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Associations of residential exposure to agricultural pesticides with asthma prevalence in adolescence: The PIAMA birth cohort

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ABSTRACT

Background: It has been suggested that children who are exposed to agricultural pesticides have an increased risk of asthma, but evidence for associations betweeen residential pesticide exposure and childhood asthma is inconsistent.

Objectives: To investigate the associations of residential pesticide exposure with the prevalence of asthma and related symptoms within a Dutch birth cohort study.

Methods: In this cross-sectional analysis, we included participants of the PIAMA birth cohort study with data on residential pesticide exposure and asthma from parent-completed questionnaires at age 14, collected in 2012 (N = 1473). We used spatial data on the presence of individual crops (cereals, open field vegetables, commercial crops, open field floriculture/bulbs, corn and potatoes) and pesticide application on these crops to estimate residential exposure to pesticides with known irritant properties for the respiratory system within distances of 100, 500, and 1000 m of the participants' homes. Logistic regression was used to estimate associations between exposure and outcomes, adjusting for potential confounders.

Results: No associations were found between living within 100, 500 and 1000 m of agricultural fields likely treated with pesticides and symptoms of asthma. For instance, for participants living within 100 m of fields with any crops likely treated with pesticides, the adjusted odds ratios (95% confidence interval) for the prevalence of asthma, shortness of breath and dry night cough at age 14 were 0.31 (0.07, 1.32), 0.61 (0.23, 1.57) and 1.26 (0.56, 2.80), respectively. No associations were found between estimated exposure to pesticides with known irritant properties for the respiratory system and asthma or related symptoms.

Conclusions: There was no association between living near agricultural fields likely treated with pesticides and asthma and related respiratory symptoms, among our study participants.

1. Introduction

Asthma is one of the most common chronic diseases among children (World Health Organization, 2017). Many factors have been associated with an increased risk of asthma including genetic and environmental factors.

Agricultural pesticides are frequently used to fight pests and to improve plant growth and increase agricultural production. When these pesticides are applied to agricultural fields, they can transfer through the air to nearby homes and may be harmful to health (Coronado et al., 2011; Lu et al., 2000; Deziel et al., 2017). Previous studies have suggested that children living close to agricultural treated fields may have an increased risk of asthma possibly due to the transfer of pesticides to their homes (Schwartz et al., 2015; Salameh et al., 2003).

Pesticides with respiratory irritant properties may lead to asthma through interaction with functional irritant receptors in the airways (Hernandez et al., 2011). These processes may promote neurogenic inflammation. In addition, cross talk between airway nerves and inflammatory cells can help to maintain chronic inflammation that eventually damages the bronchial epithelium (Hernandez et al., 2011).

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This has been hypothesized to increase the risk of developing asthma, exacerbate an existing asthmatic condition or trigger asthma attacks by increasing bronchial hyper-responsiveness. In addition, exposure to agricultural pesticides has been linked to increased levels of Th2 cytokines in children (Duramad et al., 2006). Th2 cytokines play an important role in the development of allergic diseases, including asthma and related respiratory symptoms (Holgate, 1999).

At present, epidemiological evidence for associations of residential pesticide exposure with childhood asthma is inconsistent (Gascon et al., 2014a; Gascon et al., 2014b; Karmaus et al., 2003; Karmaus et al., 2001; Liu et al., 2012; Mamane et al., 2015; Merchant et al., 2005; Perla et al., 2015; Reardon et al., 2009; Salam et al., 2004; Salameh et al., 2003; Sunyer et al., 2005; Sunyer et al., 2006; Tagiyeva et al., 2010; Weselak et al., 2007). As these studies were based on different designs, sample sizes, exposure and outcome definitions, it is not possible to conclude, which of these factors contributed most to the heterogeneity of the study findings. For example, in these studies, residential exposure to agricultural pesticides has been assessed in different ways, namely using (self-reported) distances from treated agricultural fields as a proxy (Salameh et al., 2003), biomonitoring (Coronado et al., 2011; Bouvier et al., 2005) as well as measurements of pesticides contaminants in house dust samples (Ward et al., 2006) and indoor air (Garron et al., 2009).

We tested our hypothesis of an association between residential exposure to pesticides and asthma and related respiratory symptoms among adolescents within our Dutch PIAMA birth cohort study. Our study is based on a very well defined cohort, and uses extensively documented methods of exposure (Bukalasa et al., 2017) and outcome (Pinart et al., 2014) assessment, which improves transparency of the findings and comparability with other studies.

2. Methodology

2.1. Study design and population

The PIAMA (Prevention and Incidence of Asthma and Mite Allergy) study is a prospective Dutch birth cohort study. The baseline study population consisted of 3963 participants from the northern, middle and western parts of the Netherlands, who were born in 1996 and 1997 (Wijga et al., 2014). The PIAMA study was designed to examine the influence of lifestyle and environmental factors on the development of asthma and allergies in children. Questionnaires were administered to parents during pregnancy, at the child's ages of 3 months and 1 year, and then annually until the age of 8 years. When the children were 11, 14 and 17 years old, questionnaires were completed by both parents and children.

The present study is a cross sectional analysis within the prospective PIAMA birth cohort study using data collected when the participants were about 14 years old. This study builds on our previous work on the assessment of pesticide exposure using proximity to agricultural fields with crops relevant for pesticide use and surface areas of these crops as a proxies for exposure among PIAMA participants (Bukalasa et al., 2017). We included all participants who were included in the exposure assessment study and who had information on at least one of the outcomes of interest, i.e. asthma and related respiratory symptoms at the age of 14. We restricted the current study population to participants with questionnaires completed in 2012, i.e. the year for which we had data on exposure, to assure that exposure preceded health outcomes (N = 1473, Fig. S1).

2.2. Health outcomes

We used data from standardized asthma outcomes questionnaires that were self-completed by the parents in the Dutch language when the children were 14 years old to define asthma and related symptoms at age 14. Asthma was defined as at least two positive answers to the following three questions: (1) has a doctor ever diagnosed asthma in your child, (2) has your child had wheezing or whistling in the chest in the last 12 months, (3) has your child been prescribed asthma medication during the last 12 months. This definition was developed by a panel of experts within the MeDALL consortium (Pinart et al., 2014). Additional outcomes of interest were shortness of breath during the past 12 months and dry night cough during the past 12 months.

2.3. Agricultural pesticides exposure assessment

The assessment of environmental pesticide exposure within the PIAMA birth cohort study has been described elsewhere (Bukalasa et al., 2017). In brief, we used areas of selected crops extracted from the Basic Registration of Crops (BRP, vector dataset with 1:10,000 underlying resolution) of 2012 (Dutch Ministry of Interior and Kingdom Relations, 2013) within 50, 100, 500 and 1000 m of the participants' home addresses at the time of the 14-year follow-up as proxies for environmental pesticide exposures. We used data for the same year for all participants. Since the 14-year questionnaires were completed by the parents between October 2011 and August 2013 we used data for 2012 (which is well within that period) to assess residential exposure to pesticides. In the present study, our assessment focused on 100, 500 and 1000 m buffers around the participants' homes to investigate exposure at short distances only (100 m buffer) and exposure at shorter and larger distances (500 and 1000 m buffers).

