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Maternal pesticides exposure in pregnancy and the risk of wheezing in infancy: A prospective cohort study

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ABSTRACT

Introduction: Pesticide exposure in pregnancy may have health effects in the offspring. We studied whether maternal pesticides exposure during pregnancy is associated with infant wheezing.
Methods: The study involved 5997 children from the Italian NINFEA birth cohort, whose mothers were recruited during pregnancy between 2005 and 2016. We used questionnaires completed during pregnancy and 6 months after delivery to derive the following indirect measures of exposure: i) Self-reported pesticide use during the first and the third trimester of pregnancy; (ii) Agricultural activities during the same trimesters. We also evaluated the exposure to agricultural pesticides applied near home using the Corine Land Cover inventory to derive the proportion of a 200-metre buffer area around maternal home address covered by agricultural crops and specific crop types (arable land, fruit trees, heterogeneous cultivations). Questionnaires completed when the child turned 18 months reported information on wheezing between 6 and 18 months of age. We estimated the odds ratios of wheezing adjusting for the following maternal characteristics: age, education, parity, asthma, atopy, smoking in pregnancy, region and area of residence, pet ownership during pregnancy. Crops proximity analyses were restricted to residents in rural areas (N = 1674).
Results: Agricultural activities during pregnancy were not associated with infant wheezing. Compared to no pesticide use, there was a weak positive association for self-reported use in the third trimester (POR: 1.30; 95 %CI 0.95–1.78) and a stronger association for use in both trimesters (POR: 1.72; 95 %CI 1.11–2.65). The relationship between the proportion of crops around the home address and the risk of infant wheezing, was J-shaped, in particular for fruit trees with the lowest risk for mid values and elevated risk for higher values.
Conclusion: We found some evidence of association for maternal pesticide use in pregnancy and residential proximity to fruit trees cultivations with infant wheezing.

1. Introduction

Pesticides are a wide group of chemical substances used to control plants, animals, fungi and microorganisms that could potentially damage human, mainly agricultural, activities (Roberts et al., 2012). Pesticides are widely used in both large and small-scale farming (Carvalho, 2017); however, less than 1% of their applied amount reaches its target, (Bernardes, et al., 2015) while the remaining can penetrate environmental media and reach non-target organisms, including humans (Tudi et al., 2021).

Acute effects of pesticides on human health are well established. Their chronic effects are less clear, due to the wide range of different chemical compounds, routes of exposure and metabolic pathways in the human body that are involved (Blair et al., 2015). Pesticide exposure has been suggested to have a negative effect on the nervous system (Alavanja et al., 2004), respiratory system (Mathew et al., 2015), male reproductive system, as well as on cancer development and endocrine and metabolic functioning (Payán-Rentería et al., 2012; Kim et al., 2017; Sugeng et al., 2013).

In this framework, pregnancy and early life might be extremely important since relevant exposures during this period can shape lifelong health trajectories (Keating and Hertzman, 1999). The epidemiological

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evidence suggests that exposure to pesticides during foetal life and infancy could adversely influence the development of immune (Gascon et al., 2012; Nakanishi et al., 1985; Glynn et al., 2008; Weisglas-Kuperus et al., 2000) and respiratory systems (Gascon et al., 2013; Buralli et al., 2020; Mamane et al., 2015; Gascon et al., 2014; Hallit, 2017; Margetaki et al., 2021). Among the respiratory disease manifestations occurring early in life, wheezing is both highly prevalent- up to 30% in the first 3 year of life (El-Gamal and El-Sayed, 2011)- and a strong predictor of asthma development and lung function later in life (Belgrave et al., 2014; Amin et al., 2014).

The relationship between pesticide exposure during pregnancy and wheezing in infancy was examined by some systematic reviews (Gascon et al., 2013; Buralli et al., 2020; Mamane et al., 2015), which included studies on both children and adults and a wide range of respiratory outcomes. Overall, there is some, though limited, evidence of association between prenatal pesticide exposure and the risk of wheezing and respiratory infections during both infancy and childhood. In addition, it has been suggested that early life pesticide exposure might increase the risk of childhood asthma. The evidence was fairly consistent across three different reviews (Gascon et al., 2013; Buralli et al., 2020; Mamane et al., 2015), while the results of more recent cohort studies, not included in the above reviews, were less consistent (Gascon et al., 2012; Gilden et al., 2020; Mora et al., 2020; Tagiyeva et al., 2010; Gascon et al., 2014). All of them measured pesticides or metabolites concentration in biological samples and found conflicting results, ranging from a decreased to an increased risk of wheezing, according to the cohort and the specific pesticide or pesticide metabolite examined. The studies included in the reviews, conversely, were heterogeneous in terms of study design and exposure assessment. Some focused on specific substances, mainly DDE and organochlorine compounds, while others considered overall pesticide exposure; some measured pesticides or metabolites concentrations in biological samples while others relied on questionnaires; finally, some examined occupational exposures while others occasional or residential exposure.

In the current study we used data of the Italian NINFEA (Nascita e Infanzia: gli Effetti dell'Ambiente) mother–child cohort to evaluate multiple- sources of pesticide exposure during pregnancy, assessed by three indirect exposure measures, and their association with wheezing occurrence in infancy.

2. Methods

2.1. Study population

The study population comes from the Italian NINFEA (Nascita e Infanzia: gli Effetti dell'Ambiente– Birth and Childhood: effects of the environment) birth cohort. The recruitment was conducted between 2005 and 2016 among pregnant women with sufficient knowledge of the Italian language and the Internet access, who could register to the NINFEA website and complete the baseline questionnaire. After the project pilot phase (2005–2007), carried out in the city of Turin, participation has been extended to the whole country. The study was advertised both passively, through the website and social media, and actively, through several obstetric clinics from Piedmont and Tuscany, where most of the participant come from. Approximately 7500 pregnant women were recruited and completed the baseline questionnaire (Q1) at any time during pregnancy. Children are followed-up with seven online questionnaires completed by mothers at 6 (Q2) and 18 (Q3) months after delivery and when children turn 4 (Q4), 7 (Q7), 10 (Q10) 13 (Q13) and 16 (Q16) years of age. Information on the follow-up response proportion at each questionnaire is available as a technical report on the project website (Progetto NINFEA, xxxx). Further information on the study design has been published previously (Richiardi et al., 2007; Blumenberg et al., 2018).

