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Association between Residential Proximity to Viticultural Areas and Childhood Acute Leukemia Risk in Mainland France: GEOCAP Case-Control Study, 2006–2013

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Background: Pesticide exposures are suspected of being a risk factor for several childhood cancers, particularly acute leukemia (AL). Most of the evidence is based on self-reported parental domestic use of pesticides, but some studies have also addressed associations with agricultural use of pesticides near the place of residence.

Objectives: The objective of the study was to evaluate the risk of AL in children living close to vines, a crop subject to intensive pesticide use.

Methods: Data were drawn from the national registry-based GEOCAP study. We included all of the AL cases under the age of 15 years diagnosed in 2006–2013 ($n = 3,711$) and 40,196 contemporary controls representative of the childhood population in France. The proximity of the vines (probability of presence within 200, 500, and 1,000 m) and the viticulture density (area devoted to vines within 1,000 m) were evaluated around the geocoded addresses in a geographic information system combining three national land use maps. Logistic regression models were used to estimate odds ratios (ORs) for all AL and for the lymphoblastic (ALL) and myeloid (AML) subtypes. Heterogeneity between regions was studied by stratified analyses. Sensitivity analyses were carried out to take into account, in particular, geocoding uncertainty, density of other crops and potential demographic and environmental confounders.

Results: In all, about 10% of the controls lived within 1 km of vines. While no evidence of association between proximity to vines and AL was found, viticulture density was positively associated with ALL [OR = 1.05 (1.00–1.09) for a 10% increase in density], with a statistically significant heterogeneity across regions. No association with AML was observed. The results remained stable in all the sensitivity analyses.

Conclusion: We evidenced a slight increase in the risk of ALL in children living in areas with high viticulture density. This finding supports the hypothesis that environmental exposure to pesticides may be associated with childhood ALL. https://doi.org/10.1289/EHP12634

Introduction

Occupational exposure to pesticides is strongly suspected of increasing the risk of lymphoid malignancies in adults, although only a few compounds have been classified as certain carcinogens.[1–3] In children, pesticide exposures have long been suspected of being risk factors for various cancers, mainly acute leukemia (AL), with most of the evidence based on reported data on parental residential use[4,5] and maternal occupational exposure during pregnancy.[6] As is the case in all high-income countries, AL is the most common type of childhood cancer in France, with about 500 new cases per year (30% of childhood cancers), 80% of which consist of lymphoblastic leukemia (ALL) and 15% of myeloid leukemia (AML).

Children mainly come into contact with pesticides by ingestion of contaminated products (food, drink, and dust for young children) and by inhalation. Children may also be exposed *in utero* via maternal occupational and domestic exposures. The presence of pesticide particles indoors and outdoors may be the consequence of domestic use, agricultural use in nearby fields (agricultural drift, volatilization, wind erosion), and transport of pesticides into the home by occupationally exposed family members (e.g., on clothes and shoes). Several studies reported higher air and dust pesticide concentrations in households close to treated fields, particularly during and soon after application. The contribution of agricultural uses to pesticides concentrations in homes is, however, difficult to quantify.[7–9]

Assessing residential exposure to agricultural pesticides remains a great challenge. Most of the studies on childhood cancer evaluated croplands in the vicinity of residences using agricultural census and photographic and satellite data.[10–18] A few studies were able to estimate pesticides spread on crops, using the Pesticide Use Reporting (PUR) system in California and using pesticide sales data in Denmark.[19–23] To date, the heterogeneity in published studies regarding agricultural landscapes and practices has precluded drawing conclusions as to the role of crop proximity and agricultural pesticide exposure in childhood AL.

The objective of this study was to evaluate the risk of childhood AL in children living close to viticultural areas. Vines are a perennial crop that undergoes intensive pesticide treatment. Previously, we conducted a nationwide ecological study that showed that AL risk was higher in the municipalities with the greatest viticultural areas.[14] The present case-control study, also nationwide, addressed the issue using precise individual data.