In addition, we assigned amounts of likely used pesticides (in gram of active ingredient per year) in the aforementioned buffers based on a 2012 farmer survey by Statistics Netherlands (CBS) in combination with the acreage of specific crops around the participants' homes as described previously (Bukalasa et al., 2017). We included in the present analysis pesticides with known irritant properties for the respiratory system identified through the pesticides properties database (PPD) and the pesticides manual (University of Hertfordshire, 2016).

For the assessment of associations with the presence of specific crops, we selected cereals, open field vegetables, commercial crops (sugar beet, cichorium, hemp (fiber), winter rapeseed, summer rapeseed, fodder beets (including topinambour), grass seeds (including clover seeds) and flax), open field floriculture/bulbs, corn and potatoes within 500 and 1000 m of the homes. We selected these crops as it is likely that they have been treated with pesticides and because they were present for at least 10% of the study participants in the the 1000 m buffer resulting in sufficient numbers of exposed children (Table 1). None of the crops met the 10% criterion with the 100 m buffer because we had only few participants living within a short distance of agricultural fields. Like for the specific crops, we restricted our analysis of associations with amounts of pesticides used to pesticides that were likely applied around at least 10% of the participants' homes. These included chlormequat, chlorothalonil, diquatdibromide, florasulam, iodosulfuron-methyl-sodium, mancozeb, mecoprop-P, mesosulfuron-

Table 1
Number and percentage of participants with relevant crops cultivated within 100, 500 and 1000 m of their home address at the time of the 14-year follow up (N = 1473).

	Radius of circular buffer		
	100 m	500 m	1000 m
	N (%)	N (%)	N (%)
Any crops	100 (6.8)	588 (39.9)	945 (64.2)
Cereals	29 (2.0)	236 (16.0)	459 (31.2)
Open field vegetables	5 (0.3)	51 (3.5)	145 (9.8)
Commercial crops	13 (0.9)	115 (7.8)	277 (18.8)
Open field floriculture/bulbs	4 (0.3)	81 (5.5)	222 (15.1)
Corn	41 (2.8)	412 (28.0)	790 (53.6)
Potatoes	30 (2.0)	188 (12.8)	336 (22.8)

methyl, metsulfuron-methyl, nicosulfuron, prosulfocarb, terbuthylazine, triadimenol and sulphur (Table S2). We restricted our study to residential exposure and did not include exposure at the school addresses because children spend most of their time at home. Also, the focus of this study was to investigate environmental agricultural pesticide exposure at the residential addresses. Therefore, household pesticides exposure, which was assessed by one single, very broad question, was not taken into account.

2.4. Covariates

Covariates have been identified from previous studies (Liu et al., 2012; Perla et al., 2015; Salameh et al., 2003) as determinants of the outcomes of interest (asthma and related respiratory symptoms). These covariates included sex of the adolescent, smoking in the adolescent's home at the time of the outcome assessment, BMI z-score of the child at the time of outcome assessment, parental education (defined as the maximum of the mother's and the father's educational level and categorized as low (primary school, lower vocational, or lower secondary education), intermediate (intermediate vocational education or intermediate/higher secondary education), and high (higher vocational education and university)), presence of furry pets (cat, dog, and/or rodent) at home at the time of outcome assessment, maternal and paternal allergy (defined as asthma ever, hay fever, and/or allergy to house dust mite and/or pets), child's ethnicity, and estimated traffic-related air pollution. Several metrics of air pollution were available: annual average of nitrogen oxides, particulate matter and 'soot' at the participant's home address at the time of the outcome assessment, estimated by a land-use regression model developed within the European Study of Cohorts for Air Pollution Effects (ESCAPE) (Beelen et al., 2013). As these metrics were highly correlated, we only adjusted for nitrogen dioxide (NO_2) as a marker of traffic-related air pollution, which has been found to be associated with asthma in earlier analyses (Gehring et al., 2015). We did not take into account active smoking of the adolescent participants because the number of participants who reported being active smokers at the time of the 14-year follow up was very small (n = 72).

2.5. Statistical analysis

We performed descriptive statistical analyses of the demographic variables at age 14 years. We used logistic regression to assess associations of the outcomes of interest with environmental pesticide exposure defined as the area of crops likely treated with pesticides and the estimated amount of agricultural pesticide used around the participant's homes at the time of the 14 years follow-up.

Our exposure variables were used as categorical variables. As few participants lived within 100 m of fields with relevant crops, the areas of crops and estimated amounts of pesticides used within the 100 m buffer were dichotomized (zero vs non-zero) and included as binary variables.

For the selected individual crops and the selected pesticides with known irritant properties for the respiratory system applied within 500 and 1000 m, we defined zero as the reference category and divided non-zero values into three categories using tertiles of non-zero values as cut-offs.

Analyses were performed with and without adjustment for the potential confounding factors described above and the impact of the potential confounders on our association estimates was assessed by comparing adjusted and unadjusted estimates. Crude association estimates were calculated for the full population and the sub-population with complete confounder data to assess whether differences between crude and adjusted estimates are due to confounding or due to selection. We first adjusted for all potential confounding factors except BMI, which has a larger number of missing values than the other confounders (13%) and then assessed potential confounding by BMI separately by adding it as another covariate to the model. Since association estimates with and without adjustment for BMI were basically the same (data not shown), the final adjusted model does not include BMI.

Associations are presented as odds ratios (ORs) with 95% confidence intervals (CIs); Wald tests were used to determine the statistical significance of the relationships with the categorical exposure variables. We tested for a linear trend across categories using Wald-Chi-squared tests in standard logistic regression by assigning numeric values (0,1,2,3) to the categories and using this numeric variable as a continuous exposure variable. Statistical analyses were conducted using SAS version 9.4.

Table 2
Characteristics of the study population (N = 1473).

Characteristic	n/N	%
Male sex	742/1473	50
Smoking in the child's home	173/1473	12
Furry pets at home (cat, dog and/or rodent)	884/1469	59
Parental education		
Low	146/1471	10
Intermediate	507/1471	34
High	818/1471	56
Maternal and paternal allergy		
Allergy father	445/1473	30
Allergy mother	397/1473	27
Both parents Dutch nationality	1315/1443	91
Asthma	97/1470	7
Shortness of breath	132/1471	9
Dry night cough	100/1467	7
	N	Mean (SD)
Age at questionnaire completion [years]	1473	14.80 (0.36)
Body mass index z-score	1278	−0.01 (1.10)
Traffic-related air pollution (NO_2) [μg/m^3]	1473	22.71 (6.62)

3. Results

Table 1 shows the prevalence of (specific groups of) crops within 100, 500, and 1000 m of the participant' homes. Distributions of the amount of individual pesticides with known irritant properties for the respiratory tract applied within 100, 500 and 1000 m are presented in Table S1.