We used information from Q1, Q2, Q3 and Q7 questionnaires of the NINFEA database (version 2021.06). All children for whom information on wheezing between 6 and 18 months of age was available at Q3 were included in the current study.

The NINFEA birth cohort was approved by the Ethical Committee of the University Hospital Città della Salute e della Scienza di Torino - Hospital Ordine Mauriziano – Health - Authority Unit Città di Torino (approval number: 45 and subsequent amendments).

2.2. Exposure variables

Exposure to pesticides during pregnancy was assessed through three different approaches.

The first approach evaluated maternal direct use of pesticides, whose information was self-reported at the Q1 and Q2 questionnaires. Q1 assessed exposures occurred during the first trimester of pregnancy, while Q2 included a section that retrospectively assessed maternal exposures during the third trimester of pregnancy. Women were asked to report the weekly frequency of use of pesticides, including herbicides and insecticides, with no distinction between indoor and outdoor use. The reported frequency was categorized as never, less than one per week (hereafter referred to as "occasional use") and once per week or more (hereafter referred to as "frequent use"). To examine the pattern of pesticide use over the whole pregnancy, we also created a 3-level variable defined as: i) no pesticide use during the first and third trimester, ii) use of pesticides in the first or in the third trimester, and iii) use of pesticides in both trimesters, regardless of the frequency.

The second approach of exposure assessment considered gardening or agricultural activities. Women were asked to report the frequency of those activities for the first (Q1) and the third (Q2) trimester of pregnancy, which we categorized as never, less than once a week ("occasional") and at least once a week ("frequent"). Similarly to the approach adopted for pesticide use, we created an additional three-level variable to identify women involved in agricultural activities i) in none of the two trimesters, ii) in the first or in the third trimester only or iii) in both trimesters. We also had information on the women's job during pregnancy, coded using the International Standard Classification of Occupations 88 (ISCO88), but very few ($n = 7$, 0.13%) of them were agricultural workers; therefore, this information was not further used in the analysis.

The exact wording of the questions used in the questionnaires for exposure assessment of all the above variables is reported in **Supplementary Material, Table S1**.

The third approach indirectly assessed the residential exposure to pesticides used in agriculture, evaluating the specific land use around the geocoded maternal addresses in pregnancy. The addresses of residence of participants have been collected at each questionnaire; to evaluate the exposure at any time during pregnancy we used the information provided at Q1. Land use information was retrieved from the European Corine Land Cover (CLC) (© European Union, Copernicus Land Monitoring Service, 2012) database, which classified land cover in Europe into 44 classes using high-resolution satellite images, automatic systems and national data. The CLC database includes information from 1985 onwards and is updated every 6 years (Gómez-Barroso et al., 2016). We used the 2012 version of the database, which is the closest to the mid-calendar year of the NINFEA cohort recruitment period. We focused on the following specific land uses, as reported by the CLC database, assumed to be potentially associated with higher exposure to pesticides on the basis of previous studies (Gómez-Barroso et al., 2016; CENTOFANTI et al., 2008; Malagoli et al., 2016; Bukalasa et al., 2018) and grouped as follows: arable lands (including irrigated arable land, permanently irrigated land, rice fields), fruit trees (including fruit and berries, vineyards, olive groves) and heterogeneous cultivations (including annual crop associated with permanent crops and complex pattern of cultivations). Consistently with previous studies (Malagoli et al., 2016), we defined a 200 m-radius circular buffer around each maternal address to derive (i) a Global Crop Index (GCI), which corresponds to the proportion of the defined area covered by any of the selected crops, and (ii) specific indices for each of the three cultivation patterns reported above, which correspond to the proportion of the defined area covered by each selected crop. Therefore, those indices could be interpreted as the extent of agricultural land (i.e. where agricultural pesticide application is more likely) that was surrounding women's home during pregnancy.

Living in proximity of crops inherently implies proximity to green areas, which has been reported to be a risk factor for wheezing, asthma, and allergic rhinitis risk in childhood, probably due to higher pollens concentrations (Parmes et al., 2020). To take this mechanism into account, in a sensitivity analysis we used CLC to create a green area indicator, as a further exposure variable, using the same approach that we used for the GCI, i.e. considering the percentage of the 200 m buffer area around each home address covered by land with potentially relevant presence of plants and pollens, namely pastures, green urban, agro forestry, forests, natural grassland, moors and heathland, sclerophyllous and transitional woodland-shrub.

2.3. Outcome variables

The main outcome of interest was the occurrence of wheezing between 6 and 18 months of age, reported by mothers when the child turned 18 months of age (Q3).

In addition, since in the first years of life wheezing could be the manifestation of different associated disorders (e.g. bronchiolitis and infections, allergy or asthma) (RUSCONI et al., 1999) and could behave differently over time, we studied, as a look-up analysis presented as supplementary material, the association of pesticide exposure in pregnancy with school-age wheezing (child respiratory health was not assessed at Q4, when the child turned 4 years). Specifically, we used information from Q7, collected at 7 years of age, to assess the occurrence of at least one episode of wheezing or whistling in the chest in the past 12 months. We created two outcome variables: wheezing in the 6th year of life (yes vs. no), and ever wheezing either in infancy or in the 6th year of life (ever vs. never).

