%-increase in the total exposure score to agricultural crops during pregnancy (Table 3). No association was found with changes in daily living skills or socialization scores in this group. In children with ASD and ID, none of the VABS-II subdomain scores was significantly associated with the total exposure score to agricultural crops (Table 4).

There was a decrease in the communication score (β= -1.90 points, 95%CI: -3.68 to -0.11) for children with ASD without ID for each 20% increase in the total exposure score to agricultural crops occurring during the first two years of the children's life (Table 4). No significant association was observed for the same group of children for daily living skills or socialization (Table 5). Exposure to agricultural crops was not significantly associated with changes in the VABS-II subdomain scores for children with ASD and ID (Table 4).

2.3.Sensitivity analyses

Additional adjustments and associations by subgroups of crops

In final model additionally adjusted, the association remained significant for the communication score in children with ASD without ID for both pregnancy and the first two years (Table S3, S4). In addition, we observed a significant association between the exposure score and daily living skills score (β= -1.88 points, 95%CI: -3.74 to -0.01) for children without ID for the pregnancy period (Table S3). No association was found for children with ASD and ID (Table S3, S4).

Exposure to crops group 1 was not significantly associated with changes in VABS-II subdomain scores for the pregnancy period (Table S5). However, for the first two years of life of the children, the exposure score was associated with an increase in communication score for children with ID (Table S7).

For exposure to crops group 2 during the pregnancy (table S6) and the first two years of life of the children (Table S8), no significant association was found with changes in VABS-II subdomain scores for either children with or without ID in the "exposure score > median" group relative to the reference group.

Cumulative exposure to crops and VABS-II subdomains scores

Cumulative exposure to crops was associated with a significant decrease of communication (-2.33, 95%CI: -4.25 to -0.40) and socialization (-1.60, 95%CI: -3.10 to -0.10) scores in children without ID. No association was found in the subgroup of children with ID (Table S9).

Exposure score in a 500-m radius and the VABS-II subdomains scores

The total exposure score to agricultural crops was significantly associated with a decrease of 2.38 points (95%CI: -4.47 to -0.29) in the communication score during the pregnancy period (Table S10), and of 1.39 points (95%CI: -2.78 to -0.01) in the socialization score during the first two years of the children's life (Table S11) for children with ASD without ID. No association was found in children with ASD and ID.

3. Discussion

Early residential exposure to agricultural crops was negatively associated with communication skills in children with ASD without ID in our sample. Each increase of 20% in crop acreage within a 1000-m radius around residential addresses was associated with a decrease of approximately 2 points on the VABS-II communication subscore during both the prenatal and early postnatal periods. No significant association was observed for children with ID.

There has been no previous epidemiological study about the effects of proximity to crops or pesticides biological levels on adaptive behaviors in children with ASD with which we could compare our findings. Nevertheless, our observations are in accordance with studies in neurotypical children investigating effects of early exposures to pesticides in traits relatives to adaptive behaviors in ASD. Handal et al. (2007) found, in 283 Ecuadorian children aged 3 to 64 months residing in communities with a high potential for exposure to OP and carbamate pesticides, lower scores on socialization and communication skills measured by the ages and stages questionnaire. In 246 14-years-old Californian children, prenatal OP urinary metabolites [dialkyl phosphates (DAPs)] were associated with higher scores in the Social Responsiveness Scale (SRS2), indicating more impairments in social behavior and communication (Sagiv et al., 2018). Each 10-fold increase in total prenatal urinary DAPs was associated with a 2.7-points (95%CI: 0.9 to 4.5) increase in the SRS2 score (Sagiv et al., 2018). A study conducted in 4000 British girls aged 15 to 38 months found that maternal organochlorine pesticides serum levels were associated with communication impairments measured by the MacArthur Bates Communicative Development Inventories for Infants and Toddlers (Jeddy et al., 2018). A study in American children aged 6 years or younger from the general population found, although non-significant, a mean difference in the communication, daily living skills or socialization VABS

subscores between children highly exposed to methyl parathion (MP), another OP, in house dust (n=218, MP>1000µg/cm^2) and the unexposed ones (n=147, MP<25µg/100cm^2) (Ruckart et al., 2004).