Materials and Methods

Population

GEOCAP is a nationwide case-control study based on a geographic information system (GIS) that has been conducted since 2002 to investigate the role of environmental factors in pediatric cancers.

The cases were all residents of mainland France diagnosed with primary AL between 1 January 2006 and 31 December 2013 and were <15 years of age at the end of the year of diagnosis. They were identified and documented by the French national registry of childhood cancers (RNCE) (https://rnce.inserm.fr), which provides an exhaustive coverage of the French pediatric

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population thanks to the number and quality of its information sources and is regularly certified by the health authorities.[24] A total of 3,711 cases were included, comprising 3,088 cases of ALL, 552 of AML, and 71 of undifferentiated or mixed phenotype leukemia. The RNCE provided diagnoses coded as per the International Classification of Diseases for Oncology (ICD-O-3) based on cytology, cytogenetics, and molecular biology. The ALL cases were further classified in terms of the presence of markers of early initiating genetic event in leukemia cells, i.e., *KMT2A* (MLL) transcript, *ETV6*/*RUNX1* (TEL/AML1) transcript, or hyperdiploidy >50 chromosomes, except for 9% of the cases for whom the information was missing.

The controls were randomly selected annually by the French National Institute for Statistics and Economic Studies (INSEE) from the anonymous income and council tax databases. The control set, of about 5,000 controls per year, was representative of the French population under 15 years (age at the end of the year) in terms of age, household income, and the sociodemographic characteristics of the municipality of residence (municipalities are the smallest administrative units, and France accounts more than 36,000 municipalities). Eight children who had the same age, the same year of inclusion and the same geocode (see below) as a case were excluded to limit the risk of including cases in the control group. A total of 40,196 controls were included in the study for the period of 2006 to 2013.

The study protocol complied with the French regulations relating to databases and ethics (Commission Nationale de l'Informatique et des Libertés receipt 2077682 v0), and the research undertaken with the RNCE data is covered by agreements on the ethical use of data and the protection of personal data, and has been approved by French national authorities.

Geocoding

The addresses of the residences at diagnosis for the cases and at inclusion for the controls were geocoded by an external partner blind to case or control status. Geocodes were obtained with an imprecision estimated to be <100 m for 83% of the addresses, of which *a*) 62% geocoded at the entrance of the residential plot, *b*) 9% by projection toward the road, and *c*) 12% by interpolation between neighboring addresses. The remaining addresses were located *d*) in the middle of the street (5%), *e*) in the middle of an urban residential neighborhood (1%), *f*) in the middle of a rural hamlet (10%), or *g*) in the absence of an address, *h*) at the town hall of the municipality (1%). Category *f* is characteristic of rural areas (Table S1), with imprecision estimated to be of 300 m on average.

Exposure Assessment

Individual proximity to vines was estimated using buffers of radius 200, 500, and 1,000 m centered on the geocoded address. Three sources were combined in a GIS: *a*) the Graphic Parcel Register (RPG) recording the farmers' annual statements for European Common Agricultural Policy subsidies (scale: 1:5,000), available annually since 2007 with information on 28 crop types (wine monocultures cannot receive subsidies and are therefore absent from this source); *b*) Corine Land Cover (CLC), based on visual interpretation of high-resolution satellite imagery (scale: 1:100,000) available for the years 2006 and 2012, with information on perennial crops (including vines), pastures, and arable land; and *c*) the vegetation layer of the BD Topo database (VV), specific to viticulture and arboriculture (scale: 1:5,000), developed by the National Institute of Geographic and Forest Information (IGN), available nationwide for the period of 2012–2015. It is not possible to use the VV source over our entire study period (2006–2013) because vine uprooting campaigns took place between 2000 and 2010.

