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Exploring associations between residential exposure to pesticides and birth outcomes using the Dutch birth registry

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ABSTRACT

Background: Maternal occupational exposure to pesticides has been linked to adverse birth outcomes but associations with residential pesticide exposures are inconclusive.
Objectives: To explore associations between residential exposure to specific pesticides and birth outcomes using individual level exposure and pregnancy/birth data.
Methods: From all 2009–2013 singleton births in the Dutch birth registry, we selected mothers > 16 years old living in non-urban areas, who had complete address history and changed addresses at most once during pregnancy (N = 339,947). We estimated amount (kg) of 139 active ingredients (AI) used within buffers of 50, 100, 250 and 500 m around each mother's home during pregnancy. We used generalized linear models to investigate associations between 12 AIs with evidence of reproductive toxicity and gestational age (GA), birth weight (BW), perinatal mortality, child́s sex, prematurity, low birth weight (LBW), small for gestational age (SGA) and large for gestational age (LGA), adjusting for individual and area-level confounders. For the remainder 127 AIs, we used minimax concave penalty with a stability selection step to identify those that could be related to birth outcomes.
Results: Regression analyses showed that maternal residential exposure to fluroxypyr-meptyl was associated with longer GA, glufosinate-ammonium with higher risk of LBW, linuron with higher BW and higher odds of LGA, thiacloprid with lower odds of perinatal mortality and vinclozolin with longer GA. Variable selection analysis revealed that picoxystrobin was associated with higher odds of LGA. We found no evidence of associations with other AIs. Sensitivity and additional analysis supported these results except for thiacloprid.
Discussion: In this exploratory study, pregnant women residing near crops where fluroxypyr-meptyl, glufosinate-ammonium, linuron, vinclozolin and picoxystrobin were applied had higher risk for certain potentially adverse birth outcomes. Our findings provide leads for confirmatory investigations on these compounds and/or compounds with similar modes of action.

1. Introduction

Maternal exposure to pesticides has been linked to adverse birth outcomes such as low birth weight, decreased gestational age, being small for the gestational age, prematurity, changed child's sex and stillborn and infant mortality.(Hu et al., 2020; Mostafalou and Abdollahi, 2017; Stillerman et al., 2008) There is a substantial body of literature supporting these associations among mothers occupationally exposed to pesticides, but the picture is less clear when mothers are residentially exposed. Although research has demonstrated that pesticides are found in residences located near crops (Coronado et al., 2011; Gooijer et al., 2019; Ward et al., 2006), studies on the typically low-dose non-occupational exposure and birth outcomes present inconsistent results. This discrepancy may be due to the application of different exposure assessment methodology (often based on (single time point) measurement of biomarkers of pesticide exposure, questionnaires or proximity of residencies to agricultural plots) or differences between countries regarding agricultural scenarios and permitted types of

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pesticides and pesticide application methods. For example, some studies reported associations between exposure to pesticides and decreased birth weight and/or gestational age, these associations were not shown in other studies.(Fucic et al., 2021; Kamai et al., 2019; Khoshhali et al., 2020; Windham and Fenster, 2008) Clear evidence that residential exposure to pesticides presents a health risk for pregnant women and their babies is thus still lacking and, consequently, making it uncertain whether precautionary measures are needed to reduce pesticide exposure for this especially vulnerable population group.

In this paper we explore the possible associations between residential exposure to specific active ingredients during pregnancy and several birth outcomes, namely gestational age, birth weight, perinatal mortality and child's sex. We used crop maps and farmer's surveys to individually estimate residential exposure and the Dutch birth registry for outcome assessment. We first investigated active ingredients reported to have reproductive and developmental effects (i.e. hypothesis testing) and then further used a variable selection method to identify other relevant active ingredients among 139 active ingredients used during the exposure period assessed (2009–2013) (discovery analyses).

2. Methods

2.1. Study population

The Perinatale Registratie Nederland (PRN) comprises data on pregnancy and births registered by medical professionals such as midwives, general practitioners, gynecologists and paediatricians/neonatologists. The data are linked to the municipal registration (GBA - Gemeentelijke Basis Administratie) within Statistics Netherlands (CBS - Centraal Bureau voor de Statistiek). The resulting dataset includes all mother-infant pairs for which mothers were registered at the GBA and infants had a gestational age of 22 weeks or more at birth.

For this study we selected singleton births that occurred before 01–01–2014 for which the day of conception was estimated to be on or after 01–01–2009. We excluded mothers that were aged $\leq$ 16 years at the child's birth, mothers with an unknown address sometime during pregnancy, and mothers who changed addresses more than once during pregnancy. Furthermore, mothers who lived within 500 m of the borders with Germany or Belgium, and for whom we were unable to compute exposure, were excluded. Finally, we restricted our study to mothers living in non-urban areas of The Netherlands (<1500 addresses per km^2), thus excluding those whose health behaviors, lifestyles and environmental exposures are likely different from those living in rural areas and whose residences are likely not located near any crops (Fig. 1).

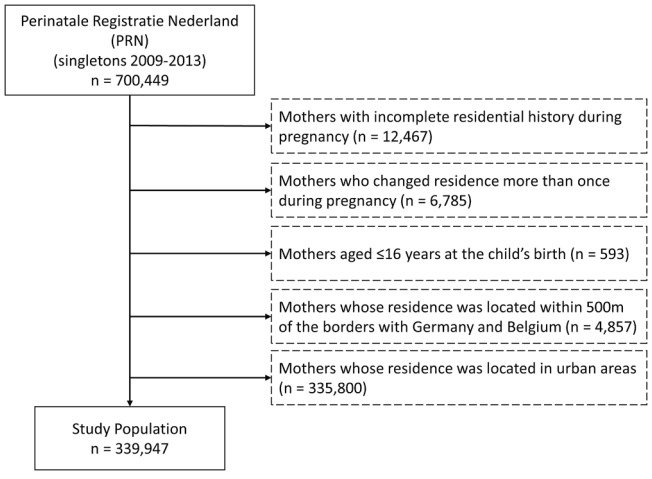

Fig. 1. Flow chart of the study population.

2.2. Birth outcomes

We evaluated the following main outcomes: gestational age, birth weight, perinatal mortality (up to 1 year of age) and child's sex. Child's sex was investigated to assess whether prenatal (mother and father) exposure to pesticides could result in either differential embryo loss by sex or in effects on sperm that would affect pre-conception differentially by sex. We further explored transformations of the outcomes gestational age and birth weight as low birth weight, small for gestational age, large for gestational age and prematurity. Definitions of these outcomes are as follows:

- **gestational age**: the number of days between the last menstruation and birth;
- **birth weight**: weight at birth, in grams;
- **low birth weight**: less than 2500 g at birth (binary variable),
- **small for gestational age** and **large for gestational age**: we constructed birth weight curves based on this study population (singletons, years 2009–2013) using the Lambda Mu and Sigma (LMS) method (library GAMLSS from R) considering gestational age (in days), sex of the baby (male, female), migration background of the mother (Dutch, Western, Non-Western) and parity (primipara, multipara). These curves were used to estimate the 10th and 90th birth weight centiles, which defined the thresholds for small for gestational age and large for gestational age, respectively (binary variables);(Overpeck et al., 1999)
- **perinatal mortality**: a binary composite variable including still births and infant mortality within the first year of life;
- **prematurity**: birth occurring before 37 weeks of gestation (binary variable);("ACOG Committee Opinion No 579: Definition of term pregnancy.," 2013)
- **child's sex:** sex assigned at birth (binary variable).