In our study, the magnitude of the effect observed in children with ASD without ID is relatively small. Indeed, each increase of 20% in the crop acreage within a 1000-m radius i.e., an increase in crop acreage of approximately 63 hectares, corresponding to the average acreage of farms in France (https://www.insee.fr/fr/statistiques/4277860?sommaire=4318291), was associated with a two-point decrease in the VABS-II communication subscore. Such a two-point decrease represents approximately 3% of the mean communication subscore. Therefore, the two-point decrease would appear to be unlikely to drastically modify the clinical expression of ASD in the study population.

Different dimensions of adaptive behaviors measured with the VABS-II appear to be affected according to the intensity and duration of exposures. When considering the radius of exposure, we observed the same trend in the impairment of communication skills in the subgroup of children without ID, whether exposures occurred within 500 or 1000-m around the residential addresses during the pregnancy period. In addition, exposure occurring during the first two years of the children's life within a 500-m radius, which may correspond to more intense exposure to pesticides, significantly decreased the socialization skills in the same subgroup of children. Considering the cumulative exposure to crops, in addition to a significant impairment of communication skills, socialization skills were also significantly decreased in children without ID.

We obtained an unexpected result for children with ID following exposure to crops group 1. In this subgroup of children, residential proximity to crops group 1 within a 1000-m radius during their first two years of life significantly increased communication scores of children highly exposed to this group of crops than those exposed at a lower level. However, this result should be interpreted with caution due to the limited sample size of the subgroups of children with ID.

Exposures to crops group 2, widely represented by cereal crops in France (https://agreste.agriculture.gouv.fr/), was not significantly associated with changes in the VABS-II subdomains scores for either window of exposure. However, the association has the same magnitude for the communication score as that found for the total exposure score to crops for children without ID for both windows of exposure. This observation, along with the fact that the acreage of crops group 2 is greater than that of group 1, suggests that the main results,

i.e., the negative association between the total exposure score to agricultural crops for children without ID and communication score, may be mainly driven by exposure to crops group 2. Indeed, certain pesticides, such as OP, carbamates or pyrethroids, used on the main crop of this group, cereals, are frequently associated with ASD in the literature (Roberts *et al.*, 2019).

We also observed that the influence of early exposure to agricultural crops on the VABS-II subscores differed according to the ID status of the children. Although the mean exposure score was comparable for children whether they had an ID or not, the VABS-II subscores were lower in the ID subgroup. Nevertheless, the variability of the VABS-II subscores was similar in the two groups, excluding the possibility that our results could be due to a limited capacity of the VABS-II to evaluate adaptive behaviors in one or the other ID group.

Our results thus suggest that adaptive behaviors of children with ASD without ID may be sensitive to environmental influences. On the contrary, among those with ID, heterogeneity in adaptive skills may be influenced by other determinants and genetics can be assumed to play an important role, as it does in the ASD etiology (Chiurazzi et al., 2020).

Strengths and limitations

The main strength of this study was the large study population of the ELENA cohort for which the ASD diagnosis was ascertained by trained clinicians using standardized tools. We collected all residential addresses for each period of exposure allowing us to consider moves when estimating the exposure to crops. We considered variability in land use by using CLC versions close to the birth year of each child. We also obtained consistent results across statistical models after adjusting for confounding factors, as well as in sensitivity analyses.