We created two maps using RPG and CLC sources, the only sources available on the whole period: the "2007 map," which was based on the 2007 RPG and 2006 CLC sources, and the "2012 map," which was based on the 2012 RPG and CLC sources. The 2007 and 2012 maps were used to evaluate residential proximity to crops for cases and controls included during the periods 2006–2009 and 2010–2013, respectively. As viticulture is a perennial crop, we assumed that the viticulture areas remained stable during each of the two periods. For the period 2010–2013, we also created the "2012-VV map" using the VV source in addition to the 2012 RPG and 2012 CLC sources. The maps were developed by Santé publique-France in close cooperation with the Inserm team. The methods have been described elsewhere.[25,26] Briefly, combining the previously cited sources in a GIS taking into account administrative boundaries enabled partition of mainland France into millions of polygons. Allocation of a crop type to the polygons relied on an algorithm selecting the most reliable source and its associated crop. For viticulture in particular, RPG was considered the most reliable source for the 2007 and 2012 maps, and VV for the 2012-VV map.

According to the 2010 national agricultural census, the gold standard on the national scale, 788,633 hectares (ha) were allocated to viticulture in mainland France. The total area was underestimated by 35% when the areas were allocated to viticulture using the 2012 RPG, and overestimated by 23% using the 2012 CLC. The VV source yielded the most accurate total (−1% with 781,152 ha). Exposure assessment accounted for the uncertainties (see below).

In the main analysis, which addressed all of the 2006–2013 inclusions, the proximity of vines was estimated from the 2007 and 2012 maps, which were based on the RPG and CLC sources, since the VV source was not available for the whole period. A complementary analysis was conducted on the 2010–2013 inclusions, which included the VV source in addition to the 2012 RPG and CLC sources.

The presence of vines within 1,000 m of the geocoded address of residence was described by a six-category variable as follows: *a*) no vines and no other crops within 1,000 m and geocoded address located in an urban unit with a population ≥100,000; *b*) no vines and no other crops within 1,000 m and geocoded address located in an urban unit with a population of <100,000; *c*) no vines but presence of another crop within 1,000 m but not within 500 m; *d*) no vines but presence of another crop within 500 m; *e*) possible presence of viticulture within 1,000 m; and *f*) probable presence of viticulture within 1,000 m.

In the main analysis, the presence of viticulture in a buffer was considered "possible" when the buffer included viticulture plots identified only by CLC, the least precise source (scale: 1:100,000 and large crop groups) and "probable" when the buffer included at least one viticulture plot identified by RPG (scale: 1:5,000). For any other crop, the crop was considered present in a buffer if it included at least one polygon with the crop, irrespective of source. In the 2010–2013 analysis, the presence of viticulture in a buffer was considered "probable" if the buffer included at least one polygon with viticulture according to the RPG or VV sources.

A 10-category variable was also used when the numbers were sufficient, with the same first 5 categories and the sixth divided into five subcategories as follows: *f*) probable presence of viticulture within 1,000 m but not within 500 m; *g*) probable presence of viticulture within 1,000 m and possibly within 500 m; *h*) probable presence of viticulture within 500 m but not within 200 m; *i*) probable presence of viticulture within 500 m and possibly within 200 m; and *j*) probable presence of viticulture within 200 m.

The viticulture density within 1,000 m of the geocoded address of residence is a quantitative variable obtained by dividing the area allocated to viticulture in the 1,000-m buffer by the total area of the buffer (~314 ha).

We also considered the weighted viticulture density, an indicator defined as the sum of the areas allocated to viticulture in the 200-m buffer and in the 200- to 500-m and 500- to 1,000-m rings, weighted by the inverse of the average distance between the buffer/ring and the residence (100, 350, and 750 m, respectively). This indicator made it possible to distinguish situations where the vines were close to the residence and those where they were on the periphery of the buffer.

In the main analysis, the quantitative variables were defined based on the RPG and CLC polygons (sensible indicator) and with the RPG polygons only (specific indicator).

Confounding Factors

Several factors associated with childhood AL risk in previous studies conducted by our group were considered as potential confounding factors as follows: the degree of urbanization, defined as the size of the urban unit where the child lived (population: <5,000, population: 5,000–19,999, population: 20,000–99,999, and population: ≥100,000)[27]; the French deprivation index FDep, defined as a linear combination of four census variables (the median income and the proportions of high school graduates, blue-collar workers, and unemployed persons in the municipality)[27,28]; the average daily ultraviolet (UV) radiation level in the municipality[29,30] (data from the European EUROSUN project); and the length of major roads within 150 m of the geocoded address[31] (annual HERE road maps; https://www.here.com).