Distributions of demographic characteristics of the study population (n = 1473) and respiratory symptoms at age 14 are given in Table 2. Approximately half of the adolescents were male, the mean age for the study participants at the time of questionnaire completion was 14.8 years, 12% of the parents reported smoking in the child's home, approximately 60% of the parents were highly educated, and about 30% of the mothers and fathers were allergic. The majority of the participants' parents were both born in the Netherlands (Table 2). The prevalence of asthma was 7%; 9% and 7% of the adolescents had shortness of breath and dry night cough, respectively (Table 2). The annual average NO_2 levels at the participants' home addresses were generally below the WHO Air Quality Guideline of 40 μ/m^3, which is identical to the European Air Quality Limit Value for this substance (European Commission, 2013).

The distributions of the prevalence of asthma, shortness of breath and dry night cough in relation to the area of crops and estimated amounts of individual pesticides are shown in Tables S2 and S3.

Crude (full population and participants with complete confounder data) and adjusted associations of respiratory symptoms with the presence of any crops, as well as the estimated amount of any pesticides applied within 100 m indicated no increased risk of asthma or related symptoms in relation to pesticide exposure (Table 3). Similarly, no associations were found between prevalence of asthma, shortness of breath and dry night cough on the one hand and the presence of any crops within 500 and 1000 m of the participants' homes on the other hand (Table 4, Table S4).

Table 3
Associations of the presence of any selected crop and the estimated amounts of pesticides applied within 100 m of the participants' homes with prevalence of asthma and related symptoms at age 14.

	Asthma			Shortness of breath			Dry night cough		
	Crude OR (95% CI)[a]	Crude OR (95% CI)[b]	Adjusted OR (95% CI)[c]	Crude OR (95% CI)[a]	Crude OR (95% CI)[b]	Adjusted OR (95% CI)[c]	Crude OR (95% CI)[a]	Crude OR (95% CI)[b]	Adjusted OR (95% CI)[c]
Exposure variable	*N* = 1, 470	*N* = 1, 434	*N* = 1, 434	*N* = 1471	*N* = 1, 435	N = 1, 435	*N* = 1467	N = 1, 431	N = 1, 431
Area of crops (m^2): > 0 vs 0	0.27 (0.07, 1.13)	0.28 (0.07, 1.15)	0.31 (0.07, 1.32)	0.52 (0.21, 1.29)	0.52 (0.21, 1.29)	0.61 (0.23, 1.57)	1.21 (0.57, 2.56)	1.23 (0.58, 2.61)	1.26 (0.56, 2.80)
Amount of pesticides (g of active ingredient/ year): > 0 vs 0	0.31 (0.08, 1.27)	0.31 (0.08, 1.29)	0.36 (0.09, 1.55)	0.58 (0.23, 1.46)	0.58 (0.23, 1.46)	0.71 (0.27, 1.85)	1.36 (0.64, 2.90)	1.39 (0.65, 2.97)	1.45 (0.65, 3.22)

[a] Crude estimates for full population.
[b] Crude estimates for the population with complete confounder data.
[c] Adjusted for sex of the child, smoking in the child's home at age 14, parental education, furry pets at home at age 14 year follow-up, maternal and paternal allergy (which includes asthma, hay fever and allergy), ethnicity of mother and father, and traffic-related air pollution (NO_2) at age 14 year follow-up.

For estimated amounts of individual pesticides applied within 500 and 1000 m buffers, no associations were observed with prevalence of asthma, shortness of breath and dry night cough among our study participants (Table 5, Table S5). The Odds ratios for tertiles of chlorothalonil and sulphur exposure are identical as these two agricultural pesticides were used on exactly the same crops, namely open field floriculture/bulbs, which means that their associations with respiratory health cannot be disentangled (Table 5).

4. Discussion

This study did not find associations between living close to agricultural fields with likely pesticide use and the prevalence of asthma, shortness of breath and dry night cough at age 14.

4.1. Residential exposure to agricultural pesticides and asthma

The association of environmental exposure to pesticides with asthma and related symptoms in children has been assessed in several cross-sectional and longitudinal studies and findings of the epidemiological studies that have been performed so far in children are mixed (see Table S6). Some studies reported significant associations of exposure to pesticides with childhood asthma (Karmaus et al., 2001; Salam et al., 2004; Salameh et al., 2003; Sunyer et al., 2006; Tagiyeva et al., 2010) or wheezing (Gascon et al., 2014b; Salameh et al., 2003; Sunyer et al., 2005; Sunyer et al., 2006; Tagiyeva et al., 2010; Gascon et al., 2014a). However, others did not find associations of exposure to pesticides with asthma (Weselak et al., 2007; Perla et al., 2015; Merchant et al., 2005; Karmaus et al., 2003) and wheeze (Perla et al., 2015; Merchant et al., 2005; Gascon et al., 2014b; Gascon et al., 2014a) in children. The inconsistency in published epidemiological findings could at least partially be due to differences in the pesticide exposure assessment (although self-reported exposures and biomonitoring were used in both, studies showing and not showing an association with asthma) as well as the age of the study participants, the exposure period studied and the study design used.

We acknowledge that comparability of our findings with the findings of the published epidemiological studies of the association between residential pesticide exposure is limited for similar reasons. Only one other study assessed associations of asthma with postnatal exposure to pesticides similar to those assessed in our study. The findings of that study were in line with our findings, i.e. no associations were found between exposure to dialkylphosphate (DAP) metabolites of organophosphate and risk of asthma ever, current asthma and current wheeze in children aged 6–15 years (Perla et al., 2015). Also, our findings are consistent with those of other studies showing no association between prenatal exposure to recently used agricultural pesticides (piperonyl butoxide, pyrethroids, chlorpyrifos and other organophosphate pesticides) and the risks of asthma (Liu et al., 2012), any respiratory symptoms (Raanan et al., 2015) and cough without a cold (Reardon et al., 2009) in children. However, as acknowledged previously, findings of studies using biomarkers of exposure (Gascon et al., 2014a; Gascon et al., 2014b; Karmaus et al., 2003; Karmaus et al., 2001; Sunyer et al., 2006; Sunyer et al., 2005) and studies assessing the relevance of prenatal exposure (Liu et al., 2012; Raanan et al., 2015; Reardon et al., 2009) rather than postnatal exposure, are not directly comparable with ours relying on postnatal exposure estimated using proximity to fields.

4.2. Residential exposure to agricultural pesticides

Since exposure assessment by biomonitoring or environmental monitoring is often not feasible in large population studies, we relied on indirect methods like some of the previous studies. However, we did not rely on distance only, but we used areas of (specific) crops extracted from a basic registration of crops and amounts of pesticides used within selected distances from participants' home at age 14-year as proxies for residential pesticide exposures as previously described (Bukalasa et al., 2017).