2.3. Exposure assessment

We estimated mothers' residential exposure to pesticides by computing the amount (kg) of specific active ingredients (AIs) used within buffers of 50, 100, 250 and 500 m around their residences during pregnancy. For this we used the Basisregistratie Adressen en Gebouwen containing geocoded residences from 2016 (BAG) and the annual polygon land use maps from 2009 to 2013 (Basisregistratie Gewaspercelen, BRP) to compute the area, in hectares (ha), of 12 groups of crops grown in open fields (greenhouses thus excluded) within these buffers: maize, winter wheat, summer barley, summer wheat, potatoes for consumption, potatoes for starch, seed potatoes, beets, ornamental plants and tree nurseries, vegetables, fruit trees and flower bulbs.(Dutch Ministry of Interior and Kingdom Relations, 2016; Nationaal Georegister (NGR), 2016) These crops account for 86–87% of the total area of arable land (excluding grassland) of the Netherlands in 2009–2013. (Statistics Netherlands (CBS), 2013). For computational reasons, we converted the land use maps to raster maps with a resolution of 10 m by 10 m and used a moving average to obtain squared buffers that correspond roughly to radii of 50 m, 100 m, 250 m and 500 m, as previously described.(Simoes et al., 2022) We then used data from the 2008 and 2012 CBS's Farmers' Survey, a national survey administered to a sample of farmers roughly every 4 years, to obtain information on the average annual dosage of active ingredients used (amount of AI used per hectare of treated crop, kg/ha) for each crop group. The total amount of active ingredient used in a crop within a buffer around a residence was then estimated by multiplying the dosage used by the estimated crop area. The total annual amount of AI used within a buffer around a residence was then obtained by summing the amounts used for all crops present in the buffer. We used these estimates as proxies for the amount of AIs mothers were exposed to at their residences during pregnancy. When conception and birth occurred in different years, we used the average of estimates for the separate years, weighted by the number of gestation days in each

Table 1
Active ingredients included in the study (n = 139). The first 12 active ingredients have evidence of adverse reproductive and/or developmental effects in humans and were explored using regression analyses.

Reproduction and/or development effects	Active ingredients			
EUPDB	Asulam	Glufosinate-ammonium		
Category 1B				
(H360D, H360F, H360Df, H360FD, H360Fd)	Carbetamide	Linuron		
Presumed human reproductive toxicant (evidence from animal studies)	Cyproconazole	Propiconazole		
	Epoxiconazole	Thiacloprid		
PPDB	Fluroxypyr-meptyl	Triadimenol		
Yes, known to cause a problem in reproduction and/or development	Glufosinate	Vinclozolin		
EUPDB	Abamectin	Ioxynil octanoate	Tembotrione	
	Amitrole	Mancozeb	Tepraloxydim	
Category 2 (H361d, H361f, H361fd)	Benthiavalicarb isopropyl	Maneb	Triflusulfuron-methyl	
Suspected human reproductive toxicant (some evidence from human and/or animal studies)	Cycloxydim	Penconazole		
	Cymoxanil	Spirodiclofen		
	Fenpropimorph	Spirotetramat		
	Fluazifop-p-butyl	Sulcotrione		
PPDB	Fluazinam	Tebuconazole		
Possibly capable of causing a problem in reproduction and/or development, status not identified				
EUPDB	2,4-D	Dimethoate	Iodosulfuron-methyl-sodium	Prochloraz
Not classified as reproductive toxicant	Acetamiprid	Dimethomorph	Iprodione	Procymidone
	Aclonifen	Diquat	Isoproturon	Propamocarb
PPDB	Azoxystrobin	Dithianon	Kresoxim-methyl	Propyzamide
Known not to cause a problem	Bentazone	Dodine	lambda-Cyhalothrin	Prosulfocarb
	Bifenazate	Emamectin benzoate	Mandipropamid	Prothioconazole
	Bifenox	Esfenvalerate	MCPA	Pymetrozine
	Bitertanol	Ethofumesate	Mecoprop-P	Pyraclostrobin
	Bixafen	Fenamidone	Mepanipyrim	Pyridate
	Boscalid	Fenhexamid	Mesosulfuron-methyl	Pyrimethanil
	Bupirimate	Fenoxycarb	Mesotrione	Pyroxsulam
	Captan	Fenpropidin	Metalaxyl-M	Quinoclamine
	Chlorantraniliprole	Flonicamid	Metamitron	Quizalofop-P-ethyl
	Chloridazon	Florasulam	Metazachlor	Rimsulfuron
	Chlorothalonil	Fludioxonil	Methiocarb	S-Metolachlor
	Chlorpropham	Fluopicolide	Methoxyfenozide	Spinosad
	Clomazone	Fluoxastrobin	Metiram	Sulphur
	Clopyralid	Fluroxypyr	Metoxuron	Tebufenpyrad
	Copper oxychloride	Folpet	Metribuzin	Teflubenzuron
	Cyazofamid	Foramsulfuron	Metsulfuron-methyl	Terbuthylazine
	Cydia pomonella granulovirus	Fosetyl	Nicosulfuron	Thiamethoxam
	Cyprodinil	Fosetyl-aluminium	Pencycuron	Thiophanate-methyl
	Deltamethrin	Glyphosate	Pendimethalin	Thiram
	Desmedipham	Haloxyfop-p-methyl	Phenmedipham	Tolclofos-methyl
	Dicamba	Imazalil	Picoxystrobin	Topramezone
	Difenoconazole	Imidacloprid	Pirimicarb	Tri-allate
	Dimethenamid-P	Indoxacarb	Pirimiphos-methyl	Trifloxystrobin

EUPDB = European Union Pesticide Database.
PPDB = Pesticide Properties Database.
Classification (Reg. 1272/2008):
H360D = May damage the unborn child.
H360Df = May damage the unborn child. Suspected of damaging fertility.
H360FD = May damage fertility. May damage the unborn child.
H361f = Suspected of damaging fertility.
H361d = Suspected of damaging the unborn child.
H361fd = Suspected of damaging fertility. Suspected of damaging the unborn child.

year. A similar approach was used for estimating exposure for mothers that changed address during pregnancy. A more detailed description and example calculations can be found in A1 of Appendix A.

We included 139 AIs that were used by at least 10% of the surveyed farmers in 2008 and 2012 in these calculations. Of these, 12 were classified as reproductive toxicants from Category 1B (presumed human reproductive toxicant based clear evidence of an adverse effects from animals studies) in the European Union Pesticide Database (EUPDB) or as "known" to cause a problem in reproduction or development in the Pesticide Properties Database (PPDB).(Lewis et al., 2016; The European Food Safety Authority (EFSA), 2021) Another 19 were classified as Category 2 (suspected human reproductive toxicant based on some evidence from humans or experimental animals studies) or as "possible" to cause a problem in reproduction or development in the EUPDB and the PPDB, respectively. There is no evidence of reproductive or developmental effects for the remainder AIs (Table 1).

Table 2
Demographic characteristics of the study population (before imputation).