Viticulture is less frequent in urban areas and most deprived areas where incidence of ALL was found to be decreased[27] and in areas most exposed to major roads where AML risk was found to be increased[31] (Figures S1 and S2, Table S2). Viticulture is also more frequent in the South of France where the levels of UV radiation are higher.[29] We did not test the relationships between these factors and viticulture, since the statistical power was limited for this criteria, but rather evaluated if their inclusion in the models induced at least 5% change in the estimates.

Statistical Analysis

Main analyses. Odds ratio (OR) and Wald-based 95% confidence interval (CI) were estimated by logistic regression models adjusted for age (<1 y old, 1–4 years old, 5–9 years old, and 10–14 years old), separately for all AL, ALL, and AML. Additional analyses stratified by region were conducted for all AL and ALL.

For the proximity to vines, OR and Wald-based 95% CI were estimated for each category taking as reference the second category (i.e., no vines and no other crop within 1,000 m and geocoded address located in an urban unit of population <100,000) in order to avoid taking an exclusively urban group as a reference.

For viticulture density and weighted viticulture density within 1,000 m of the geocoded address of residence, ORs were estimated for a 10% increase in density. One-sided p-values were calculated. Locally weighted polynomial regression (LOESS) models were also implemented to investigate nonlinear variations in ORs on the log scale. For the analysis by region, heterogeneity was tested in the regression model using likelihood-ratio tests on interaction terms.

Sensitivity and complementary analyses. Supplementary analyses were conducted for ALL and addressed the main cytogenetic abnormalities considered initiating events in childhood ALL, i.e., *KMT2A* (MLL), *ETV6*/*RUNX1* (TEL/AML1), and hyperdiploidy >50 chromosomes. The numbers were not sufficient to enable AML analyses by subtype.

We tested the stability of the results by stratifying by age group (0–6 y old, 7–14 y old); adjusting for the density of crops other than vines within 1,000 m; restricting the analyses to children with the best geocoded addresses [3,015 cases (81%) and 33,235 controls (83%)]; restricting the analyses to the 8 most intensive wine-growing regions [2,231 cases (60%) and 23,643 controls (59%)]; excluding the cases and controls with no agricultural area within 1,000 m [2,814 cases (76%) and 30,532 controls (76%)]; and adjusting for the potential confounding factors (each separately and all together).

We tested the interactions between variables in logistic regression models with likelihood ratio tests, except for ALL subtypes where heterogeneity was tested in polytomous regression models.

Complementary analyses were performed on the 2010–2013 inclusions (1,909 AL cases and 20,198 controls), using the 2012-VV map, with the VV source in addition to RPG and CLC.

All of the analyses were conducted with R version 4.0.5 software (R Development Core Team).

Results

The proportion of the 40,196 controls living within 1,000 m of vines was estimated at 10% based on the RPG and CLC sources and at 8.9% based on the RPG source alone, respectively, 9.4% and 8.1% for cases (Table 1). The median area allocated to viticulture in the 1,000-m buffer centered on the geocoded addresses was 21.8 ha [interquartile range (IQR): 2.8–79.6 ha] according to the RPG and CLC sources and 6.8 ha (IQR: 1.3–21.8 ha) according to the RPG source alone.

The proportion of controls living close to vines varied greatly depending on the region, ranging from <1% in the Bretagne, Normandie, Île-de-France, and Hauts-de-France to about 20% in Nouvelle-Aquitaine and Provence-Alpes-Côte d'Azur-Corse and almost 40% in Occitanie (Table 1; Figure S3). Viticultural areas within 1,000 m also showed large variations between and within regions (right-skewed distributions) and were estimated to be much higher when CLC was taken into account (median area tripled in most of the regions).