Our study also had some limitations. We cannot rule out the possibility that ELENA cohort may not be representative of children with ASD in France. Therefore, results should be carefully extrapolated. However, the study population presents characteristics (sex ratio, ID prevalence) in accordance with those frequently found in studies relating to ASD (Baxter *et al.*, 2015; Zablotsky *et al.*, 2015). Thus, although our recruitment method does not guarantee the exact representativeness of children with ASD in France, the characteristics of the study population are reassuring. The difference observed between the study population and the excluded one could also have induced a selection bias. Indeed, children excluded showed more severe ASD and lower scores for IQ and VABS-II. We used indirect methods to estimate the exposure to pesticides by measuring crop acreage near homes. This method did not enable us to identify specific pesticides, nor the quantities used and could have led to a non-differential misclassification bias. However, prior studies suggested a correlation between residential

proximity to crops and pesticide levels in biological or environmental samples (Béranger et al., 2019; Dereumeaux et al., 2020). Finally, the retrospective address collection could have led to misclassification due to reporting bias.

Conclusion

We investigated the association between early residential proximity to agricultural crops and impairments in adaptive behaviors in children with ASD. The findings suggested a significant association between exposure to agricultural crops within a 1000-m radius around residential addresses, a proxy of exposure to agricultural pesticides, during pregnancy and the first two years of the children's life and decrease in communication scores in the subgroup of children without ID. Further epidemiological studies, with prospective direct measures of pesticide exposure throughout pregnancy and early childhood, are needed to confirm our results. Such studies would help to better understand how pesticide exposure may affect the outcomes of children and open new perspectives for a better understanding of ASD phenotypes.

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Table 1. Characteristics [n (%) or mean (standard deviation)] of the study population at the inclusion in the ELENA cohort (n=183).

Variables	ASD (all; n=183)	ASD with ID (n=71)	ASD without ID (n=112)	P-Value***
Children age (years)	6.1 (3.5)	**4.7 (2.9)**	**6.9 (3.5)**	**<.0001**
Children sex				*0.741*
Male	142 (78%)	56 (79%)	86 (77%)	
Female	41 (22%)	15 (21%)	26 (23%)	
Gestational age at the child birth (amenorrhea weeks)				*0.514*
<37 amenorrhea weeks	15 (8%)	7 (10%)	8 (7%)	
≥37 amenorrhea weeks	168 (92%)	64 (90%)	104 (93%)	
Children intellectual quotient (IQ)	76.9 (28.9)	**46.8 (14.4)**	**96.00 (17.0)**	***<.0001***
Higher parental education level in the household				*0.495*
≤ High school	49 (27%)	21 (30%)	28 (25%)	
University	134 (73%)	50 (70%)	84 (75%)	
Total exposure score to agricultural crops during pregnancy	29% (27%)	32% (28%)	27% (26%)	*0.300*
Exposure score to "crops group 1"* during pregnancy	12% (21%)	14% (22%)	10% (20%)	*0.220*
Exposure score to "crops group 2" during pregnancy**	17% (21%)	18% (20%)	17% (22%)	*0.242*

VABS-II subdomains scores				
Communication	73.0 (15.8)	**62.5 (12.7)**	**79.7 (13.9)**	***<.0001***
Daily Living Skills	74.8 (13.6)	**66.7 (12.5)**	**79.9(11.7)**	***<.0001***
Socialization	71.8 (11.3)	**66.5 (10.8)**	**75.1 (10.3)**	***<.0001***
Maternal alcohol consumption during pregnancy				*0.314*
≤ 1 glass/week	149 (81%)	62 (87%)	87 (78%)	
> 1 glass/week	25 (14%)	7 (10%)	18 (16%)	
Missing data	9 (5%)	2 (3%)	7 (6%)	
Maternal smoking during pregnancy				*0.878*
No	132 (72%)	53 (75%)	79 (71%)	
Yes	41 (22%)	15 (21%)	26 (23%)	
Missing data	10 (6%)	3 (4%)	7 (6%)	
Maternal folic acid intake during pregnancy				*0.265*
No	69 (38%)	23 (33%)	46 (41%)	
Yes	85 (46%)	35 (49%)	50 (45%)	
Missing data	29 (16%)	13 (18%)	16 (14%)	
Child birth season				*0.201*
Spring	39 (21%)	13 (18%)	26 (23%)	
Summer	40 (22%)	21 (30%)	19 (17%)	
Autumn	54 (30%)	21 (30%)	33 (30%)	
Winter	50 (27%)	16 (22%)	34 (30%)	
Recruiting center in the ELENA Cohort				*0.114*