	Study Population (n = 339,947)
Pregnancy Outcomes	
Gestational age (days) [mean ± sd]	276.2 ± 14.1
Birth weight (g) [mean ± sd]	3,460.5 ± 589.3
Perinatal mortality [n (%)]	2,926 (0.9)
Infant sex (boys) [n (%)]	174,373 (51.3)
Premature babies (<37 weeks) [n (%)]	20,792 (6.1)
Low birth weight [n (%)]	15,738 (4.6)
Small for gestational age [n (%)]	32,951 (9.7)
Large for gestational age [n (%)]	35,141 (10.3)
Individual covariates	
Parity	
1 [n (%)]	147,231 (43.3)
≥2 [n (%)]	192,716 (56.7)
Migration background	
Dutch [n (%)]	288,446 (84.9)
Non-Dutch, western [n (%)]	27,597 (8.1)
Non-western [n (%)]	23,904 (7.0)
Maternal age at delivery	
17–19 [n (%)]	3,158 (0.9)
20–29 [n (%)]	138,841 (40.8)
30–34 [n (%)]	129,847 (38.2)
35–40 [n (%)]	57,877 (17.0)
≥40 [n (%)]	10,224 (3.0)
Maternal education level	
Primary and lower secondary education [n (%)]	7,164 (2.1)
Higher secondary education [n (%)]	125,446 (36.9)
Higher professional and university education [n (%)]	111,824 (32.9)
Missing [n (%)]	95,513 (28.1)
Household income (quintiles)	
1st quintile [n (%)]	49,741 (14.6)
2nd quintile [n (%)]	64,929 (19.1)
3rd quintile [n (%)]	91,518 (26.9)
4th quintile [n (%)]	80,799 (23.8)
5th quintile [n (%)]	49,444 (14.5)
Missing [n (%)]	3,516 (1.0)
Marital status	
Married/living together [n (%)]	210,795 (62.0)
Single/divorced/widowed [n (%)]	129,152 (38.0)
Mother's job status	
Employed [n (%)]	277,110 (81.5)
Unemployed [n (%)]	62,837 (18.5)
Country/neighborhood level covariates	
Year of birth	
2009 [n (%)]	19,764 (5.8)
2010 [n (%)]	83,687 (24.6)
2011 [n (%)]	82,032 (24.1)
2012 [n (%)]	79,072 (23.3)
2013 [n (%)]	75,392 (22.2)
Urbanization degree	
1000–1500 addresses per km^2 [n (%)]	129,313 (38.0)
500–1000 addresses per km^2 [n (%)]	113,692 (33.4)
≤500 addresses per km^2 [n (%)]	96,934 (28.5)
Missing [n (%)]	8 (0.0)

n = number of observations, sd = standard deviation.

2.4. Potential confounders

We included the following individual covariates as potential confounders: gestational age (not for the gestational age and prematurity analyses), sex of the baby (not for the child's sex analyses), parity, mother's migration background, maternal age at delivery, mother's educational level, mother's household income, mother's marital status, mother's job status, and year of birth. We further considered one area level covariate, namely urbanization degree of the neighborhood where the mother lived. Classes of these covariates can be seen in Table 2.

2.5. Statistical analysis

2.5.1. Imputation

Some of the covariates had missing data: household income (1.0%), educational level (28.1%) and degree of urbanization (0.002%). We used multiple imputation by chained equations (MICE) to impute missing values, using the *MICE* package in R, and included all outcome variables, all covariates and the total area of crops in the 500 m buffer for the imputation models. Additionally, we also considered available variables that were determined to be highly predictive of the variables with missing values: job sector of mother and father's job, proportion of people employed in the neighborhood and proportion of people with low income in the neighborhood. Variables were deemed predictors and included in the imputation models when their correlation to the variable being imputed was > 0.20 and the proportion of usable cases was > 0.25. Collinearity of the selected variables was assessed by the variance inflation factor (VIF). Variables with VIF > 5 were considered collinear and the variable with highest VIF was excluded from the imputation model. Due to the large number of observations in the dataset, we used the predictive mean matching to impute all variables. Since the predictive mean matching algorithm only imputes values that are already present in the data, the original classes of categorical variables were maintained.(van Buuren and Groothuis-Oudshoorn, 2011) We imputed 5 data sets, using 8 iterations, to limit computational overhead. We assessed the imputed datasets by evaluating plots of the mean and standard deviation of the imputed values, per iteration. These showed that convergence was fast and achieved after the second or third iteration, with very little trend (not shown). The kernel density estimates for the marginal distributions showed that the densities of the observed data and the five imputed data sets, per variable, had essentially the same shape.

2.5.2. Regression analyses and exposure variables selection.

We investigated associations between the amount of AIs used in the vicinity of pregnant women's residences and birth outcomes using two approaches.

One, from the pool of 139 AIs, we selected those classified as Category 1B or "known to cause problems" (henceforth referred to as "*a priori* selected AIs", n = 12, see Table 1), i.e, AIs with clear evidence for toxic effects on reproduction and fetal development. For these AIs we investigated associations with gestational age and birthweight using linear regression models, and with perinatal mortality, childs sex, prematurity, low birth weight, small for gestational, and large for gestational age using logistic regression models. Each model included all other AIs which correlation to the AI under investigation was below 0.7 (see A2 for correlations between AIs and the footnote from Table 3 for the AIs included in the models). Associations were explored separately for each buffer size. We considered that the narrower buffers (i.e with a radius of 50 and 100 m) were more likely to capture direct spray drift of pesticide droplets. This drift has an exponential decrease in concentration with distance and is highest within the first meters of application, although it can be detected up to 100 m away from a field edge depending on the application technique and meteorological conditions.(Rautmann et al., 2001; Wolters et al., 2008) The larger two buffers were considered to capture secondary emission processes such as volatilization. Moreover, a Dutch pesticide exposure assessment study reported high contrasts in pesticide concentration in air and house dust between residences located within 250 m and beyond 500 m from flower bulb crops.(Gooijer et al., 2019) For these reasons, we considered that relevant residential exposure occurred within 500 m and each buffer model was adjusted for the amount of AI used in the area up to 500 m, a variable we named "complimentary donut" (for example, for the 50 m buffer model we included the amount of AI used in a "donut" of 50 to 500 m around the

residence as a covariate). By adding the "complementary donut", models are adjusted for exposure that might occur beyond the buffer under investigation. Consequently, the referent ("unexposed") group in our analyses consisted of mothers with zero kilograms of (specific) active ingredient within 500 m of their residences. Buffers and complementary donuts were used as continuous variables in the analyses. We also explored increasingly adjusted models, starting with a *basic* model adjusted for gestational age (when gestational age or prematurity were not the outcomes), sex of the baby (when child's sex was not the outcome), parity and the complementary donut, followed by an *intermediate* model consisting of the basic model and further adjusted for household income, mother's education, mother's marital status, mother's origin, mother's age at birth and mother's job status, and a *full* model, which additionally included the degree of urbanization of the residence location and year of birth of the baby. For binary outcomes, analyses were performed when there were at least 10 exposed cases.

Second, from the remainder 127 AIs, we included those with correlations below 0.90 in the 500 m buffer to run the variable selection models (A3). Consequently, AIs were selected from a pool of 47 AIs (Table 4). The models were adjusted for all considered covariates (i.e., equivalent to the full model of the regression analyses) and for the AIs for which the previous regression analyses showed evidence of an association with a birth outcome - no penalization was applied to the coefficients for these covariates and they were therefore not subject to variable selection. Variable selection was performed using penalized regression with the minimax concave penalty (MCP) for which the appropriate level of penalization was selected with 10-fold cross-validation. We then applied a stability selection step to estimate selection probabilities for each variable under random resampling of the data. This approach allows for (multiple-testing) error control and yields more consistent selections. For the stability step we used R's *stabs* package, but modified the algorithm to allow use of the ncvreg() function with the MPC penalty. Since this approach has exploratory purposes, stability selection models were run with per-family error rate (PFER) set at the value of 1, a rather lenient approach in regard to controlling for false discoveries. Furthermore, the model sampled from the five different imputed data sets in each subsampling iteration, using stratified sampling so that every dataset was used as often as the others.