Overall, there was no evidence of association between the indicator of proximity to vines and ALL or AML (Table 2). ORs were close to one in all the categories without statistically significant heterogeneity.

Viticulture density, however, was associated with ALL [OR = 1.05 (1.00–1.09) for a 10% increase in density] but not with AML [OR = 0.95 (0.84–1.08)]. Using the RPG source alone to estimate viticulture density generated similar results [OR for ALL = 1.12 (0.99–1.26) and OR for AML = 0.73 (0.47–1.13)]. Similar results were observed with the weighted viticulture density (Table 2). An additional analysis actually showed a strong correlation between the viticulture densities in the buffers of 1,000 m, 500 m, and 200 m (Pearson correlation coefficient of 0.86 between the viticulture densities in the buffers of 200 m and 500 m and of 0.89 between the buffers of 500 m and 1,000 m).

The ORs for proximity of vines were similar for ALL with *KMT2A* rearrangement (121 cases) and ALL with *ETV6*/*RUNX1* transcript or hyperdiploidy >50 chromosomes (1,290 cases) and were not significantly different from that for ALL with none of these cytogenetic abnormalities (1,397 cases). Of note, the estimate for the association with density was higher for ALL with *KMT2A* rearrangement, although still not significantly greater than the unit (Table 3).

The associations with viticulture density remained unchanged, particularly for ALL, in the sensitivity analyses adjusted for the density of other crops [OR = 1.05 (1.00–1.10)], restricted to the best geocoded addresses [OR = 1.06 (1.01–1.12)], restricted to the 8 most intensive vine-growing regions [OR = 1.04 (0.99–1.09)],

Table 1. GIS-based assessment of presence of vines within 1,000 m, using both RPG and CLC sources or using the RPG source only: number of controls and cases living within 1,000 m of vines, and distribution of the areas dedicated to vines within 1,000 m of the geocoded address, by region (GEOCAP, 2006–2013).

			Viticulture within 1,000 m, RPG and CLC										Viticulture within 1,000 m, RPG only									
	All controls (*n*)	All cases (*n*)	*n* (%)		Buffer area allocated to viticulture (hectares)								*n* (%)		Buffer area allocated to viticulture (hectares)							
			Controls	Cases	Mean	SD	Minimum	P25	P50	P75	P95	Maximum	Controls	Cases	Mean	SD	Minimum	P25	P50	P75	P95	Maximum
Total mainland France	40,196	3,711	4,023 (10.0)	348 (9.4)	49.3	60.1	<0.1	2.8	21.8	79.6	179.3	291.4	3,566 (8.9)	299 (8.1)	16.9	24.5	<0.1	1.3	6.8	21.8	68.5	213.0
Region																						
Occitanie	3,223	297	1,215 (37.7)	100 (33.7)	63.5	64.0	<0.1	6.8	41.7	106.8	188.7	267.7	1,093 (33.9)	93 (31.3)	21.7	27.2	<0.1	3.2	11.9	28.7	84.0	178.0
Nouvelle-Aquitaine	3,251	319	698 (21.5)	59 (18.5)	55.9	65.0	<0.1	4.3	27.5	92.3	193.7	285.3	588 (18.1)	48 (15.0)	22.7	30.6	<0.1	1.9	10.6	32.2	89.4	213.0
Provence-Alpes-Côte d'Azur-Corse	3,078	293	635 (20.6)	58 (19.8)	36.8	49.4	<0.1	2.3	14.3	54.5	145.3	291.4	532 (17.3)	43 (14.7)	12.0	18.1	<0.1	1.3	4.7	15.4	48.8	119.0
Auvergne-Rhône-Alpes	4,942	455	534 (10.8)	35 (7.6)	32.1	57.0	<0.1	0.5	4.1	33.5	183.8	274.6	511 (10.3)	32 (7.0)	11.8	20.9	<0.1	0.4	2.5	12.6	56.5	149.1
Bourgogne-Franche-Comté	1,706	168	150 (8.8)	13 (7.7)	48.6	56.7	0.1	3.5	25.2	78.1	169.3	223.0	141 (8.3)	11 (6.5)	10.7	15.6	<0.1	1.0	4.2	14.8	38.8	97.1
Centre-Val-de-Loire	1,615	156	151 (9.3)	18 (11.5)	32.5	43.7	<0.1	1.7	10.6	49.9	121.3	224.4	145 (9.0)	18 (11.5)	11.8	14.7	<0.1	1.4	5.1	17.1	43.3	67.2
Grand Est	3,381	337	307 (9.1)	35 (10.4)	51.1	59.0	<0.1	3.3	28.7	83.0	174.6	235.5	262 (7.7)	25 (7.4)	14.2	23.6	<0.1	0.6	4.3	13.4	67.1	114.2
Pays de la Loire	2,447	206	307 (12.5)	30 (14.6)	40.6	53.2	<0.1	1.2	15.8	60.5	158.5	231.8	270 (11.0)	29 (14.1)	14.5	18.7	<0.1	0.8	6.4	20.0	58.7	80.4
Hauts-de-France	4,111	383	24 (0.6)	0 (0.0)	46.8	35.2	0.7	20.4	43.5	69.4	103.4	107.3	22 (0.5)	0 (0.0)	5.1	5.6	<0.1	0.8	3.9	7.1	16.7	21.1
Île-de-France	8,270	713	2 (<0.1)	0 (0.0)	2.5	1.2	1.7	—	—	—	—	3.3	2 (<0.1)	0 (0.0)	2.5	1.2	1.7	—	—	—	—	3.3
Normandie	2,115	196	0 (0.0)	0 (0.0)	—	—	—	—	—	—	—	—	0 (0.0)	0 (0.0)	—	—	—	—	—	—	—	—
Bretagne	2,057	188	0 (0.0)	0 (0.0)	—	—	—	—	—	—	—	—	0 (0.0)	0 (0.0)	—	—	—	—	—	—	—	—