Occitanie	134 (73%)	51 (72%)	83 (74%)
Ile-de-France	15 (8%)	10 (14%)	5 (5%)
Auvergne-Rhône-Alpes	14 (8%)	3 (4%)	11 (9%)
Grand Est	13 (7%)	6 (9%)	7 (6%)
Provence-Alpes-Côte d'Azur	6 (3%)	1 (1%)	5 (5%)
Nouvelle Aquitaine	1 (1%)	0 (0%)	1 (1%)

Abbreviations: ASD=autism spectrum disorder; **ID**=intellectual disability; **VABS-II**= Vineland Adaptive Behavior Scales 2nd edition

According to the Corine Land Cover classification (CLC; French Ministry of Environment, Statistics and Observation Department, scale 1:100 000), we defined crop groups as:

*** Crops group 1**=*vineyards, fruit trees, and berry plantations*

**** Crops group 2**= non-irrigated arable land (cereals, fodder crops, root crops and fallow land, flower and tree cultivation, and vegetables); annual crops associated with permanent crops (woody crops like shrubs, olives in combination with either non-permanent crops like fodder roots, fodder maize, forage kale, etc., or permanent grass surfaces) and land principally occupied by agriculture with significant areas of natural vegetation.

*** Wilcoxon or Student tests for quantitative variables, and Chi2 test for qualitative variables.

Table 2. Comparison of main characteristics between the study population (n=183) and the Excluded one (n=706) in children with ASD from the ELENA cohort.

Characteristics	study population (n=183)	Excluded Population (n=706)	P value*
Children age at inclusion	6.1 (3.5)	6.00 (3.38)	0.596
Children's sex			0.059
Males	142 (78%)	590 (84%)	
Females	41 (22%)	116 (16%)	
Children intellectual quotient (IQ)		*n=612*	**0.004**
IQ	**76.9 (28.9)**	**70.1 (27.9)**	
Intellectual disability (ID) Status		*n=612*	**0.009**
ID	**71 (39%)**	**305 (50%)**	
Non ID	**112 (61%)**	**307 (50%)**	
Higher level of parental education in the household		*n=552*	0.489
≤High school	49 (27%)	160 (29%)	
University	134 (73%)	392 (71%)	
VABS-II subdomains scores		*n=674*	
Communication	**73.0 (15.8)**	**68.7 (15.0)**	**0.001**
Daily living skills	74.8 (13.6)	72.8 (12.8)	0.064
Socialization	**71.8 (11.3)**	**69.1 (10.57)**	**0.003**
ADOS-CSS	n=150	n=604	**0.043**
ADOS-CSS score	**6.8 (1.83)**	**7.1 (1.99)**	
ASD Severity	n=150	n=604	0.098
Mild (ADOS-CSS : 1-4)	15 (10%)	72 (12%)	
Moderate (ADOS-CSS : 5-7)	82 (55%)	271 (45%)	
Severe (ADOS-CSS>7)	53 (35%)	261 (43%)	
Parental characterization of their level of information on ASD	n=157	n=308	0.877
Excellent	10 (6%)	22 (7%)	

Good	76 (48%)	137 (44%)	
Insufficient	62 (40%)	129 (42%)	
Very insufficient	9 (6%)	20 (7%)	
Parental training in ASD workshop	n=158	n=308	0.060
Yes	44 (28%)	62 (20%)	
No	114 (72%)	246 (80%)	
Parental membership in an ASD association	n=158	n=312	0.584
Yes	29 (18%)	51 (16%)	
No	129 (82%)	261 (84%)	

Abbreviations:

ASD: autism spectrum disorder

ADOS-CSS: Autism Diagnostic Observation Schedule calibrated severity score. It measures the severity of ASD on a scale from 1 to 10 with 10 for the most severe (Lord et al., 1999)

** Wilcoxon or Student tests for quantitative variables and Chi2 test for qualitative variables.*

Table 3. Associations [β (CI95%)], between each 20% increase in total exposure score to agricultural crops within a 1000m radius around maternal residential address during pregnancy and VABS-II subdomains scores[a] in children with autism spectrum disorder from the ELENA cohort (n=183).