The exact wording of all the questions used for outcome assessment is reported in **Supplementary Material-Table S1**. All questions on wheezing were based on the standardized questionnaire of the International Study of Asthma and Allergies in Childhood (ISAAC) study (Solé, 1998).

2.4. Confounding factors

The following confounding factors were selected a-priori and assessed from the data collected at Q1 and Q2: maternal smoking in pregnancy; parity (nulliparous, multiparous); maternal age, maternal asthma and maternal atopy (defined as ever-diagnosis of allergic rhinitis and/or atopic dermatitis); maternal educational level (primary school, secondary school and university degree); pet ownership during pregnancy; region of residence (Piedmont region, Tuscany region, other Northern Italian regions, the rest of the country); urbanization degree of the area of residence according to the GHS Settlement Model layers (GHS-SMOD) indicator (Florczyk et al., 2019). All the analyses were additionally adjusted for child sex.

2.5. Statistical methods

We applied a complete case approach for all the analyses. For the main analysis we used logistic regression models to estimate the prevalence odds ratios (POR) and 95% confidence intervals (CIs) of wheezing between 6 and 18 months of age in association with each of the selected exposure variables of interest. For each exposure, we fitted a crude and a model adjusted for the covariates listed in section 2.4.

The crop indices were analysed as continuous variables using restricted cubic splines with three knots (at values 0 0.5 and 0.8 of each index) to allow for non-linear relationships with wheezing (Steenland and Deddens, 2004). Since the degree of urbanization of the living area was highly collinear with crop proximity, and hence with GCI and specific crop indices, we did not include it in the model for residential analyses. Thus, to control for the well-known inverse association between living in a rural area and infant wheezing (Han et al., 2017) (Jie, 2013; Zhu et al., 2015; Lawson et al., 2017), we performed the analyses for global and specific crop index first on the whole population, and then restricting to women living in rural areas (namely who lived in a *peri*-urban, or less urbanized grid category, according to the GHS-SMOD index).

As sensitivity analysis, we also estimated the crude and adjusted POR of wheezing in association with urban vs. rural maternal residence in pregnancy. Additional sensitivity analyses were performed to avoid possible misclassification in the residential crop proximity assessment due to the change of address during pregnancy. In the sensitivity analysis we included only children whose mothers did not change their residence address between enrolment, collected at Q1, and 6 months after delivery, collected at Q2.

In the look-up analysis on wheezing in the 6th year of life, we used the same methods and confounding factors applied in the main analysis on wheezing between 6 and 18 months of age. This analysis, however, was limited to self-reported exposure to pesticides during pregnancy as the variables based on the residential proximity to crops could not distinguish between prenatal and postnatal exposure. Results of the look-up analyses are reported as supplementary material for the sake of completeness and to allow the comparison of future studies on school-age asthma with our results.

All the analyses were conducted using Stata 16 (Stata Corporation, College Station, TX, USA).

3. Results

3.1. Study population

The study population included 5997 children for whom we had information on wheezing between 6 and 18 months. Table 1 summarizes the main characteristics of the population and all variables included in the main analysis, except for the indices used to evaluate residential proximity to crops and green areas. These are shown in Table 2 where we reported global and specific crop index values for the entire and the rural population (1674 subjects).

The complete case analysis approach led to the exclusion of 11% of the subjects due to missing data in at least one of the variables used in the study (exposures and/or confounding factors), leaving 5346 children for the main analyses (1652 for the rural population).

Use of pesticides in the first trimester was reported by 9.9 % of the women, while 4.7% reported use in the third trimester; 2% of the women used pesticides in both trimesters, regardless of the frequency. Involvement in agricultural activities was reported by 21.3% in the first trimester and 13.7% in the third trimester; 9.5% of the women did agricultural activities in both trimesters, regardless of the frequency. Wheezing prevalence between 6 and 18 months was 17.1%.

Fig. 1 reports the distribution of the GCI for the whole population and for women living in rural areas. While 9.9% of the whole population had a GCI higher than 0.50, this proportion raised to 30.8% when considering only rural areas.

Arable land was the most frequent agricultural land use type, followed by heterogeneous cultivation pattern and fruit trees (Table 2).

3.2. Pesticide use and agricultural activities

The results of the analysis on the association between self-reported pesticide use and involvement in agricultural activities in pregnancy and the risk of wheezing between 6 and 18 months of age are shown in Table 3.

In the first trimester there was no evidence of association for any of

Table 1
Cohort main characteristics.

	n°	Mean (SD) or %		n°	Mean (SD) or %
Child sex			**Pesticide use 1st trimester**		
Male	3043	50.78%	No	5040	90.05%
Female	2949	49.22%	Occasional	513	8.55%
Missing values	5	—	Frequent	84	1.40%
Smoke in pregnancy			Missing values	0	
Yes	447	7.53%	**Pesticide use 3rd trimester**		
No	5486	92.47%	No	5714	95.28%
Missing values	64	—	Occasional	244	4.07%
Maternal age	5997	33.75 (4.24)	Frequent	39	0.65%
Missing values	0	—	Missing values	0	—
Maternal education			**Pesticide use overall**		
Primary school	253	4.25%	No	5239	87.36%
Secondary school	1914	32.13%	Only one trimester	636	10.61%
University degree	3790	63.62%	Both trimestres	122	2.03%
Missing values	40	——	Missing values	0	—
Parity			**Agricultural activities 1st trimester**		
Nulliparous	4174	70.89%	No	4717	78.66%
Multiparous	1703	29.11%	Rarely	893	14.89%
Missing values	147	—	Frequently	387	6.45%
Maternal asthma			Missing values	0	——
Yes	482	8.25%	**Agricultural activities 3rd trimester**		
No	5361	91.75%	No	5178	86.34%
Missing values	154	—	Rarely	577	9.62%
Maternal atopy			Frequently	242	4.04%
Sì	966	16.54%	Missing values	0	—
No	4847	83.46%	**Agricultural activities overall**		
Missing values	157	—	**No**	4465	74.46%
Pets in pregnancy			Only one trimester	965	16.09%
Yes	2044	34.77%	Both trimestres	567	9.45%
No	3835	65.23%	Missing values	0	—
Missing values	118	—	**Wheezing 6–18 months**		
Area of residence			Yes	1027	17.13%
Rural/Suburban	1674	27.49%	No	4970	82.87%
Urban	4003	70.51%	Missing values	0	—
Missing values	320	—			
Region of residence			**Total**	**5997**	**100.0**
Piedmont	3912	65.23%	**Wheezing 6th year[2]**		
Tuscany	1203	20.06%	Yes	213	5.79%
Northern Italy	508	8.47%	No	3464	94.21%
Other regions	374	6.24%	Missing values	0	—
Missing values	0	**—**	**Ever wheezing[3]**		
Change of residence in pregnancy[1]			Yes	770	20.94%
Yes	835	14.10%	No	2907	79.06%
No	5085	85.90%	Missing values	0	—
Missing values	77	—	**Total**	**3677**	**100.0**