We observed that only a small proportion of our study participants lived within short distances (< 100 m) of agricultural fields. Larger percentages of study homes, however, were within 500 and 1000 m of agricultural fields (Bukalasa et al., 2017). Area of (treated) crops and estimated amounts of pesticides used in vicinity of the residence, have been used to estimate environmental/ambient exposure to pesticides in other studies (Brouwer et al., 2018; Nuckols et al., 2007; Rull et al., 2009), none of them assessing associations with childhood asthma. While we do not have direct information on the validity of our exposure estimates in terms of measured internal or external dose, one previous study conducted in the Netherlands found a moderate to high correlation between pesticide measurements in air and precipitation at (fixed) monitoring stations and pesticide concentration estimates based on crop cultivation within 500 and 1000 m buffer around these stations (Brouwer et al., 2018). In addition, a recent meta-analysis of published data from the United States showed that pesticides were detected in house dust samples at a distance of 1000 m from treated agricultural fields. However, the concentrations of pesticides in house dust samples decreased sharply with increasing distance from the fields and the magnitude of the decrease varied by pesticide type (Deziel et al., 2017). Moreover, the findings from the United States, where aerial spraying is common, may not be directly transferable to the Dutch situation, where no aerial spraying is used. However, to the best of our knowledge, no study like this has been conducted in the Netherlands or elsewhere in Europe.

Table 4
Associations of the presence of the selected crops within 1000 m of the participants' homes with prevalence of asthma and related symptoms at age 14.

	Asthma			Shortness of breath			Dry night cough		
	Crude OR (95% CI)[a]	Crude OR (95% CI)[b]	Adjusted OR (95% CI)[c]	Crude OR (95% CI)[a]	Crude OR (95% CI)[b]	Adjusted OR (95% CI)[c]	Crude OR (95% CI)[a]	Crude OR (95% CI)[b]	Adjusted OR (95% CI)[c]
Area of crops (m^2)	N = 1, 470	*N* = 1, 434	N = 1, 434	*N* = 1471	*N* = 1435	N = 1435	N = 1467	*N* = 1431	N = 1431
Any crop	0.78	0.77	0.88	0.94	0.94	1.13	1.00	0.99	1.08
> 0 vs 0	(0.51, 1.19)	(0.50, 1.17)	(0.54, 1.44)	(0.65, 1.36)	(0.65, 1.37)	(0.73, 1.74)	(0.65, 1.52)	(0.64, 1.51)	(0.66, 1.76)
Cereals	*p* = 0.912[d]	*p* = 0.872[d]	*p* = 0.760[d]	*p* = 0.606[d]	*p* = 0.683[d]	*p* = 0.341[d]	*p* = 0.465[d]	*p* = 0.429[d]	*p* = 0.418[d]
> 0–37,040 vs 0	0.45	0.47	0.52	0.47	0.48	0.54	1.64	1.56	1.63
	(0.18, 1.14)	(0.18, 1.17)	(0.20, 1.33)	(0.22, 1.04)	(0.22, 1.05)	(0.24, 1.21)	(0.91, 2.95)	(0.85, 2.86)	(0.87, 3.06)
> 37,040–173,093 vs 0	1.10	1.03	1.10	1.06	0.99	1.08	1.25	1.30	1.36
	(0.57, 2.14)	(0.52, 2.05)	(0.53, 2.30)	(0.59, 1.91)	(0.54, 1.81)	(0.57, 2.05)	(0.64, 2.44)	(0.67, 2.54)	(0.68, 2.73)
> 73,093 vs 0	0.99	1.00	1.16	1.24	1.24	1.44	1.11	1.13	1.16
	(0.51, 1.91)	(0.52, 1.94)	(0.57, 2.38)	(0.73, 2.12)	(0.73, 2.12)	(0.80, 2.59)	(0.57, 2.16)	(0.58, 2.20)	(0.57, 2.37)
Open field vegetables	*p* = 0.730[d]	*p* = 0.790[d]	*p* = 0.885[d]	*p* = 0.781[d]	*p* = 0.747[d]	*p* = 0.692[d]	*p* = 0.591[d]	*p* = 0.528[d]	*p* = 0.588[d]
> 0–14,798 vs 0	0.29	0.29	0.31	0.44	0.43	0.43	1.63	1.65	1.74
	(0.04, 2.14)	(0.04, 2.16)	(0.04, 2.32)	(0.11, 1.82)	(0.10, 1.81)	(0.10, 1.87)	(0.63, 4.22)	(0.64, 4.27)	(0.67, 4.56)
> 14,798–80,865 vs 0	0.58	0.59	0.60	0.89	0.88	0.88	0.94	0.94	0.93
	(0.14, 2.44)	(0.14, 2.47)	(0.14, 2.60)	(0.32, 2.53)	(0.31, 2.50)	(0.30, 2.58)	(0.29, 3.07)	(0.29, 3.10)	(0.28, 3.09)
> 80,865 vs 0	1.25	1.32	1.38	1.44	1.49	1.54	1.28	1.35	1.27
	(0.44, 3.55)	(0.46, 3.76)	(0.47, 4.05)	(0.60, 3.45)	(0.62, 3.59)	(0.63, 3.80)	(0.45, 3.63)	(0.47, 3.85)	(0.44, 3.67)
Commercial crops	*p* = 0.762[d]	*p* = 0.706[d]	*p* = 0.543[d]	*p* = 0.549[d]	*p* = 0.548[d]	*p* = 0.407[d]	*p* = 0.646[d]	p = 0.692[d]	*p* = 0.545[d]
> 0–37,762 vs 0	1.64	1.66	2.14	1.72	1.71	2.00	0.84	0.85	0.90
	(0.82, 3.28)	(0.83, 3.33)	(1.03, 4.44)	(0.95, 3.14)	(0.94, 3.11)	(1.07, 3.74)	(0.36, 1.98)	(0.36, 2.00)	(0.38, 2.13)
> 37,762–115,504 vs 0	1.51	1.55	1.46	1.57	1.57	1.53	0.99	1.01	0.90
	(0.70, 3.24)	(0.72, 3.33)	(0.64, 3.31)	(0.81, 3.04)	(0.81, 3.06)	(0.75, 3.10)	(0.42, 2.33)	(0.43, 2.39)	(0.37, 2.20)
> 115,504 vs 0	0.71	0.73	0.85	0.79	0.79	0.90	0.80	0.82	0.75
	(0.25, 1.99)	(0.26, 2.04)	(0.29, 2.52)	(0.34, 1.86)	(0.34, 1.87)	(0.37, 2.23)	(0.32, 2.04)	(0.32, 2.08)	(0.28, 1.99)
Open field floriculture	*p* = 0.336[d]	*p* = 0.290[d]	*p* = 0.252[d]	*p* = 0.612[d]	*p* = 0.633[d]	*p* = 0.682[d]	*p* = 0.167[d]	*p* = 0.139[d]	*p* = 0.092[d]
> 0–5088 vs 0	1.03	1.07	1.02	1.34	1.37	1.35	1.23	1.28	1.39
	(0.40, 2.62)	(0.42, 2.73)	(0.39, 2.68)	(0.65, 2.77)	(0.67, 2.83)	(0.64, 2.85)	(0.52, 2.92)	(0.54, 3.05)	(0.58, 3.33)
> 5088–14,330 vs 0	1.79	1.85	1.83	1.06	1.07	1.06	1.77	1.82	1.96
	(0.83, 3.87)	(0.86, 3.99)	(0.82, 4.12)	(0.48, 2.37)	(0.48, 2.38)	(0.46, 2.41)	(0.82, 3.81)	(0.84, 3.92)	(0.89, 4.30)
> 14,330 vs 0	1.12	1.15	1.28	0.61	0.610 (0.22, 1.71)	0.64	1.37	1.41	1.51
	(0.44, 2.86)	(0.45, 2.95)	(0.48, 3.38)	(0.22, 1.69)		(0.22, 1.83)	(0.57, 3.25)	(0.59, 3.35)	(0.62, 3.68)
Corn	*p* = 0.619[d]	*p* = 0.609[d]	*p* = 0.788[d]	*p* = 0.116[d]	*p* = 0.148[d]	*p* = 0.489[d]	*p* = 0.556[d]	*p* = 0.433[d]	*p* = 0.590[d]
> 0–53,686 vs 0	0.96	1.00	1.14	1.15	1.19	1.33	1.24	1.27	1.38
	(0.55, 1.69)	(0.57, 1.77)	(0.62, 2.08)	(0.73, 1.83)	(0.75, 1.89)	(0.81, 2.18)	(0.73, 2.11)	(0.75, 2.15)	(0.80, 2.41)
> 53,686–164,363 vs 0	0.64	0.68	0.81	0.70	0.73	0.82	0.78	0.74	0.76
	(0.34, 1.23)	(0.35, 1.30)	(0.40, 1.63)	(0.41, 1.20)	(0.42, 1.25)	(0.46, 1.47)	(0.42, 1.44)	(0.39, 1.39)	(0.39, 1.49)
> 164,363 vs 0	1.01	0.98	1.22	0.71	0.73	0.87	0.91	0.87	0.93
	(0.58, 1.74)	(0.56, 1.72)	(0.64, 2.32)	(0.42, 1.21)	(0.43, 1.24)	(0.48, 1.57)	(0.52, 1.62)	(0.48, 1.56)	(0.48, 1.78)
Potatoes	*p* = 0.840[d]	*p* = 0.773[d]	*p* = 0.288[d]	*p* = 0.881[d]	*p* = 0.877[d]	*p* = 0.382[d]	*p* = 0.408[d]	*p* = 0.359[d]	p = 0.372[d]
> 0–56,848 vs 0	0.57	0.59	0.73	0.63	0.63	0.75	0.58	0.60	0.62
	(0.20, 1.59)	(0.21, 1.65)	(0.26, 2.10)	(0.27, 1.47)	(0.27, 1.48)	(0.31, 1.79)	(0.21, 1.63)	(0.22, 1.69)	(0.22, 1.77)
> 56,848–227,078 vs 0	1.47	1.50	1.94	1.49	1.49	1.81	2.29	2.35	2.39
	(0.76, 2.85)	(0.77, 2.92)	(0.95, 3.98)	(0.84, 2.66)	(0.83, 2.66)	(0.97, 3.37)	(1.29, 4.08)	(1.31, 4.19)	(1.29, 4.43)
> 227,078 vs 0	0.91	0.93	1.17	0.85	0.85	1.03	0.78	0.80	0.80
	(0.41, 2.02)	(0.42, 2.07)	(0.49, 2.79)	(0.42, 1.73)	(0.42, 1.73)	(0.48, 2.21)	(0.33, 1.84)	(0.34, 1.88)	(0.32, 1.99)