Spatial analyses to compute the crop areas within buffers around residences was performed using ArcGIS/ArcPy 10.4 (2016) and STATA/MP 14. Statistical analyses, as well as the imputations and the calculation of the birth weight curves, were performed in R versions 3.4.1 (2017–06–30) and 3.6.3 (2019–12–12), within the remote secure environment of CBS.

2.5.3. Criteria for interpretation

After assessing whether effect sizes of the AIs materially changed with increasing confounder adjustment in the regression analyses, we based the interpretation of the results on a pre-defined set of criteria, similarly to what we used in previous studies from our research group. (Simoes et al., 2022; Simões et al., 2022) We considered that there was evidence of an association between an AI and a birth outcome (a *finding*) when results from the regression analyses met all the following criteria:

- Consistency among buffer models: the associations had the same direction across all buffers
- Trend in strength of the associations (monotonicity): there was a decreasing monotonic trend from the smallest to the largest buffer
- Statistical significance: at least one statistically significant result among the four buffers (the 95% confidence interval (95% CI) did not include unity)

We further defined a criterium to interpret the results from variable selection analysis:

- the AI was selected in at least three of the buffers

If the variable selection analyses pointed to an association between an AI and a birth outcome in at least three buffers, we conducted regression analyses and applied the 3 criteria to assess if there was evidence of an association between the selected AI and the birth outcome.

2.6. Sensitivity and additional analyses

We performed several sensitivity analyses for the associations that were considered findings according to the abovementioned criteria. First, we excluded gestational age in the models where it was used as a covariate, since it is unclear whether (low) gestational age is a confounder or (proxy for) some intermediate factor on the causal path to other birth outcomes. Second, we excluded all mothers that worked in the agricultural sector as they may experience occupational pesticide exposure besides residential exposure. Third, we excluded all mothers and fathers that worked in the agricultural setting, focusing analysis on residential exposures only. By excluding mothers working in agriculture during pregnancy we excluded sources maternal occupational exposure to pesticides. Since fathers working in the agriculture could be carriers of pesticides into their homes and there may also be an association between paternal occupational pesticide exposure and adverse birth outcomes, excluding both parents further decreased the contribution of occupational and *para*-occupational sources of exposure to pesticides. Fourth, we restricted analyses to mothers living in the most rural areas (<1000 addresses per km^2), to assess potential confounding from living in a semi-urban environment. Fifth, we restricted analyses to autochthonous mothers, since having a migration background may correlate both with exposure and different (health) behaviors during pregnancy and delivery. Sixth, we performed a complete case analysis, to assess whether data could be missing not at random.(Sterne et al., 2009) Seventh, since exposure was estimated based on annual usage of pesticides and did not take into account the time of year when each AI was applied, changes in address may have contributed to exposure misclassification. To decrease uncertainty around the exposure estimates, we performed an analysis restricted to mothers that did not change addresses during pregnancy. Finally, for the findings which outcomes were birth weight or low birthweight we conducted an analysis restricted to term babies.

Additionally, for associations that were considered findings, we performed analyses including an interaction term between sex and the AI and stratified analyses by sex if there was at least some evidence of differential effects from experimental or toxicological studies for the AI under investigation.

3. Results

We included a total of 339,947 mother–child pairs in our analysis. Table 2 describes the demographic characteristics of the study population. The relatively small number of births in 2009 reflects the fact that we only included pregnancies conceived after 01–01–2009. Exposure to at least one active ingredient occurred 6%, 14%, 40% and 70% of mothers living within 50 m, 100 m, 250 m and 500 m of a crop, respectively. The most common active ingredients which mothers were exposed to were florasulam and fluroxypyr-meptyl (4%, 10% and 32% in the in 50 m, 100 m and 250 m) and dimethenamid (62%) in 500 m. Interquartile ranges (IQRs) of amount if AI used ranged from 0.0001 kg for florasulam to 2.5 kg for sulphur in 50 m and from 0.006 kg for rimsulffuron to 79.2 kg for sulphur in 500 m (see A4 for descriptive statistics of each AI). Among exposed mothers, the median number of

Table 3
Findings from the regression analysis on the 12 a priori selected active ingredients.

Active ingredient (AI)	Outcome	Buffer size	Estimate / OR [95% CI]
Fluroxypyr_meptyl [a]	Gestational age	50 m	β = 9.5e-03 (-0.01, 0.03)
		100 m	β = 5.0e-03 (8.9e-04, 9.0e-03)
per 1 g increase		250 m	β = 8.7e-04 (2.2e-04, 1.5e-03)
		500 m	β = 6.5e-05 (-6.1e-05, 1.9e-04)
Glufosinate_ammonium [b]	Low birth weight	50 m	OR = 1.01 (1.00, 1.02)
		100 m	OR = 1.00 (1.00, 1.00)
per 1 g increase		250 m	OR = 1.00 (1.00, 1.00)
		500 m	OR = 1.00 (1.00, 1.00)
Linuron [a]	Birth weight	50 m	β = 256.85 (25.27, 488.43)
		100 m	β = 66.05 (21.12, 110.98)
per 1 kg increase		250 m	β = 13.24 (6.43, 20.04)
		500 m	β = 2.54 (1.25, 3.84)
Linuron [a]	Large for gestational age	50 m	OR = 4.19 (0.80, 22.13)
		100 m	OR = 1.43 (1.03, 1.98)
per 1 kg increase		250 m	OR = 1.07 (1.02, 1.13)
		500 m	OR = 1.01 (1.00, 1.02)
Thiacloprid [c]	Perinatal mortality	50 m	OR = 0.98 (0.95, 1.02)
		100 m	OR = 1.00 (0.99, 1.00)
per 1 g increase		250 m	OR = 1.00 (1.00, 1.00)
		500 m	OR = 1.00 (1.00, 1.00)
Vinclozolin [a]	Gestational age	50 m	β = 0.49 (-0.56, 1.53)
		100 m	β = 0.04 (-0.18, 0.26)
per 1 g increase		250 m	β = 7.1e-03 (-0.03, 0.04)
		500 m	β = 8.4e-03 (3.1e-03, 0.01)

The referent ("unexposed") group in all models was mothers with zero kilogram of specific AI within 500 m of their residences.
All models were further adjusted for the amount of AI used in the area up to 500 m ("complimentary donut"), gestational age (when gestational age or prematurity were not the outcomes), sex of the baby (when child's sex was not the outcome), parity, household income, mother's education, mother's marital status, mother's origin, mother's age at birth, mother's job status, urbanization degree and year of birth.
AIs included in the models (assuring that the correlations between the AIs included in the models was < 0.70):
[a] carbetamide, cyproconazole, epoxiconazole, glufosinate, linuron, fluroxypyr-meptyl, propiconazole, triadimenol and vinclozolin.
[b] carbetamide, cyproconazole, epoxiconazole, glufosinate, linuron, fluroxypyr-meptyl, glufosinate-ammonium and vinclozolin.
[c] cyproconazole, epoxiconazole, glufosinate, linuron, fluroxypyr-meptyl, propiconazole, thiacloprid, triadimenol and vinclozolin.