The table shows the absolute (n°) and relative (%) frequencies for categorical variables. The total number of observation (n°) and their mean value (Mean) with Standard Deviation (SD) are shown for continuous variables. The number of missing values is reported for each of the variables but excluded from the proportion (%) count.

1. The variable was not included in the main analysis, but used in the supplementary analysis to avoid residential proximity to crop misclassification.
2. For wheezing reported during the 6th year of life and ever wheezing the total number of subjects is lower because the cohort follow-up is still ongoing.
3. Ever wheezing refers to the occurrence of wheezing either between 6 and 18 months or at 7 years (yes vs no).

the assessed exposures; in the third trimester, the POR of wheezing between 6 and 18 months weakly increased for self-reported pesticide use vs. no use. We found an adjusted POR of 1.27 with a 95% Confidence Interval (CI) of 0.93–1.74 for any pesticide use during the third trimester vs. none, and 1.26 (95 %CI 0.90–1.77) and 1.35 (95 %CI 0.61–2.99) for occasional and frequent use in the third trimester, respectively.

Conversely, for any vs no agricultural activities in the third trimester, we found an adjusted POR of wheezing between 6 and 18 months of 0.83 (95% CI 0.67–1.04), and the PORs for occasional and frequent agricultural activities in the trimester were 0.81 (95 %CI 0.63–1.05) and 0.89 (95 %CI 0.61–1.30), respectively.

Children born from mothers who reported pesticide use in both trimesters had a POR of wheezing between 6 and 18 months of 1.66 (95 % CI 1.08–2.55) compared with prenatally unexposed children. We found no association between agricultural activities in both trimesters and infant wheezing.

3.3. Residential proximity to crops

Results of the regression analyses for the crop index exposures, modelled used restricted cubic spline interpolation, are reported in Fig. 2 and Fig. 3.

The graphs show the Global Crop Index and wheezing at 6–18 months' relationships modelled with restricted cubic splines. Panel A refers to the whole population and Panel B to the rural population. Models are adjusted for the following covariates: sex, smoke in pregnancy; parity; maternal age, asthma and atopy; maternal educational level; place of residency; pet owning during pregnancy.

The association between GCI and infant wheezing assumed a J shape for the whole population. However, the inverse association between GCI and wheezing observed for the middle range values of GCI was considerably reduced after restriction to the rural population, in which we found a slightly elevated risk of wheezing for the highest levels of GCI (Fig. 2). Albeit some differences, the same pattern of association was observed in the analyses of specific crop indices. The highest POR estimates were observed for fruit trees, with ORs above 1.6 for the highest levels of the index compared to the reference value of zero (Fig. 3).

3.4. Sensitivity analyses

We found an adjusted POR of infant wheezing of 1.19 (95 %CI 1.00–1.40) for mother living in an urban vs. rural environment during pregnancy.

The analyses on residential proximity to crops restricted to women who did not change their residence during pregnancy (N = 5085 in entire and N = 1452 women in rural population) revealed little or no change in the magnitude and shape of the associations (results for GCI in rural population are shown in the **Supplementary material-Figure S1**).

Results of the analysis of green area indicator and wheezing occurrence between 6 and 18 months, modelled with restricted cubic spline showed a green area's protective effect on wheezing at 6–18 months both for the whole and for the rural populations; graphs are reported in Fig. 4.

The graphs show the green area indicator and wheezing at 6–18 months' relationships modelled with restricted cubic splines. Panel A refers to the whole population and Panel B to the rural population. Models are adjusted for the following covariates: sex, smoke in pregnancy; parity; maternal age, asthma and atopy; maternal educational level; place of residency; pet owning during pregnancy).

Table 2
Residential proximity to crops and green areas.

	Whole population					Rural population				
	N°	High exposure[1] (%)	Percentiles			N°	High exposure[1] (%)	Percentiles		
			%75	%90	%95			%75	%90	%95
GCI[2]	5994	593 (9.9%)	0.09	0.5	0.92	1650	511 (30.6%)	0.61	1	1
Arable land	5600	212 (3.5%)	0	0.17	0.38	1650	175 (10.5%)	0.15	0.5	0.85
Fruit trees	5600	98 (1.7%)	0	0	0	1650	92 (5.5%)	0	0.21	0.54
Heterogeneous	5600	258 (4.3%)	0	0.15	0.45	1650	227 (13.6%)	0.14	0.67	0.92
Green areas	5600	95 (1.6%)	0	0	0.17	1650	84 (5.0%)	0	0.29	0.5
Missing (%)	394	6.6%				22	1.3%			
Tot.	5994	100.00 %				1674	100.0%			

The table shows the total number of observations (n°), number and percentage of observations with high exposure (High exposure, (%)), and 75th, 90th and 95th percentiles for each residential indicator (i.e. the proportion of a buffer area of 200 m around the home address covered by the crop of interest or green areas). Data are shown for both the whole population and only for mothers living in rural areas.