[a] Crude estimates for full population.
[b] Crude estimates for the population with complete confounder data.
[c] Adjusted for sex of the child, smoking in the child's home at age 14, parental education, furry pets at home at age 14 year follow up, maternal and paternal allergy (which includes asthma, hay fever and allergy), ethnic group of mother and father, and traffic-related air pollution (NO_2) at age 14 year follow up.
[d] *p*-Value trend test.

4.3. Generalizability of study findings

The present study was conducted in the Netherlands within the Dutch PIAMA birth cohort study. For the PIAMA study, participants were recruited from the general population as described previously (Wijga et al., 2014), to represent the general Dutch population of all children living in the Netherlands. However, children of highly educated parents were over-represented and children of parents from non-western countries were underrepresented. Since there is currently no evidence for an increased or decreased susceptibility of children of highly educated parents or children of parents from non-western countries, this most likely did not affect the generalizability of our findings to the general population of all adolescents living in the Netherlands.

Pesticide application techniques within the European Union are subject to a degree of EU regulation (European Commission, 2017). However, our findings may not be generalizable to all European countries because of differences in allowed pesticides, application techniques and farming-scale. In addition, climate and plant disease pressure can be very different across Europe. Extrapolation of our findings to countries outside the European Union is likely limited, too, given differences in pesticide application techniques. For instance, they would likely not apply in countries such as the United States, Israel and Canada, where aerial spraying of agricultural fields is still permitted (Pearce et al., 2002; Gordon and Richter, 1991; Kahn et al., 1992; Weppner et al., 2006).

Table 5
Associations of the estimated amounts of individual pesticides applied within 1000 m of the participants' homes with prevalence of and asthma and related symptoms at age 14.