Total exposure score to crops	**VABS-II subdomains scores**		
	ASD without ID		
	Communication β (CI95%)	**Daily living skills β (CI95%)**	**Socialization β (CI95%)**
Crude model	**-2.33 (-4.30 to -0.35)**	-0.92 (-2.63 to 0.78)	-1.41 (-2.88 to 0.07)
Adjusted model	**-2.21 (-4.16 to -0.27)**	-1.27 (-3.05 to 0.50)	-1.25 (-2.78 to 0.28)
	ASD with ID		
	Communication β (CI95%)	**Daily living skills β (CI95%)**	**Socialization β (CI95%)**
Crude model	0.63 (-1.56 to 2.81)	0.57 (-1.58 to 2.73)	0.51 (-1.35 to 2.36)
Adjusted model	0.63 (-1.57 to 2.83)	0.47 (-1.70 to 2.64)	0.44 (-1.31 to 2.20)

Adjusted model on Child's sex (female, male), age at the inclusion in the ELENA cohort (≤median, >median), higher level of parental education in the household (≤ high school, university)

a*: negative Beta indicating alteration in adaptive functioning*

VABS-II*: Vineland Adaptive Behavior Scales 2nd edition*

Table 4. Associations [β (CI95%)], between each 20% increase in total exposure score to agricultural crops within a 1000m radius around residential address during the first two years of life and VABS-II subdomains scores[a] in children with autism spectrum disorder from the ELENA cohort (n=193).

Total exposure score to crops	**VABS-II subdomains scores**		
	ASD without ID		
	Communication β (CI95%)	**Daily living skills β (CI95%)**	**Socialization β (CI95%)**
Crude model	**-1.87 (-3.70 to -0.05)**	-0.83 (-2.40 to 0.73)	**-1.49 (-2.83 to -0.15)**
Adjusted model	**-1.90 (-3.68 to -0.11)**	-1.02 (-2.63 to 0.59)	-1.31 (-2.68 to 0.06)
	ASD with ID		
	Communication β (CI95%)	**Daily living skills β (CI95%)**	**Socialization β (CI95%)**
Crude model	1.17 (-1.11 to 3.46)	0.94 (-1.21 to 3.09)	0.45 (-1.35 to 2.25)
Adjusted model	1.01 (-1.26 to 3.29)	0.83 (-1.28 to 2.95)	0.29 (-1.39 to 1.98)

Adjusted model on Child's sex (female, male), age at the inclusion in the ELENA cohort (≤median, >median), higher level of parental education in the household (≤ high school, university)