1 High exposure is defined as Crop Index value >= 0.50.

2 Global Crop Index: namely the proportion of the 200 m around the home address covered by any crop type.

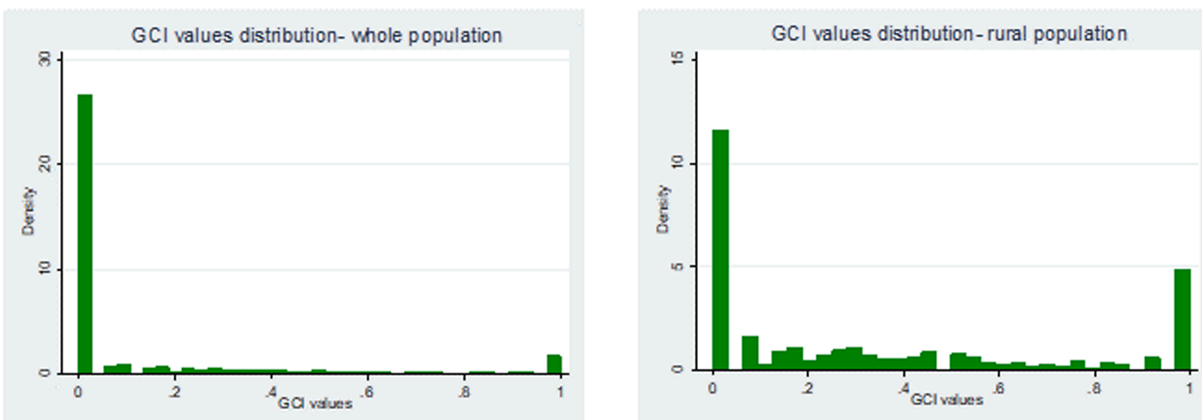

Fig. 1. Density of frequency of GCI in the whole and only rural population.

Table 3
Self-reported exposures and wheezing at 6–18 months.

	First trimester			Third trimester				Both trimestres		
	% (cases /exposed)	POR(CI)$_{crude}$	POR(CI)$_{adj}$	% (cases /exposed)	POR(CI)$_{crude}$	POR(CI)$_{adj}$		% (cases /exposed)	POR(CI)$_{crude}$	POR(CI)$_{adj}$
Pesticide use							**Pesticide use**			
None (ref.)	17.1 (818/ 4792)			16.9 (861/ 5087)			None (ref.)	17.8 (793/ 4664)	1.00	1.00
Any	17.7 (98/ 554)	1.04 (0.83–1.32)	1.01 (0.80–1.28)	21.24 (55/ 259)	1.32 (0.97–1.80)	1.30 (0.95–1.78)	One trimester	15.9 (93/ 585)	0.91 (0.73–1.16)	0.88 (0.69–1.11)
Occasional	17.6 (83/ 471)	1.04 (0.81–1.33)	1.01 (0.79–1.31)	21.1 (47/ 223)	1.31 (0.94–1.82)	1.29 (0.92–1.80)	Both trimestres	26.3 (30/ 114)	1.73 (1.14–2.65)	1.72 (1.11–2.65)
Frequent	18.1 (15/ 83)	1.07 (0.61–1.88)	0.96 (0.54–1.71)	22.2 (8/36)	1.40 (0.64–3.09)	1.36 (0.62–3.03)				
Agricultural activities							**Agricultural activities**			
None (ref.)	17.0 (707/ 4164)	1.00	1.00	17.4 (800/ 4592)			None (ref.)	17.3 (710/ 4114)	1.00	1.00
Any	17.7 (209/ 1182)	1.05 (0.88–1.24)	1.04 (0.87–1.24)	15.4 (116/ 754)	0.86 (0.70–1.07)	0.83 (0.67–1.04)	One trimester	16.4 (115/ 700)	0.94 (0.76–1.17)	0.94 (0.76–1.15)
Occasional	18.6 (153/ 824)	1.09 (0.89–1.31)	1.09 (0.84–1.33)	15.0 (80/ 534)	0.84 (0.65–1.07)	0.81 (0.63–1.05)	Both trimestres	17.2 (91/ 529)	1.00 (0.78–1.27)	0.95 (0.74–1.22)
Frequent	15.6 (56/ 358)	0.91 (0.67–1.24)	0.91 (0.66–1.23)	16.4 (36/ 220)	0.93 (0.64–1.34)	0.88 (0.60–1.28)				

The table shows Prevalence Odds Ratios (POR) of wheezing at 6–18 months and their 95% Confidence Interval (CI) for self-reported use of pesticides (Pesticide use) and frequency of gardening/agricultural activities (Agricultural Activities).
% (cases/exposed): wheezing proportion, defined as wheezing cases over total number of exposed, POR(CI)$_{crude}$: raw estimates and POR(CI)$_{adj}$: estimates adjusted for sex, smoke in pregnancy; parity; maternal age, asthma and atopy; maternal educational level; place of residency; urban–rural area of residence; pet owning during pregnancy. The estimates are shown for each exposure group in both trimesters, separately and together.