	Asthma			Shortness of breath			Dry night cough		
Amount of pesticides (g/year)	Crude OR (95% CI)[a]	Crude OR (95% CI)[b]	Adjusted OR (95% CI)[c]	Crude OR (95% CI)[a]	Crude OR (95% CI)[b]	Adjusted OR (95% CI)[c]	Crude OR (95% CI)[a]	Crude OR (95% CI)[b]	Adjusted OR (95% CI)[c]
	N = 1, 470	*N* = 1, 434	N = 1, 434	N = 1471	N = 1, 435	N = 1435	N = 1467	N = 1, 431	N = 1431
Any pesticides[b]	0.77	0.75	0.86	0.85	0.85	0.99	1.03	1.02	1.12
> 0 vs 0	(0.51, 1.16)	(0.49, 1.15)	(0.52, 1.40)	(0.59, 1.22)	(0.59, 1.23)	(0.65, 1.52)	(0.67, 1.56)	(0.66, 1.56)	(0.69, 1.81)
Chlormequat	$p = 0.459$[d]	$p = 0.535$[d]	$p = 0.665$[d]	$p = 0.710$[d]	$p = 0.651$[d]	$p = 0.538$[d]	$p = 0.740$[d]	$p = 0.737$[d]	$p = 0.798$[d]
> 0–2806 vs 0	1.64	1.69	1.75	1.21	1.22	1.28	1.66	1.45	1.49
	(0.76, 3.53)	(0.78, 3.63)	(0.78, 3.90)	(0.57, 2.58)	(0.57, 2.61)	(0.58, 2.79)	(0.77, 3.57)	(0.65, 3.27)	(0.66, 3.39)
> 2806–11,611	0.19	0.21	0.28	0.76	0.80	1.02	0.84	0.90	0.93
	(0.03, 1.41)	(0.03, 1.52)	(0.04, 2.10)	(0.30, 1.92)	(0.31, 2.03)	(0.39, 2.64)	(0.30, 2.37)	(0.32, 2.52)	(0.33, 2.67)
> 11,611 vs 0	0.92	0.94	0.90	1.29	1.30	1.25	1.13	1.14	1.08
	(0.36, 2.33)	(0.37, 2.39)	(0.34, 2.37)	(0.63, 2.64)	(0.63, 2.66)	(0.59, 2.64)	(0.48, 2.67)	(0.48, 2.71)	(0.45, 2.58)
Chlorothalonil	$p = 0.671$[d]	$p = 0.720$[d]	$p = 0.655$[d]	$p = 0.360$[d]	$p = 0.368$[d]	$p = 0.340$[d]	$p = 0.951$[d]	$p = 0.894$[d]	$p = 0.804$[d]
> 0–30 vs 0	1.52	1.54	1.33	1.07	1.06	0.95	1.20	1.21	1.26
	(0.64, 3.64)	(0.64, 3.68)	(0.53, 3.31)	(0.45, 2.53)	(0.45, 2.51)	(0.39, 2.30)	(0.47, 3.07)	(0.47, 3.10)	(0.49, 3.26)
> 30–80 vs 0	1.05	1.08	0.97	1.15	1.16	1.10	0.49	0.50	0.51
	(0.37, 2.98)	(0.38, 3.07)	(0.33, 2.84)	(0.48, 2.74)	(0.49, 2.76)	(0.45, 2.68)	(0.12, 2.03)	(0.12, 2.09)	(0.12, 2.13)
> 80 vs 0	0.53	0.54	0.57	0.37	0.37	0.38	1.34	1.38	1.46
	(0.13, 2.20)	(0.13, 2.26)	(0.13, 2.46)	(0.09, 1.54)	(0.09, 1.55)	(0.09, 1.62)	(0.52, 3.44)	(0.54, 3.55)	(0.56, 3.83)
Diquatdibromide	$p = 0.326$[d]	$p = 0.286$[d]	$p = 0.155$[d]	$p = 0.265$[d]	$p = 0.258$[d]	$p = 0.144$[d]	$p = 0.177$[d]	$p = 0.150$[d]	$p = 0.172$[d]
> 0–1377 vs 0	1.66	1.71	2.03	0.84	0.85	0.97	0.76	0.78	0.77
	(0.77, 3.57)	(0.79, 3.68)	(0.89, 4.61)	(0.36, 1.99)	(0.36, 2.00)	(0.40, 2.35)	(0.27, 2.14)	(0.28, 2.20)	(0.27, 2.20)
> 1377–5192 vs 0	0.18	0.19	0.26	0.40	0.40	0.50	1.59	1.63	1.62
	(0.03, 1.34)	(0.03, 1.38)	(0.04, 1.88)	(0.12, 1.27)	(0.12, 1.28)	(0.15, 1.64)	(0.74, 3.42)	(0.76, 3.51)	(0.73, 3.55)
> 5192 vs 0	2.02	2.07	2.17	2.08	2.09	2.13	1.53	1.57	1.55
	(1.00, 4.06)	(1.03, 4.18)	(1.04, 4.55)	(1.14, 3.82)	(1.14, 3.85)	(1.13, 4.03)	(0.71, 3.28)	(0.73, 3.37)	(0.71, 3.37)
Florasulam	$p = 0.523$[d]	$p = 0.517$[d]	$p = 0.936$[d]	$p = 0.102$[d]	$p = 0.132$[d]	$p = 0.413$[d]	$p = 0.466$[d]	$p = 0.357$[d]	$p = 0.454$[d]
> 0–3 vs 0	0.88	0.92	1.03	1.14	1.17	1.30	1.30	1.32	1.44
	(0.50, 1.56)	(0.52, 1.63)	(0.56, 1.90)	(0.72, 1.81)	(0.73, 1.86)	(0.79, 2.14)	(0.77, 2.19)	(0.78, 2.23)	(0.83, 2.50)
> 3–9 vs 0	0.76	0.80	0.89	0.78	0.82	0.88	0.86	0.83	0.85
	(0.42, 1.38)	(0.44, 1.46)	(0.46, 1.71)	(0.47, 1.31)	(0.49, 1.37)	(0.50, 1.54)	(0.48, 1.54)	(0.45, 1.51)	(0.45, 1.61)
> 9 vs 0	0.90	0.88	1.10	0.65	0.66	0.80	0.83	0.78	0.82
	(0.51, 1.60)	(0.49, 1.58)	(0.56, 2.14)	(0.37, 1.13)	(0.38, 1.16)	(0.43, 1.48)	(0.46, 1.51)	(0.42, 1.45)	(0.41, 1.62)