Note: CLC, Corine Land Cover; GIS, geographic information system; P25, P50, P75, and P95: 25th, 50th, 75th, and 95th percentiles of viticulture area; RPG, Graphic Parcel Register; SD, standard deviation.

excluding children with no agricultural area within 1,000 m [OR = 1.04 (1.00–1.09)], or adjusted for the available potential confounding factors [OR = 1.04 (0.99–1.09)] (Table 4). Stratifying the analyses on ALL by age in 2 classes did not reveal any heterogeneity (Table S3).

The association between viticulture density and the risk of ALL was significantly heterogeneous across regions (Table 5). The association was statistically significant (one-sided test) in the Pays de la Loire, Grand-Est, Occitanie, and Provence-Alpes-Côte d'Azur-Corse regions and similar although not significant in the Centre-Val-de-Loire. An OR less than one was observed for Auvergne-Rhône-Alpes. The associations did not deviate from log-linearity in any of the analyses except for Occitanie with the indicator combining CLC and RPG. The LOESS model suggested that the deviation was only for the lowest densities of viticulture and for the most extreme density. This deviation is not found with the indicator using RPG only (Figure S4, Table S4).

In the sensitivity analysis restricted to the period of 2010 to 2013, using the 2012 map, which included the VV source, 16.1% of the control addresses were classed as probably close to vines and only 0.1% as possibly close to vines (Table 6). As in the main analysis, vine proximity was not associated with ALL or AML, whereas the viticulture density was associated with ALL [OR = 1.07 (1.01–1.13) per 10% increase in density] but not AML [OR = 0.88 (0.72–1.08)].

Discussion

In this nationwide GIS-based case-control study, we observed a small increase in ALL risk for children living within 1,000 m of vines. Over the whole study period, the increase was 5% for a 10% increase in viticulture density with the RPG and CLC sources and 12% with the RPG source alone. The association remained stable in the various sensitivity analyses, in particular using the more accurate and exhaustive source VV over the period of 2010 to 2013 (7% for a 10% increase in viticulture density). The results were heterogeneous between the regions. No association with the qualitative indicator of proximity to the vines was evidenced. No association with AML was found.