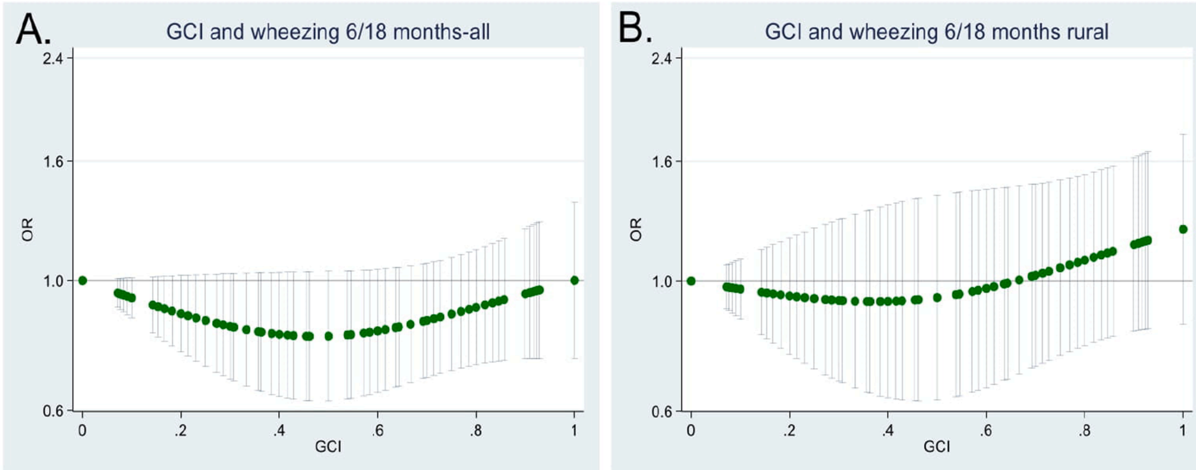

Fig. 2. GCI and wheezing at 6–18 months.

3.5. *Look-up analysis: Wheezing at school-age*

Because of the dynamic nature of the cohort, we had information on wheezing during the 6th year of life for a smaller population of 3677 individuals. The prevalence of the school age wheezing was 5.79%, and the prevalence of ever wheezing was 20.94%.

For pesticide use and wheezing in the 6th year the POR estimates remained in line with the results of the analyses on wheezing in infancy, even though the risk for pesticide use in the first trimester (adjusted POR: 1.33 95 %CI 0.85–2.09) was slightly higher than the risk for any use in the third trimester (adjusted POR: 1.08 95 %CI 0.58–2.01). However, confidence intervals were much wider as a consequence of the smaller sample size, which made these estimates difficult to interpret.

Finally, ever wheezing was found to be associated with pesticide use during the third trimester (adjusted POR for any use 1.48 95 %CI 1.04–2.09) and both trimesters (adjusted POR 1.97 95 %CI 1.19–3.26). All results for school age and ever wheezing analyses are reported in **Supplementary material- Table S2.**

4. Discussion

In a large Italian birth cohort, we found some evidence of association for self-reported pesticide use during pregnancy and infant wheezing in the offspring. We observed no, weak and stronger evidence for pesticide use in the first, third and both trimesters, respectively. We did not find any association between self-reported agricultural activities for occupational or recreational aims during the first or/and third trimester of pregnancy and wheezing in infancy. Residence in rural areas and the proportion of green areas in a 200 m buffer area around the residence where both inversely associated with the risk of infant wheezing. However, a high proportion of land used for fruit trees cultivations in the same 200 m buffer area was associated with an increased risk of infant wheezing, the other crop indices showed a similar shape, with the exceptions of heterogeneous cultivation crops, but the increase found for the highest index values was smaller and of limited relevance..

Few previous studies examined pesticide use in pregnancy, either self- reported or measured in biological samples, and the risk of wheezing in the offspring, and provided conflicting results (Gascon et al., 2012; Gilden et al., 2020) (Mora et al., 2020). Even less is known about pesticide exposure in specific trimesters, being often assessed in an undefined period or summarised as the mean value of several measurements in time (Gascon et al., 2012). To our knowledge, only one study examined the association between specific pesticide metabolites concentration in urine samples in specific different periods during pregnancy and early-life respiratory outcomes (Mora et al., 2020). This study assessed the exposure in two different time periods (≤20 and > 20 weeks of gestation) separately and found a weak positive association between the ETU (Ethylenethiourea) concentration during the first 20 weeks of pregnancy and Lower Tract Respiratory Infection (LRTI) occurrence in the first year of life, and an inverse association for ETU concentration after the 20th week of pregnancy and wheezing in the first year.

Our analyses suggest stronger evidence of association between self-reported pesticide use during the last trimester of pregnancy, which corresponds to the saccular phase of lung development (Schittny, 2017), and infant wheezing. Different exposure pathways, pesticide molecular structure and modes of actions may explain the difference between our findings and those of Mora et al. (Mora et al., 2020), but further studies are needed to identify specific windows of susceptibility during pregnancy. Results of the look up analysis were supporting this hypothesis, showing a higher risk for ever wheezing (i.e. either in infancy or at school age) for pesticide use during the third trimesters and in both trimesters. At 7 years we did not have a large enough sample to obtain clear and interpretable results.

In our cohort, only seven women were agricultural workers, while most of the mothers used pesticides for non-occupational purposes and reported a low frequency of use. Thus, the cohort was probably exposed to a low cumulative dose, which, although it is representative of the actual exposure at the population level, may explain our overall weak estimates of association. However, when we analyzed pesticide use in both trimesters we found a stronger evidence of association. This might be explained by a continuative use of pesticides with higher cumulative doses, that might also affect other phases of lung development (i.e. embryonic, pseudo glandular and canalicular) (Schittny, 2017).