Iodosulfuron, Methyl, Sodium	$p = 0.459$[d]	$p = 0.535$[d]	$p = 0.665$[d]	$p = 0.710$[d]	$p = 0.651$[d]	$p = 0.538$[d]	$p = 0.740$[d]	$p = 0.737$[d]	$p = 0.798$[d]
> 0–13 vs 0	1.64	1.69	1.75	1.21	1.22	1.28	1.66	1.45	1.49
	(0.76, 3.53)	(0.78, 3.63)	(0.78, 3.90)	(0.57, 2.58)	(0.57, 2.61)	(0.58, 2.79)	(0.77, 3.57)	(0.65, 3.27)	(0.66, 3.39)
> 13–53 vs 0	0.19	0.21	0.28	0.76	0.80	1.02	0.84	0.90	0.93
	(0.03, 1.41)	(0.03, 1.52)	(0.04, 2.10)	(0.30, 1.92)	(0.31, 2.03)	(0.39, 2.64)	(0.30, 2.37)	(0.32, 2.52)	(0.33, 2.67)
> 53 vs 0	0.92	0.94	0.90	1.29	1.30	1.25	1.13	1.14	1.08
	(0.36, 2.33)	(0.37, 2.39)	(0.34, 2.37)	(0.63, 2.64)	(0.63, 2.66)	(0.59, 2.64)	(0.48, 2.67)	(0.48, 2.71)	(0.45, 2.58)
Mancozeb	$p = 0.562$[d]	$p = 0.652$[d]	$p = 0.905$[d]	$p = 0.889$[d]	$p = 0.927$[d]	$p = 0.627$[d]	$p = 0.909$[d]	$p = 0.847$[d]	$p = 0.819$[d]
> 0–2917 vs 0	0.81	0.84	0.76	0.68	0.69	0.66	0.69	0.71	0.73
	(0.38, 1.71)	(0.39, 1.78)	(0.35, 1.66)	(0.33, 1.38)	(0.34, 1.40)	(0.32, 1.36)	(0.31, 1.53)	(0.32, 1.56)	(0.32, 1.63)
> 2917–83,323 vs 0	0.62	0.65	0.76	1.33	1.36	1.55	0.84	0.75	0.74
	(0.26, 1.45)	(0.28, 1.52)	(0.31, 1.86)	(0.76, 2.33)	(0.78, 2.40)	(0.85, 2.83)	(0.39, 1.78)	(0.34, 1.67)	(0.32, 1.69)
> 83,323 vs 0	1.01	1.03	1.28	0.83	0.83	1.01	1.10	1.11	1.09
	(0.51, 2.00)	(0.52, 2.05)	(0.59, 2.78)	(0.43, 1.59)	(0.43, 1.59)	(0.49, 2.07)	(0.57, 2.12)	(0.57, 2.14)	(0.52, 2.28)
Mecoprop,P	$p = 0.621$[d]	$p = 0.546$[d]	$p = 0.771$[d]	$p = 0.798$[d]	$p = 0.833$[d]	$p = 0.622$[d]	$p = 0.716$[d]	$p = 0.639$[d]	$p = 0.641$[d]
> 0–9 vs 0	1.40	1.41	1.23	1.29	1.28	1.17	0.92	0.93	0.98
	(0.62, 3.13)	(0.63, 3.17)	(0.53, 2.86)	(0.63, 2.65)	(0.62, 2.62)	(0.56, 2.46)	(0.36, 2.33)	(0.37, 2.36)	(0.38, 2.52)
> 9–73 vs 0	0.91	0.94	0.85	0.81	0.81	0.76	1.09	1.12	1.12
	(0.32, 2.56)	(0.33, 2.64)	(0.29, 2.48)	(0.32, 2.05)	(0.32, 2.06)	(0.29, 1.96)	(0.43, 2.79)	(0.44, 2.87)	(0.43, 2.89)
> 73 vs 0	1.28	1.34	1.24	0.89	0.92	0.83	1.21	1.27	1.25
	(0.50, 3.27)	(0.52, 3.44)	(0.46, 3.31)	(0.35, 2.27)	(0.36, 2.33)	(0.31, 2.17)	(0.47, 3.10)	(0.49, 3.25)	(0.48, 3.28)
Mesosulfuron-Methyl	$p = 0.459$[d]	$p = 0.535$[d]	$p = 0.665$[d]	$p = 0.710$[d]	$p = 0.651$[d]	$p = 0.538$[d]	$p = 0.740$[d]	$p = 0.737$[d]	$p = 0.798$[d]
> 0–32 vs 0	1.64	1.69	1.75	1.21	1.22	1.28	1.66	1.45	1.49
	(0.76, 3.53)	(0.78, 3.63)	(0.78, 3.90)	(0.57, 2.58)	(0.57, 2.61)	(0.58, 2.79)	(0.77, 3.57)	(0.65, 3.27)	(0.66, 3.39)
> 32–132 vs 0	0.19	0.21	0.28	0.76	0.80	1.02	0.84	0.90	0.93
	(0.03, 1.41)	(0.03, 1.52)	(0.04, 2.10)	(0.30, 1.92)	(0.31, 2.03)	(0.39, 2.64)	(0.30, 2.37)	(0.32, 2.52)	(0.33, 2.67)
> 132 vs 0	0.92	0.94	0.90	1.29	1.30	1.25	1.13	1.14	1.08
	(0.36, 2.33)	(0.37, 2.39)	(0.34, 2.37)	(0.63, 2.64)	(0.63, 2.66)	(0.59, 2.64)	(0.48, 2.67)	(0.48, 2.71)	(0.45, 2.58)
Metsulfuron-Methyl	$p = 0.518$[d]	$p = 0.547$[d]	$p = 0.387$[d]	$p = 0.533$[d]	$p = 0.590$[d]	$p = 0.407$[d]	$p = 0.483$[d]	$p = 0.534$[d]	$p = 0.490$[d]
> 0–9 vs 0	1.62	1.41	1.31	1.14	0.98	0.91	1.74	1.82	1.78
	(0.72, 3.66)	(0.59, 3.37)	(0.53, 3.26)	(0.51, 2.55)	(0.41, 2.31)	(0.37, 2.21)	(0.81, 3.75)	(0.84, 3.93)	(0.81, 3.95)
> 9–23 vs 0	1.54	1.56	1.52	1.49	1.49	1.50	0.92	0.94	0.90
	(0.64, 3.67)	(0.65, 3.74)	(0.61, 3.78)	(0.69, 3.21)	(0.69,3.21)	(0.67, 3.34)	(0.33, 2.58)	(0.33, 2.65)	(0.31, 2.59)