AIs mothers were exposed to was 22 [minimum 9, maximum 107] in 50 m, 25 [9,121] in 100 m, 34 [9, 133] in 250 m and 50 [9, 139] in 500 m. In the 500 m buffer, among the 12 *a priori* selected AIs, correlations were high (>0.70) between glufosinate-ammonium and propiconazol, between glufosinate-ammonium and triadimenol, between thiacloprid and carbetamide, between asulam and thiacloprid, and between asulam and vinclozolin (A2).

Models adjusted for all potential confounders showed differences in effect sizes > 10% in more than half of the models where GA and BW were the outcomes, showing mostly smaller effect sizes. For conciseness, Table 3 shows the results of the fully adjusted regression analyses for the associations that met our interpretation criteria (findings), expressed as increase in days for gestational age, increase in grams for birth weight and the Odds Ratio (OR) for the other outcomes per 1 g increase in AI (for AIs with a median usage ≤ 20 g) or 1 kg increase in AI (median usage > 20 g) used within the buffer. Results from all regression analyses as well as results from the basic and intermediate models are shown in A5). Among the *a priori* investigated AIs, six findings emerged that met our criteria for being considered a finding: maternal residential exposure to fluroxypyr-meptyl was associated with longer GA, glufosinate-ammonium was associated with higher risk of having LBW babies, linuron was associated with higher BW and higher odds of having LGA babies, thiacloprid was associated with lower risk of perinatal mortality, and vinclozolin was associated with longer GA. Variable selection indicated that picoxystrobin was associated with being LGA and with perinatal mortality (Table 4). Posteriorly, regression analysis showed that exposure to picoxystrobin was associated with higher odds of LGA and complied with the interpretation criteria, rendering this result an additional finding (Table 5). Regression results for the association between picoxystrobin and mortality did not meet or interpretation criteria and the association was not considered a finding.

Results were mostly robust to sensitivity analyses (Fig. 2 and A6). Although some sensitivity analyses showed relevant changes in effect sizes (more than 10% change compared to the main analysis effect size), the majority of results complied with our interpretation to be considered findings. The exceptions to this were the sensitivity analysis on the association between exposure to vinclozolin and increased GA, in which most sensitivity analysis did not follow the interpretation criteria, and on the association between exposure to thiacloprid and lower odds of perinatal mortality, in which none complied with the interpretation criteria. Sensitivity analyses restricted to term babies were robust for the association between exposure to linuron and BW but not for the association between exposure to glufosinate-ammonium and being LGA. Given that linuron and vinclozolin have antiandrogenic effects and thiacloprid has estrogenic effects that could result in sex-differential effects,(Gray et al., 1994; Lambright et al., 2000; Zhang et al., 2020) we further conducted an analysis including an interaction term for sex these and AIs and analyses stratified by sex. The interaction term sex: linuron was statistically significant in the 50 m (BW and LGA) and 100 m (BW) buffers, where we correspondingly observed larger differences in effect sizes between sexes, with significant effects in girls only. In effect, for both outcomes, stratified analyses provided evidence of an association in girls but not in boys, given non-compliancy with the interpretation criteria (Table 6). For the associations between vinclozolin and GA and between thiacloprid and perinatal mortality, we observed that none of the interaction terms across the buffers were statistically significant, while stratified analyses showed that results did not comply with the interpretation criteria.

Table 4
Results of the variable selection models.

Pool of AIs	Buffer	Gestational age[a]	Birth weight[b]	Child's sex	Perinatal mortality[c]	Prematurity	Low birth weight[d]	Large for gestational age[b]	Small for gestational age
azoxystrobin, boscalid, clopyralid, cymoxanil, dimethoate, diquat, phenmedipham, fenpropimorph, flonicamid, fluroxypyr, fosetyl, haloxyfop-p-methyl, imidacloprid, copper oxychloride, kresoxim-methyl, mancozeb, mcpa, mecoprop-p, metamitron, metiram, metribuzin, metsulfuron-methyl, pirimicarb, prosulfocarb, pyraclostrobin, quinoclamine, rimsulfuron, spinosad, sulcotrione, tebufenpyrad, teflubenzuron, thiophanate-methyl, tolclofos-methyl, topramezone, trifloxystrobin, triflusulfuron-methyl, aclonifen, emamectin benzoate, fenamidone, fenpropidin, penconazole, pyroxsulam, tembotrione, thiamethoxam, thiram, sulphur	50 m	diquat emamectin benzoate	diquat		diquat picoxystrobin		diquat metiram picoxystrobin	picoxystrobin	diquat
	100 m		copper oxychloride		picoxystrobin		tebufenpyrad	picoxystrobin	copper oxychloride
	250 m		fenpropidin	diquat tebufenpyrad	picoxystrobin	triflusulfuron-methyl pyroxsulam		picoxystrobin, fenpropidin	triflusulfuron-methyl
	500 m	rimsulfuron, sulcotrione	tolclofos-methyl		sulcotrione	rimsulfuron	sulcotrione		prosulfocarb

All models were adjusted for gestational age (when gestational age or prematurity were not the outcomes), sex of the baby (when child's sex was not the outcome), parity, household income, mother's education, mother's marital status, mother's origin, mother's age at birth, mother's job status, urbanization degree and year of birth. Models were further adjusted for the amount of AIs used in the area up to 500 m ("complimentary donut"). Finally, models were adjusted for AIs (and their complementary donuts) for which evidence for an association was determined in the previous (linear regression) analyses:

[a] fluroxypyr-meptyl and vinclozolin.
[b] linuron.
[c] thiachloprid.
[d] glufosinate-ammonium.

Table 5
Results of the regression analyses on the associations between picoxystrobin and the birth outcomes large for gestational age and perinatal mortality.

Active ingredient (AI)	Buffer size	Large for gestational age	Perinatal mortality
Picoxystrobin [a] per 1 g increase	50 m	OR = 1.056 (0.995, 1.119)	OR = 1.031 (0.843, 1.259)
	100 m	OR = 1.02 (1.008, 1.031)	OR = 1.006 (0.963, 1.05)
	250 m	OR = 1.003 (1.001, 1.004)	OR = 1.006 (0.999, 1.013)
	500 m	OR = 1.000 (1.000, 1.001)	OR = 1.001 (0.999, 1.002)

The referent ("unexposed") group in all models was mothers with zero kilogram of specific AI within 500 m of their residences.

[a] Adjusted for asulam, carbetamide, cyproconazole, epoxiconazole, glufosinate, linuron, fluroxypyr-meptyl, propiconazole and triadimenol.