A few studies have investigated the role of environmental exposure to agricultural pesticides in the risk of childhood leukemia[10–23,32]; even fewer have addressed viticulture. The majority of the studies evaluated the association between childhood AL and total crop or specific crop densities, and most of them were conducted in the United States using different exposure assessment methods. Two American ecological studies found an increased incidence rate of childhood AL in counties with the highest densities of specific crops [dry beans (AL), sugar beet (ALL), and oats (AML)[11]; cotton, oats, and soybeans (AML)[12]]. Two Texan ecological studies based on the residence at birth,[16,18] in which viticulture was again not studied, found no association with childhood AL. A Spanish GIS-based case-control study found associations with specific crop densities within 1,000 m estimated using CLC but not for viticulture.[15] In that study, the exposure periods were around the time of diagnosis for the cases and around birth for the controls, which may have introduced biases. An Italian case-control study found no association with viticulture density within 100 m of the geocoded addresses of children, but the authors remained prudent in their conclusion because of the imprecise estimates due to small numbers (111 AL and 444 controls).[17] Several ecological and case-control studies conducted in California used information from the pesticide use reporting database to estimate the quantities of pesticide used in the vicinity of children's homes.[19–23,32] Some pesticides and chemical classes, not specifically used in viticulture, were associated with an elevated risk of childhood AL, but the results need to be confirmed.

Table 2. Association between childhood acute leukemia and indicators of proximity to vines (GEOCAP inclusions 2006–2013, GIS-based assessment of exposure based on RPG and CLC sources).

	Controls (n=40,196)	All acute leukemia ($n = 3,711$)			Acute lymphoblastic leukemia ($n = 3,088$)			Acute myeloid leukemia ($n = 552$)		
	[n (%)]	n (%)	OR[a] (95% CI)	p[b]	n (%)	OR[a] (95% CI)	p[b]	n (%)	OR[a] (95% CI)	p[b]
Presence of vines within 1,000 m										
No vines, no other crops, UU ≥100,000 inhabitants	8,614 (21.4)	794 (21.4)	0.91 (0.73, 1.13)	—	623 (20.2)	0.86 (0.68, 1.09)	—	157 (28.4)	1.17 (0.70, 1.97)	—
No vines, no other crops, UU <100,000 inhabitants	1,050 (2.6)	103 (2.8)	1 (Ref)	—	85 (2.8)	1 (Ref)	—	16 (2.9)	1 (Ref)	—
No vines, other crops[c] ≤1,000 m but none ≤500 m	4,973 (12.4)	451 (12.2)	0.90 (0.72, 1.13)	—	380 (12.3)	0.92 (0.72, 1.18)	—	61 (11.1)	0.80 (0.46, 1.39)	—
No vines, other crops[c] ≤500 m	21,544 (53.6)	2,016 (54.3)	0.95 (0.77, 1.17)	—	1,696 (54.9)	0.96 (0.76, 1.21)	—	281 (50.9)	0.86 (0.52, 1.43)	—
Possible presence of vines ≤1,000 m[d]	455 (1.1)	49 (1.3)	1.09 (0.76, 1.56)	—	44 (1.4)	1.19 (0.81, 1.74)	—	5 (0.9)	0.72 (0.26, 1.98)	—
Probable presence of vines ≤1,000 m[e]	3,560 (8.9)	298 (8.0)	0.86 (0.68, 1.08)	—	260 (8.4)	0.90 (0.70, 1.17)	—	32 (5.8)	0.60 (0.33, 1.09)	—
Probable >500 m, not ≤500 m	1,162 (2.9)	97 (2.6)	0.87 (0.65, 1.16)	—	81 (2.6)	0.88 (0.64, 1.20)	—	—	—	—
Probable >500 m, possible ≤500 m	320 (0.8)	35 (0.9)	1.13 (0.75, 1.70)	—	33 (1.1)	1.30 (0.85, 1.98)	—	—	—	—
Probable ≤500 m but not ≤200 m	853 (2.1)	56 (1.5)	0.65 (0.47, 0.92)	—	52 (1.7)	0.73 (0.51, 1.04)	—	—	—	—
Probable ≤500 m, possible ≤200 m	355 (0.9)	31 (0.8)	0.88 (0.58, 1.35)	—	24 (0.8)	0.82 (0.51, 1.32)	—	—	—	—
Probable ≤200 m	870 (2.2)	79 (2.1)	0.93 (0.69, 1.27)	—	70 (2.3)	1.00 (0.72, 1.40)	—	—	—	—
Density of vines within 1,000 m[f]										
RPG and CLC (sensible indicator)	—	—	1.04 (0.99, 1.08)	0.05	—	1.05 (1.00, 1.09)	0.03	—	0.95 (0.84, 1.08)	0.77
RPG only (specific indicator)	—	—	1.07 (0.95, 1.20)	0.15	—	1.12 (0.99, 1.26)	0.04	—	0.73 (0.47, 1.13)	0.92
Weighted density of vines within 1,000 m[g]										
RPG and CLC (sensible indicator)	—	—	1.04 (0.99, 1.08)	0.05	—	1.04 (1.00, 1.09)	0.03	—	0.96 (0.84, 1.09)	0.75
RPG only (specific indicator)	—	—	1.04 (0.95, 1.13)	0.19	—	1.07 (0.98, 1.17)	0.06	—	0.80 (0.58, 1.10)	0.92