To our knowledge, our study is the first to examine, using a geospatial approach, the relationship between crop indices, calculated during pregnancy, as a proxy for agricultural pesticide exposure, and infant wheezing. Overall, we found an inverse association between living in a rural area and infant wheezing; conversely, residential proximity to fruit trees, was positively associated with infant wheezing. The indices were calculated as the proportion of crops in the 200 m buffer area around the home address to keep a higher specificity of exposure to the pesticides that are used in the crops. In the current study, crop proximity was highly collinear with green areas proximity, which implies a possibly higher pollen concentration that may directly increase wheezing risk in children. A study that involves nine European cohorts (Parmes et al., 2020) indeed, found a positive association when examining green areas within a 500 m buffer from the residence address and wheezing occurrence at 3–14 years. However, this study has some important differences from ours: first, they focused on wider buffer

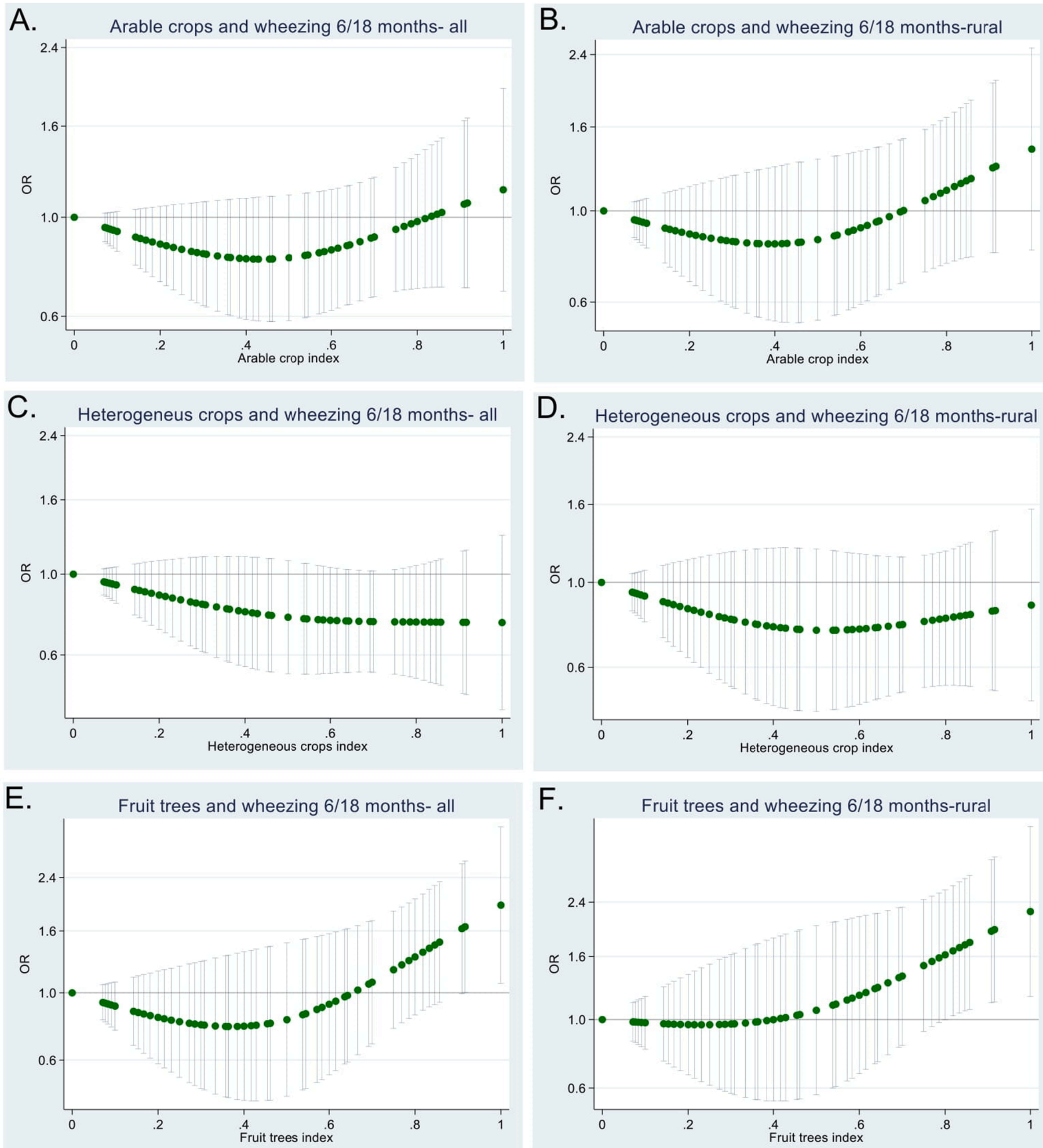

Fig. 3. Crop indices and 6–18 months wheezing.

areas, which means a higher number of exposed children, but to lower concentrations (Costanzini et al., 2018). Second, they did not consider exposure during pregnancy but at a later age (3 to 14 years), when exposures act directly on the child and wheezing is more often a manifestation of an atopic background (Vrbova et al., 2018).

We wanted to assess indirectly if allergies to pollen would explain the relationship we observed between crop indices and wheezing, repeating the analyses using the green area indicator as the exposure. In our cohort, the green area indicator was inversely associated with the risk of wheezing between 6 and 18 months. This suggests that exposure to pollen is an unlikely mechanism underlying the increased risk of wheezing that we found for the crop index.

Our findings varied according to the crop types: the risk of wheezing was highest for fruit trees, while no meaningful association was found for arable lands and heterogeneous cultivations. These results might be consistent with the differential pesticide use in the different crop types. According to the United States Department of Agriculture report (https://www.ers.usda.gov/webdocs/publications/43854/46734_eib124.pdf/// Fernandez-Cornejo, 2014), and the PEST-CHEMGRID database, which includes also European data (Maggi et al., 2019), all the cultivations we included in the fruit trees category, namely orchard, grapes and fruit cultivations, are among the most treated crops with pesticides. The same applies to corn and soybeans which, although not as frequent in Italy as in the US, were included in arable land category. This is further supported by an Eurostat report (Use, 2007) that examined the amount of pesticide application amount per crop type per country: in Italy in 2003 grapes/vines, fruit trees and vegetables were the most treated crops, with 17.5, 12.5 and 7 kg of active substance applied per hectare, respectively, while, for instance, cereals showed levels of 0.2 kg active substance per hectare in the same