4. Discussion

We used the Dutch national birth registry to build a birth cohort and investigate associations between maternal exposure to 139 active ingredients used in the vicinity of pregnant women's residences and several birth outcomes. After defining a set of three criteria to evaluate the results (same direction of effect, monotonic trend and statistical significance in at least one buffer), we identified seven findings: maternal residential exposure to fluroxypyr-mepty during pregnancy was associated with longer GA, glufosinate-ammonium with higher odds of having LBW, linuron with higher BW and higher odds of being LGA (namely in baby girls), thiacloprid with lower odds of perinatal mortality, vinclozolin with longer GA, and picoxystrobin with higher odds of being LGA. The first six associations arose from an investigation on a set of 12 AIs known to cause reproductive and/or developmental problems. Picoxystrobin was identified to be associated to LGA using a variable selection method that was applied to the remainder 127 AIs. After performing regression analysis and applying the interpretation criteria, we classified this association as an additional finding. We also observed that picoxystrobin was selected as a variable associated to perinatal mortality but regression analyses did not meet the *a priori* interpretation criteria of an effect. Sensitivity and additional analyses supported these results, with exception of those pertaining the association between thiacloprid and lower risk of perinatal mortality. They also revealed that the effects of linuron on BW and being LGA were more pronounced in girls, with at least one buffer where the interaction term (sex:linuron)

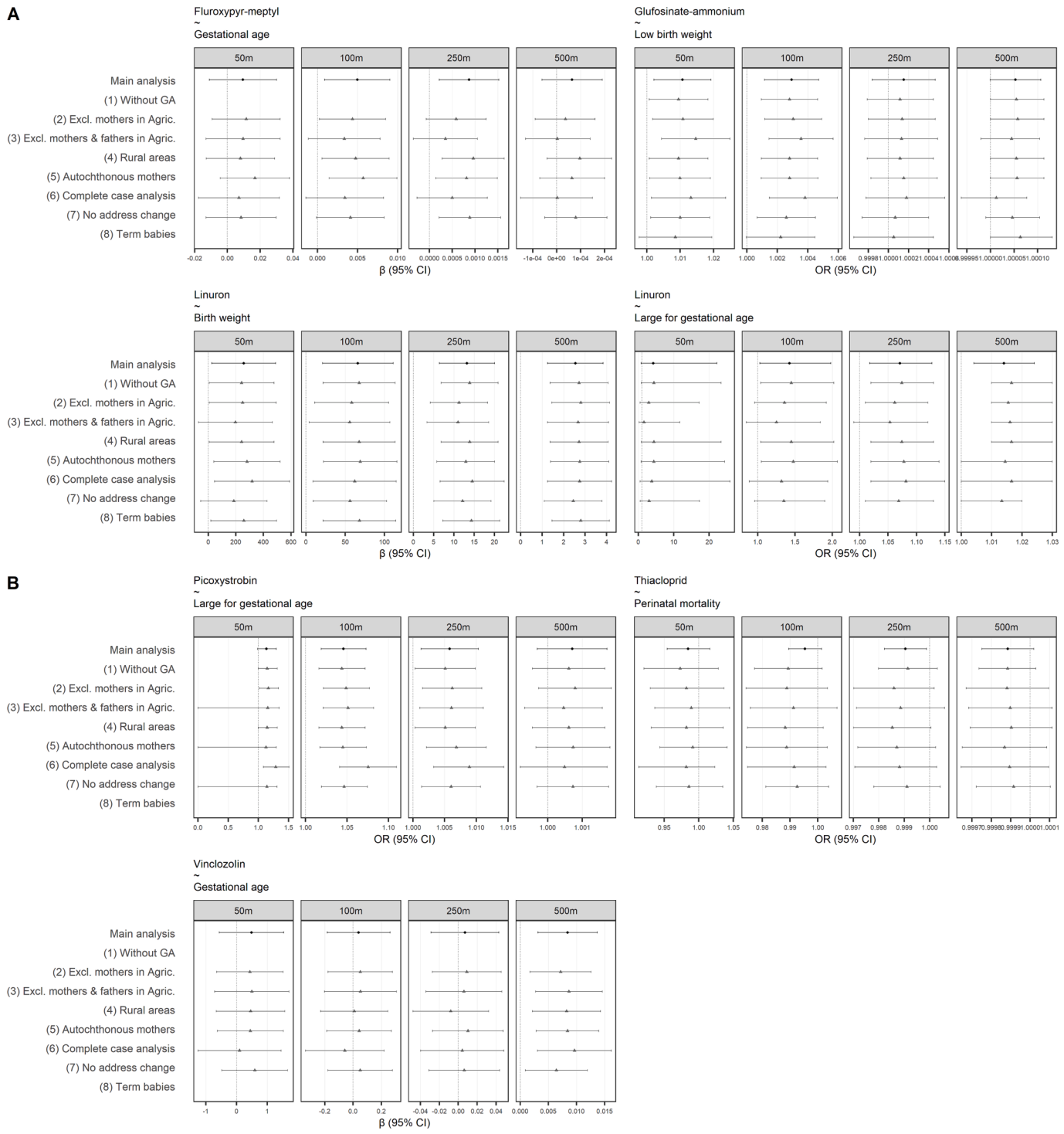

Fig. 2. Results of the sensitivity analyses performed on the associations that were considered findings.

was statistically significant.

By using the birth registry we were able to include complete information collected and registered by medical professionals on birth outcomes for all singleton births among mothers living in rural areas of the Netherlands. We were thus able to obtain a large study population of nearly 340,000 mother-infant pairs and circumvent selection bias. We further enriched the data set by including covariables from other administrative microdata, namely mother's educational level, household income, marital status and job status. Another advantage of using administrative data is access to the exact address information and residential history, which allowed for exposure assignment at individual level. Indeed, we were able to assess residential exposure for several active ingredients by estimating the amount of active ingredients used in the vicinity of the residences. This objective exposure assessment was based on registry-based annual land use maps and information on pesticide usage from two Farmers' Surveys. Although our exposure assessment was not based on measurements, previous studies have previously shown that the area of crops around residences is suitable for estimating pesticide levels in residences located near crops,(Figueiredo et al., 2021; Ward et al., 2006) and the Farmers' Surveys were conducted

Table 6
Results of the additional analysis performed for the findings pertaining AI with reported sex-differential effects.

Finding	Buffer size	Model with interaction term between sex and the AI			Stratified analysis by sex	
		Sex	AI	Sex:AI	AI (boys)	AI (girls)
Linuron ~ Birth weight	50 m	−142.515 (−145.379, −139.651)	61.675 (−218.36, 341.711)	402.317 (77.577, 727.058), p = 0.015	−50.985 (−379.351, 277.381)	575.22 (248.547, 901.892)
	100 m	−142.639 (−145.52, −139.758)	32.512 (−20.873, 85.898)	69.399 (9.723, 129.075), p = 0.023	14.185 (−49.422, 77.792)	118.811 (55.322, 182.300)
	250 m	−142.668 (−145.616, −139.72)	10.665 (2.928, 18.403)	5.166 (−2.234, 12.565), p = 0.171	10.881 (1.156, 20.607)	15.402 (5.888, 24.915)
	500 m	−142.965 (−146.043, −139.887)	1.998 (0.484, 3.512)	1.125 (−0.498, 2.748), p = 0.174	2.642 (0.809, 4.475)	2.428 (0.605, 4.251)
Linuron ~ Large for gestational age	50 m	1.003 (0.981, 1.025)	1.258 (0.155, 10.214)	10.577 (1.011, 110.610), p = 0.049	0.580 (0.047, 7.098)	26.574 (2.828, 249.744)
	100 m	1.002 (0.980, 1.025)	1.195 (0.804, 1.779)	1.426 (0.922, 2.204), p = 0.110	1.144 (0.716, 1.830)	1.779 (1.127, 2.81)
	250 m	1.004 (0.981, 1.027)	1.065 (1.005, 1.129)	1.012 (0.957, 1.069), p = 0.684	1.079 (1.004, 1.159)	1.064 (0.99, 1.144)
	500 m	1.004 (0.980, 1.028)	1.013 (1.002, 1.025)	1.002 (0.989, 1.014), p = 0.811	1.012 (0.998, 1.026)	1.017 (1.003, 1.031)
Thiacloprid ~ Perinatal mortality	50 m	1.000 (1.000, 1.000)	0.984 (0.963, 1.006)	1.014 (0.991, 1.037), p = 0.228	0.979 (0.952, 1.007)	0.998 (0.982, 1.015)
	100 m	1.000 (1.000, 1.000)	0.997 (0.994, 1.001)	1.002 (0.998, 1.005), p = 0.401	0.996 (0.992, 1.001)	1.000 (0.996, 1.003)
	250 m	1.000 (1.000, 1.000)	1.000 (0.999, 1.000)	1.000 (1.000, 1.000), p = 0.990	1.000 (0.999, 1.000)	1.000 (0.999, 1.000)
	500 m	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)	1.000 (1.000, 1.000), p = 0.572	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)
Vinclozolin ~ Gestational age	50 m	5.77e−04 (4.82e−04, 0.001)	0.291 (−1.032, 1.614)	0.436 (−1.367, 2.239), p = 0.635	304.43 (−1150.26, 1759.12)	728.18 (−786.37, 2242.74)
	100 m	5.76e−04 (4.82e−04, 0.001)	−0.020 (−0.298, 0.257)	0.127 (−0.229, 0.483), p = 0.483	−19.31 (−332.91, 294.29)	109.35 (−208.87, 427.57)
	250 m	5.76e−04 (4.81e−04, 0.001)	0.004 (−0.039, 0.046)	0.007 (−0.039, 0.052), p = 0.776	6.04 (−44.82, 56.91)	8.03 (−42.43, 58.49)
	500 m	5.75e−04 (4.80e−04, 0.001)	0.007 (0, 0.015)	0.002 (−0.008, 0.012), p = 0.684	6.66 (−0.94, 14.27)	10.18 (2.87, 17.48)