a*: negative Beta indicating alteration in adaptive functioning*

VABS-II*: Vineland Adaptive Behavior Scales 2nd edition*

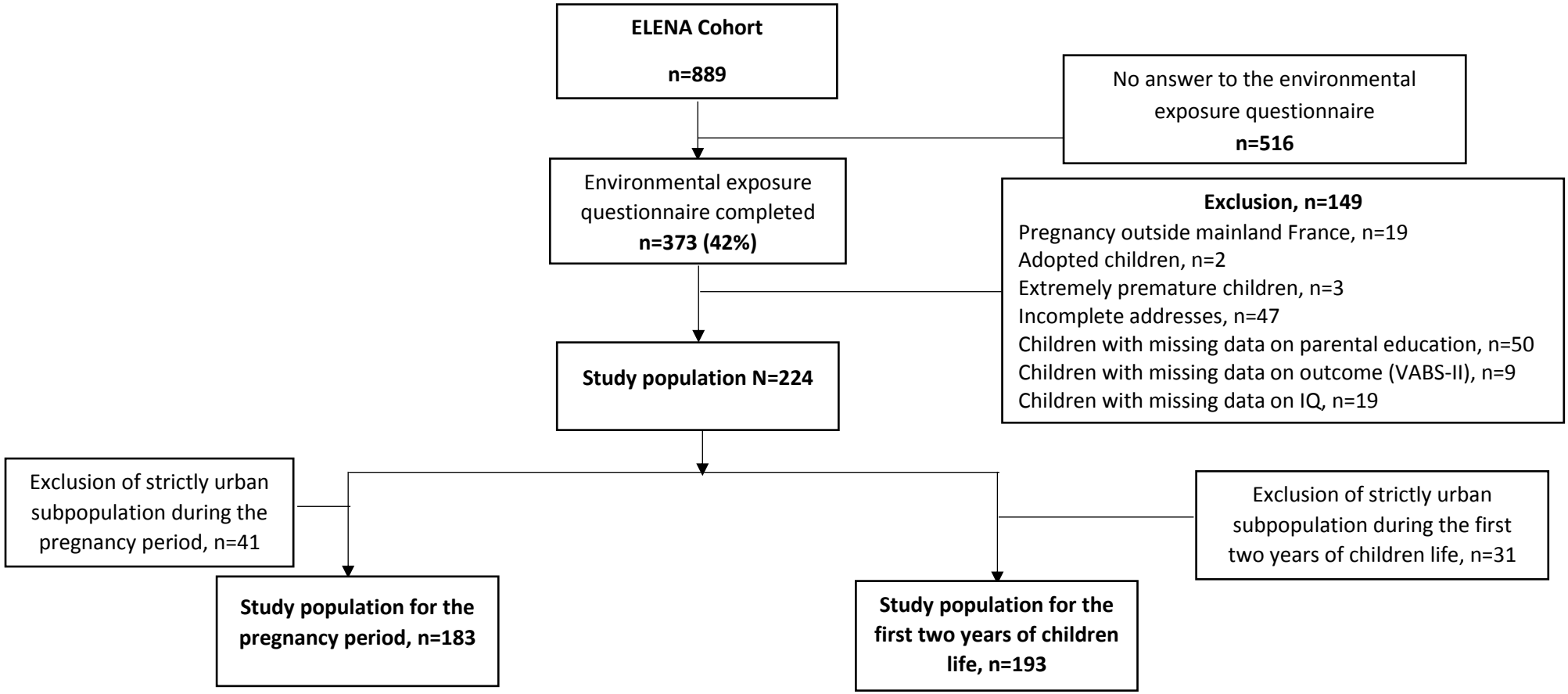

Fig 1. Selection process of the study population on associations between residential proximity to agricultural crops and adaptive behaviors in children with autism spectrum disorder, from the French ELENA cohort, by developmental exposure periods.

Abbreviations: VABS-II*= Vineland Adaptive Behavior Scales 2nd edition;* ***IQ=*** *intellectual quotient*

Highlights

- The influence of environmental exposures on the clinical expression of ASD is unknown.
- We investigated associations between early residential exposure to agricultural crops and adaptive behaviors in children with ASD.
- Residential exposure to agricultural crops was estimated by crops acreage within a 1000m radius around homes.
- Adaptive behaviors were assessed using the communication, daily living skills and socialization subscores of the VABS-II scale.
- Early residential exposures to agricultural crops decreased communication skills in the subgroup of children with ASD without intellectual disability.

Association between residential proximity to agricultural crops and adaptive behaviors in children with autism spectrum disorder from the French ELENA cohort

Running head: Proximity to crops and adaptive behaviors in children with ASD

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Association between residential proximity to agricultural crops and adaptive behaviors in children with autism spectrum disorder from the French ELENA cohort

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Conflict of interest

The authors declare that they have no conflict of interest associated with this manuscript.