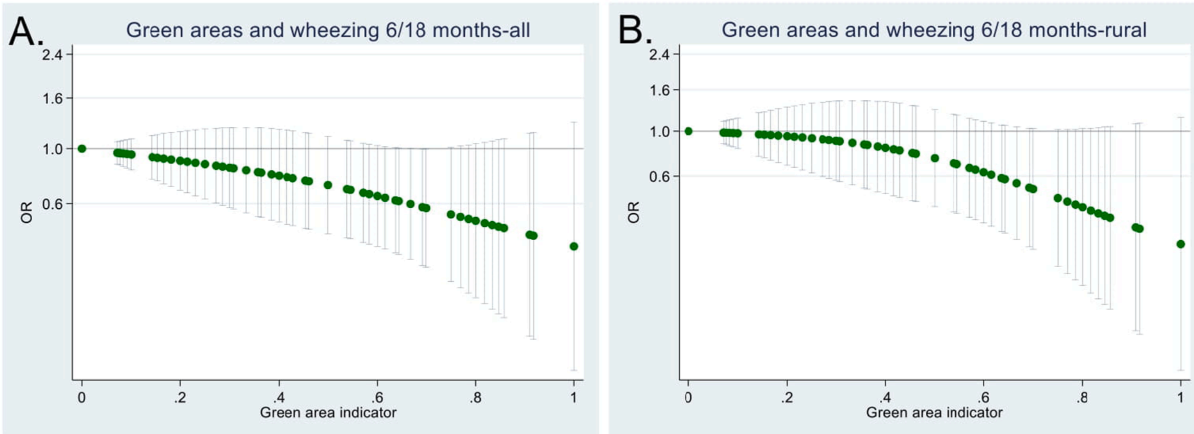

Fig. 4. Green areas and wheezing 6–18 months. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

year. By contrast, the heterogeneous cultivation pattern category, for which we found lower wheezing PORs, included not permanently cultivated land and a consistent number of small-scale private gardens and abandoned fields where a high dose pesticide use is less likely.

Our study has some limitations. First, all exposures variables were at risk of non-differential misclassification since they were only a proxy of exposure to pesticides, some of them being more likely to represent the actual pesticide exposure (e.g. self-reported direct use) than others (e.g. gardening activities frequency, which in particular had a lower, and probably too low, specificity for the exposure of interest).Exposure misclassification could be also related to the timing of exposure assessment, as Q1 assessed exposure in the first trimester of the pregnancy but could have been completed at any time during pregnancy, and Q2, which was completed when the child turned 6 months, assessed retrospectively the exposure in the third trimester of the pregnancy. Although women had to recall the exposure status, thus reducing the accuracy of the assessment, it was prospectively and independently collected from the outcome of interest, which occurred later and was assessed at Q3, when child turned 18 months. Therefore, the risk of recall bias is limited. For what concerns residential exposure assessment, we were able to rule out misclassification due to residence changes by carrying out sensitivity analyses only on women that did not move during pregnancy, which did not change our findings substantially. However, the observed association between residential proximity to crops and infant wheezing could be partly due to post-natal exposures, which was not possible to distinguish from the exposure occurring prenatally.

For the self-reported pesticide use, misclassification was probably due to underreporting, which, as the exposure prevalence was low, is expected to have a low impact of non-differential misclassification (Rothman et al., 2008). Self–reported wheezing instead, although widely accepted in large epidemiological studies, might overestimate the presence of the condition, as parents might label a single episode of noisy breathing as wheezing (Brand et al., 2008).

In our cohort, we did not have the possibility to measure the concentrations of specific pesticides in biological samples to validate the questionnaire information. Nevertheless, since the commonest substances used as insecticides have a short half-life and a short persistence in the body and the environment (Maund, et al., 2011) the use of questionnaires enabled us to determine the exposure during a greater period compared to what would have been possible using biological samples. In addition, the use of self-reported information on pesticide use allowed us to focus on a specific route of exposure, which is probably easier to prevent than, for example, dietary exposure. In addition, our approach provides a comprehensive view on two specific routes of exposure during pregnancy at population level, namely the use of pesticides for non-occupational activities and the exposure due to the residential proximity to crops. To our knowledge, this is the first study that followed this approach.

5. Conclusion and future implications

In conclusion, our findings suggest some evidence of association for self-reported use of pesticides and residential proximity to fruit trees crops. Our results are in line with the current literature and suggest the need of further studies to explore and investigate the topic, both from a compound-specific and a general approach.

There is the emerging need to build a strong body of evidence to support legislative decision-making and make cost-benefit assessments concerning a safe and sustainable use of pesticides in agricultural practices.

CRediT authorship contribution statement

Silvia Maritano: Conceptualization, Methodology, Software, Formal analysis, Investigation, Visualization. **Giovenale Moirano:** Conceptualization, Methodology, Software, Resources. **Maja Popovic:** Conceptualization, Methodology, Resources, Data curation. **Antonio D'Errico:** Methodology, Software. **Franca Rusconi:** Resources, Data curation. **Milena Maule:** Conceptualization, Methodology, Resources, Data curation, Supervision. **Lorenzo Richiardi:** Conceptualization, Methodology, Software, Validation, Resources, Project administration, Funding acquisition, Supervision.

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.

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Ethical issues

The Ethical Committee of the San Giovanni Battista Hospital and CTO/CRF/Maria Adelaide Hospital of Turin approved the NINFEA study (approval No. 45 and following amendments) and the informed consent was obtained from all the participants.

Research data for this article

Due to the sensitive nature of the questions asked in this study, survey respondents were assured raw data would remain confidential and would not be shared. The Corine Land Cover public database was used for the residential exposure assessment and is available at the following link https://land.copernicus.eu/pan-european/corine-land-cover.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107229.

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