in a representative sample of Dutch farmers, covering all the main crops grown in the country. Nevertheless, the computed proxies are not exempt of assumptions and limitations that resulted in exposure misclassification. Firstly, they do not consider all sources of exposure to pesticides. We did not consider time-activity patterns, presence at the residence during spraying events (which may influence exposure levels) and occupational exposures. Of these, we were able to assess the impact of working in agriculture by doing sensitivity analyses excluding mothers and excluding mothers and fathers working in this sector. These analyses showed important differences (>10%) when compared to the main analyses, especially in the smaller buffer sizes but overall remained indicative of the effects of the AIs on birth outcomes even when occupational exposure was excluded. We could not account for usage of pesticides in and around the home or for nutritional exposure to pesticides. However, it is questionable that these constitute strong confounding factors as it is unlikely that they differ greatly across the exposures to specific AIs, especially within the short distances that we assessed. Secondly, we used symmetric (squared) buffers, not considering wind direction and speed and thus disregarding the actual spread from both direct and secondary drift. The most suitable non-symmetrical shape of the buffer is difficult to determine but previous studies have shown that area of crop, even within symmetrical buffers, is among the most important variables to assess residential pesticides levels.(Figueiredo et al., 2021; Ward et al., 2006) Thirdly, Farmers' Surveys pertain to an average pesticide usage among a sample of farmers and no information on the actual dose used in each field was available. In this study, we assumed that all fields growing a certain crop used the dosage of all AIs reported in the survey. Fourthly, because Farmers' Surveys were available only for 2008 and 2012, we assumed that the dosages used in the years between surveys were either the same or an average of the two available years (see A1), but it is likely that important changes in usage occurred. Furthermore, the availability of information was only on the annual usage of AIs and we could not take into account that most AIs have a seasonal application (which further precluded analyses by trimester, when vulnerability to chemical aggressors may change). Finally, the fact that some mothers (9%) changed addresses during pregnancy may have resulted in some degree of change in the type of pesticides they were exposed to by moving to a residence that could be near other types of crops, especially regarding the closest crops. To tackle this, we computed weighted averages of the exposure for the different addresses, and additionally performed a sensitivity analysis restricted to mothers that did not change addresses. These analyses showed mostly attenuated estimates (closer to the null) in the two smaller buffers, but no major differences in the larger buffers. This may be related to the abovementioned differences in type of crop that resulted in a "dilution" of the exposure in the smaller buffers after computing the weighted average. Of note, none of these factors contributing to exposure misclassification would be considered non-differential, which means that they may have led to underestimation of effects from the regression analyses.

Since we used administrative databases, we were unable to account for individual level lifestyle factors such as smoking, alcohol use, drug use or pre-pregnancy Body Mass Index (BMI). For most of these factors one would not expect that they are associated to exposure to specific AIs and it is also unlikely that they differ substantially within the short distances investigated. Major differences in lifestyle are seen between urban and rural populations and to reduce this potential residual confounding we conducted a sensitivity analysis restricted to mothers living in the most rural areas (<1000 addresses per km^2). These analyses showed no material differences from the estimates of the main analysis that would change the overall interpretation of results. Furthermore, a similar study on residential proximity to crops and depression and perceived health on a sample of the Dutch population, several of these lifestyle factors were taken into account in the models, but results showed no major changes in the estimates compared to simpler models (Simões et al., 2022). Naturally, the potential for residual confounding

Table 7
Additional information on the AIs for which evidence of associations with birth outcomes was identified.

Active ingredient	Observed association	Pesticide type	Chemical group	Mode of action	Reproductive/ Developmental effects	Toxicologic/ experimental studies	Current approval in EU	Correlation > 0.80 with other AIs
fluroxypyr-meptyl	longer GA	Herbicide	pyridine compound	Root Growth Inhibitor	Category1B[1]	classified on PPDB as "known to cause a problem", but EFSA's peer-review on its parent compound (fluroypyr) reports no evidence of reproductive or developmental effects	approved	florasulam
glufosinate-ammonium	increased odds of LBW	Herbicide	phosphinic acid	Glutamine Synthesis Inhibitor	Category1B	lower fertility, abortions, fetus death and premature deliveries	not approved	fenamidone fosetyl-al acetamiprid propiconazole penconazole quinoclamine
linuron	higher BW and increased odds of LGA	Herbicide	urea	Photosynthesis Inhibitor (Photosystem II)	Category1B	endocrine disruptor, with antiandrogenic effects - impaired in male reproductive development	not approved	metribuzin
vinclozolin	longer GA	Fungicide	dicarboximides	Osmotic signal transduction, prevents spore germination and mycelial growth	Category1B	endocrine disruptor, with antiandrogenic effects - inhibited male sex differentiation	not approved	tolclofos-methyl haloxyfop-p-methyl
picoxystrobin	higher odds of LGA	Fungicide	methoxy-acrylates	Mitochondrial respiration inhibition	none	–	not approved	none

[1] Category1B (EU Pesticides Database) = Presumed human reproductive toxicant (evidence from animal studies).

in our analyses still cannot be completely excluded and it is also possible that effects are different according to lifestyle factors' status (e.g. smokers vs non-smokers), rendering these factors potentially relevant effect modifiers. From the potential confounders we were able to adjust for, education presented a relative large proportion of missing values (28.1%). Even though we cannot exclude the possibility of data being missing not at random (MNAR), we were able to use other available data to impute missing values for education. Furthermore, because this is registry-based information study, there was no self-selection of subjects into the study population, which matches more closely to the target population than the study population of a questionnaire-based study (in which subjects for which the data is missing may refuse to take part).