(*continued on next page*)

Table 5 (*continued*)

	Asthma			Shortness of breath			Dry night cough		
Amount of pesticides (g/year)	Crude OR (95% CI)[a]	Crude OR (95% CI)[b]	Adjusted OR (95% CI)[c]	Crude OR (95% CI)[a]	Crude OR (95% CI)[b]	Adjusted OR (95% CI)[c]	Crude OR (95% CI)[a]	Crude OR (95% CI)[b]	Adjusted OR (95% CI)[c]
	N = 1, 470	*N* = 1, 434	N = 1, 434	N = 1471	N = 1, 435	N = 1435	N = 1467	N = 1, 431	N = 1431
> 23 vs 0	0.94 (0.34, 2.66)	0.96 (0.34, 2.70)	1.24 (0.41, 3.75)	1.03 (0.43, 2.43)	1.03 (0.43, 2.43)	1.25 (0.50, 3.14)	0.43 (0.10, 1.78)	0.44 (0.11, 1.83)	0.43 (0.10, 1.86)
Nicosulfuron	$p = 0.619$[d]	$p = 0.609$[d]	$p = 0.788$[d]	$p = 0.116$[d]	$p = 0.148$[d]	$p = 0.489$[d]	$p = 0.556$[d]	$p = 0.433$[d]	$p = 0.590$[d]
> 0–121 vs 0	0.96 (0.55, 1.69)	1.00 (0.57, 1.77)	1.14 (0.62, 2.077)	1.15 (0.73, 1.83)	1.19 (0.75, 1.89)	1.33 (0.81, 2.18)	1.24 (0.73, 2.11)	1.27 (0.75, 2.15)	1.38 (0.80, 2.41)
> 21–371 vs 0	0.64 (0.34, 1.23)	0.68 (0.35, 1.30)	0.81 (0.40, 1.63)	0.70 (0.41, 1.20)	0.73 (0.42, 1.25)	0.82 (0.46, 1.47)	0.78 (0.42, 1.44)	0.77 (0.39, 1.39)	0.76 (0.39, 1.49)
> 371 vs 0	1.01 (0.58, 1.74)	0.98 (0.56, 1.72)	1.22 (0.64, 2.32)	0.71 (0.42, 1.21)	0.73 (0.43, 1.24)	0.87 (0.48, 1.57)	0.91 (0.52, 1.62)	0.87 (0.48, 1.56)	0.93 (0.48, 1.78)
Prosulfocarb	$p = 0.235$[d]	$p = 0.200$[d]	$p = 0.157$[d]	$p = 0.1560$[d]	$p = 0.147$[d]	$p = 0.121$[d]	$p = 0.281$[d]	$p = 0.243$[d]	p = 0.290[d]
> 0–5945 vs 0	1.39 (0.54, 3.56)	1.43 (0.56, 3.68)	1.58 (0.58, 4.27)	0.77 (0.27, 2.16)	0.78 (0.28,2.19)	0.83 (0.29, 2.40)	0.77 (0.24, 2.51)	0.79 (0.24, 2.59)	0.74 (0.22, 2.46)
> 5945–20,630 vs 0	0.49 (0.12, 2.04)	0.50 (0.12, 2.10)	0.63 (0.15, 2.65)	0.72 (0.26, 2.01)	0.723 (0.26, 2.03)	0.87 (0.30, 2.47)	1.54 (0.64, 3.68)	1.58 (0.66, 3.79)	1.56 (0.64, 3.76)
> 20,630 vs 0	2.10 (0.97, 4.55)	2.16 (1.00, 4.70)	2.12 (0.94, 4.75)	2.16 (1.10, 4.25)	2.18 (1.11, 4.30)	2.09 (1.04, 4.23)	1.46 (0.61, 3.48)	1.50 (0.63, 3.58)	1.45 (0.60, 3.50)
Terbuthylazine	$p = 0.619$[d]	$p = 0.609$[d]	$p = 0.788$[d]	$p = 0.116$[d]	$p = 0.148$[d]	$p = 0.489$[d]	$p = 0.556$[d]	$p = 0.433$[d]	$p = 0.590$[d]
> 0–1736 vs 0	0.96 (0.55, 1.69)	1.00 (0.57, 1.77)	1.14 (0.62, 2.08)	1.15 (0.73, 1.83)	1.19 (0.75, 1.89)	1.34 (0.81, 2.18)	1.24 (0.73, 2.11)	1.27 (0.75, 2.15)	1.38 (0.80, 2.41)
> 1736–53,16 vs 0	0.64 (0.34, 1.23)	0.68 (0.35, 1.30)	0.81 (0.40, 1.63)	0.70 (0.41, 1.20)	0.72 (0.42, 1.25)	0.82 (0.46, 1.47)	0.78 (0.42, 1.44)	0.74 (0.39, 1.39)	0.76 (0.39, 1.49)
> 5316 vs 0	1.01 (0.58, 1.74)	0.98 (0.56, 1.72)	1.22 (0.64, 2.32)	0.71 (0.42, 1.21)	0.73 (0.43, 1.24)	0.87 (0.48, 1.57)	0.91 (0.52, 1.62)	0.87 (0.48, 1.56)	0.93 (0.48, 1.78)
Triadimenol	$p = 0.460$[d]	$p = 0.559$[d]	$p = 0.520$[d]	$p = 0.626$[d]	$p = 0.709$[d]	$p = 0.647$[d]	$p = 0.818$[d]	$p = 0.658$[d]	$p = 0.654$[d]
> 0–14 vs 0	1.11 (0.50, 2.48)	1.13 (0.51, 2.52)	0.95 (0.41, 2.21)	1.06 (0.52, 2.17)	1.06 (0.52, 2.16)	0.96 (0.46, 2.01)	0.76 (0.30, 1.91)	0.76 (0.30, 1.91)	0.80 (0.31, 2.04)
> 14–90 vs 0	0.81 (0.32, 2.06)	0.87 (0.34, 2.20)	0.80 (0.31, 2.10)	0.98 (0.46, 2.08)	1.02 (0.48, 2.17)	0.93 (0.43, 2.02)	1.13 (0.51, 2.53)	1.19 (0.53, 2.67)	1.21 (0.53, 2.74)
> 90 vs 0	0.68 (0.24, 1.91)	0.72 (0.26, 2.02)	0.76 (0.26, 2.20)	0.76 (0.33, 1.79)	0.79 (0.34, 1.85)	0.82 (0.34, 1.98)	0.85 (0.34, 2.16)	0.70 (0.25, 1.96)	0.68 (0.24, 1.92)
Sulphur	$p = 0.671$[d]	$p = 0.720$[d]	$p = 0.655$[d]	$p = 0.360$[d]	$p = 0.368$[d]	$p = 0.340$[d]	$p = 0.951$[d]	$p = 0.894$[d]	$p = 0.804$[d]
> 0–777 vs 0	1.52 (0.64, 3.64)	1.54 (0.64, 3.68)	1.33 (0.53, 3.31)	1.07 (0.45, 2.53)	1.06 (0.45, 2.51)	0.95 (0.39, 2.30)	1.20 (0.47, 3.07)	1.21 (0.47, 3.10)	1.26 (0.49, 3.26)
> 777–1977 vs 0	1.05 (0.37, 2.98)	1.08 (0.38, 3.07)	0.97 (0.33, 2.84)	1.15 (0.48, 2.74)	1.16 (0.49, 2.76)	1.10 (0.45, 2.68)	0.49 (0.12, 2.03)	0.50 (0.12, 2.09)	0.51 (0.12, 2.13)
> 1977 vs 0	0.53 (0.13, 2.20)	0.54 (0.13, 2.26)	0.57 (0.13, 0.46)	0.37 (0.09, 1.54)	0.37 (0.09, 1.55)	0.38 (0.09, 1.62)	1.34 (0.52, 3.44)	1.38 (0.54, 3.55)	1.46 (0.56, 3.83)

[a] Crude estimates for full population.
[b] Crude estimates for the population with complete confounder data.
[c] Adjusted for sex of the child, smoking in the child's home at age 14, parental education, furry pets at home at age 14 year follow up, maternal and paternal allergy (which includes asthma, hay fever and allergy), ethnic group of mother and father, and traffic-related air pollution (NO_2) at age 14 year follow up.
[d] *p*-Value trend test.

4.4. Strengths and limitations

We consider the availability of data on the presence of specific crops together with data on the use of pesticide on these crops from a survey among farmers are strengths of the present study.

A limitation of our study is that we had no information regarding exposure to pesticides in the earlier years of life among ou study participants. If this had been available, it would have helped us to understand the role of pesticides exposure over a longer time period. We likewise lacked information on personal pesticides exposure in the homes of our study participants, to assess associations with respiratory outcomes. We did not have to take into account crop rotation as the analysis was restricted to children with health information collected in the year 2012. Statistical power was limited for the smaller buffers (< 100 m), where exposures are expected to be highest. However, analyses with exposures within 100 m buffers generally did not suggest an adverse effect.

In this study, we performed many comparisons tests and we acknowledge this may increase the probability of committing type I error (false positive associations). As no positive associations were observed, no false positive associations were present either.

5. Conclusion

There was no evidence found for an association between living near agricultural fields likely treated with pesticides and the prevalence of asthma and related respiratory symptoms at age 14 among our study participants. Further research is recommended on quantitative exposure assessment methods using measurements of pesticides in environmental and/or biological samples, and on methods to develop exposure models usable in large scale epidemiological studies.

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Conflict of interest statement

Professor Gerard H. Koppelman reports grants from the Lung Foundation Netherlands, TEVA Netherlands, Glaxo Smith Kline, the UBBO EMMIUS Foundation, and the TETRI Foundation outside the submitted work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.09.029.

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