The study entails a high number of tests, since several outcomes, AIs and buffer sizes were assessed. To address the resulting elevated number of false positives from the regression analyses, we applied a set of criteria for interpretation. Although we might consequently have overlooked a signal, the application of these criteria was not so stringent as to preclude identification of the most important associations. Among the six AIs that showed evidence of an association with a birth outcome according to our criteria, three pertain to pesticides that have been reported to have endocrine disruptive effects. Linuron, which we found to be associated to higher BW and higher odds of being LGA, is a herbicide that inhibits root growth (Table 7). Vinclozolin, which was associated with longer GA, is a fungicide that prevents spore germination and mycelial growth. Both linuron and vinclozolin are endocrine disruptors with antiandrogenic effects, as shown in toxicologic/experimental research in both in vitro and in vivo studies.(Ding et al., 2017; European Food Safety Authority (EFSA), 2016) While linuron was reported to be hazardous to male reproductive development, namely by hampering gonadal organ development, vinclozolin was reported to inhibit sex differentiation in males.(Gray et al., 1994) Our additional analyses showed that the effects observed for linuron were mainly seen in girls. It is unclear how exposure to linuron could have resulted in larger baby girls but the balance in testosterone/estrogen levels is likely important to fetal growth. Vinclozolin is among one of the least used active ingredients (A4). Together with the loss of power when restricting analysis to certain groups, this could at least partially contribute to why sensitivity and additional analyses did not fully corroborate the association between exposure to vinclozolin and increased GA found in the main analysis. Thiacloprid is an insecticide which was also reported to have endocrine-disrupting effects, namely estrogenic activity.(Zhang et al., 2020) Toxicological studies on rats and rabbits observed reduced maternal and fetal body weight, altered sex hormones during pregnancy leading to dystocia and delayed sexual maturation.(European Food Safety Authority (EFSA) et al., 2019) Although these effects may be relevant to humans, the reasons for observed lower risks of perinatal mortality in mothers exposed to this AI in the two larger buffers remain unclear, especially given that toxicological studies also point to reduced pup viability. This could have been a chance finding in this study, since sensitivity and additional analyses did not support this result. Toxicological and experimental literature on the potential effects of fluroxypyr-meptyl and glufosinate-ammonium is scarcer, but they are listed in the PPDB as having reproductive and developmental effects. Fluroxypyr-meptyl is a formulation of the herbicide fluroxypyr and is listed in the PPDB as "known to cause a problem", but EFSA's peer-review on its parent compound reports no evidence of reproductive or developmental effects. (European Food Safety Authority (EFSA), 2011) We observed higher risk of LBW in mothers exposed to the herbicide glufosinate-ammonium, but toxicological studies in rats and rabbits showed that this AI induced lower fertility, abortions, fetus death and premature deliveries.(European Food Safety Authority (EFSA), 2005) The association between this AI and LBW was not robust to the sensitivity analysis restricted to term babies. Of note is that glufosinate-ammonium was highly correlated to several other AIs (Table 7) including propiconazole, an AI also listed in the EUPDB as a reproductive toxicant. Our results showed that propiconazole was indeed associated with increased odds of LBW, except in the 250 m buffer, but none of the OR were statistically significant. A reason for this discrepancy could be the lower number of exposed cases, compared to glufosinate-ammonium. However, we cannot completely rule out propiconazole as potentially being associated with LBW. In effect, the associations for glufosinate-ammonium and propiconazole are likely to be mutually confounded and, consequently,

the effects sizes reported are overestimated, referring only to the scenario where the other AI was not used. This reasoning is applicable to all AIs that are highly correlated (A3).

In this exploratory study we have used a variable selection method to uncover other potential links to adverse birth outcomes. From many possibilities, we chose the MPC method since it allows for a relatively fast computation on a large data set. MPC works in a similar way to the LASSO penalty but applies less shrinkage to the nonzero coefficients, reducing bias comparatively to LASSO. We set one interpretation criterium (the AI had to be selected in at least three buffers) to reduce the risk of a Type 1 error (false positive findings) due to multiple testing and analyzing a large data set, but we were still mostly interested in identifying potential pesticide candidates for further investigation. Indeed, in this study we considered it more important to avoid a high false negative rate than to wrongly select an AI and we were already hampered by the expected weak associations due to the small effect sizes usually seen in environmental epidemiological studies and the discussed sources of exposure misclassification. We observed that the associations between picoxystrobin and LGA and perinatal mortality complied with our *a priori* interpretation criteria. These results were further investigated with regression analyses. While these later identified the association between picoxystrobin and increased risk of being LGA as an additional finding (but not the association with perinatal mortality), to the best of our knowledge, studies in rats and rabbits have not provided evidence of fertility, reproductive or developmental effects up to date. (The European Food Safety Authority (EFSA), 2016) Correlations between picoxystrobin and other AIs were low (<0.5), and therefore no other candidates for the observed effects were considered.

In general, our findings point to higher BW, higher risk of LGA and longer GA. Although lower birth weight is usually of more concern for newborns health and survival, studies have indicated that higher BW and being LGA are associated with increased risk of neonatal complications and with increased risk of obesity and cardiovascular diseases later in life.(Palatianou et al., 2014; Scifres, 2021) Except for fluroxypyr-meptyl, none of the findings' AIs are nowadays approved in the European Union (EU), but exposure via contaminated foods from countries in which it is still used is possible. Additionally, these AIs were highly correlated to other AIs (Table 7) and/or share the same modes of action with AIs that are currently in use in the EU and other countries worldwide. Therefore, future research on the effects of maternal exposure to pesticides can consider the findings of this study as leads.

5. Concusions

In conclusion, we observed associations between residential exposure to five AIs (fluroxypyr-meptyl, glufosinate-ammonium, linuron, vinclozolin and picoxystrobin) and potentially adverse birth outcomes. The underlying mechanism driving these effects are unclear, but the findings warrant more research into the effects of (non-occupational) exposure to these pesticides on human health, especially in the vulnerable population of pregnant women and their babies. AIs that were correlated or that share the same modes of action with the identified in this study may also be considered as leads for further research.

6. Data statement

The dataset on buildings and addresses (Basisregistratie Adressen en Gebouwen, BAG) was derived from the public domain. This geodatabase is available every year and is updated every few months. Available at https://data.overheid.nl/dataset/basisregistratie-adressen-en-gebouwen–bag-.

The on land use (Basisregistratie Gewaspercelen) were derived from the public domain. These geodatabases are available every year at.

http://www.nationaalgeoregister.nl/geonetwork/srv/dut/catalog.search#/metadata/b812a145-b4fe-4331-8dc6-d914327a87ff.

The data on pesticide use (active ingredients) per crop type from before 2012 is available upon request at Centraal Bureau voor de Statistiek (CBS). Data from 2012 onward is available on StatLine.

Data on pregnancy and birth outcomes are curated by Perined, the organization responsible for the integration of data from PRN (Perinatale Registratie Nederland) en PAN (Perinatale Audit Nederland). A restricted version of the data set, which was used in this study, is available upon request within the secured remote environment of CBS. These data, as well as individual covariates included in the statistical models, cannot be made publicly available due to privacy protection of individuals included the study. Data requests can be made via de Microdata services from CBS. https://www.cbs.nl/en-gb/our-services/customised-services-microdata/microdata-conducting-your-own-research. Neighborhood-level covariates were also available within the secure environment of CBS and linkable to individuals via their address.

CRediT authorship contribution statement

Mariana Simões: Conceptualization, Formal analysis, Writing – original draft. **Roel Vermeulen:** Conceptualization, Supervision, Writing – review & editing. **Lützen Portengen:** Methodology, Writing – review & editing. **Nicole Janssen:** Conceptualization, Supervision, Writing – review & editing. **Anke Huss:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

While some data sets are publicly available (links provided in 'Data declaration'), data sets containing microdata are availabe upon request from Statistics Netherlands and Perined.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.108085.

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