Note: —, no data; CI, confidence interval; CLC, Corine Land Cover; GIS, geographic information system; n, number of children; OR, odds ratio; Ref, reference; RPG, Graphic Parcel Register; UU, urban unit.

[a] OR and 95% confidence interval CI estimated by unconditional logistic regression adjusted for age.

[b] One-sided p-values for the slope parameter in the quantitative analyses with the density of vines within 1,000 m.

[c] At least one plot identified by RPG or CLC with a crop different from viticulture.

[d] The presence of viticulture was considered "possible" if at least one vine plot was identified by CLC but no vine plot was identified with RPG.

[e] The presence of viticulture was considered "probable" if at least one vine plot was identified by RPG.

[f] OR associated with a 10% increase in viticulture density within 1,000 m.

[g] OR associated with an increase equal to 10% of the maximum weighted density.

The present study addressed, for the first time, the question of AL risk among children living close to viticultural areas in France. According to the most recent French agricultural censuses (2010 and 2020), there were ∼27 million hectares of utilized agricultural area (UAA), i.e., about 50% of mainland France. It has been estimated that about 65,000 to 75,000 metric tons of agricultural pesticides, most of them fungicides, were sold annually during our study period (https://agreste.agriculture.gouv.fr/). Vines are subjected to particularly intensive pesticide treatment: about 19 times[33] per year, on average, nationwide. Viticulture covers nearly 800,000 ha, i.e., about 3% of the total UAA of France.

Our major challenge was to properly assess the presence of viticulture plots and estimate the viticulture area near homes. In our ecological study,[14] viticulture density in the municipality of

Table 3. Association between childhood acute lymphoblastic leukemia and indicators of proximity to vines, depending on the presence of *KMT2A* transcript and by the presence of *ETV6/RUNX1* transcript or of hyperdiploidy >50 chromosomes and the absence of these cytogenetic events (GEOCAP inclusions 2006–2013, GIS-based assessment of exposure based on RPG and CLC).

	Controls ($n = 40,196$)	ALL with KMT2A ($n = 121$)			ALL with ETV6/RUNX1 or hyperdiploidy >50 ($n = 1,290$)			ALL with none of the cytogenetic events ($n = 1,397$)		
	[n (%)]	n (%)	OR[a] (95% CI)	p[b]	n (%)	OR[a] (95% CI)	p[b]	n (%)	OR[a] (95% CI)	p[b]
Presence of vines within 1,000 m										
No vines and no other crops	9,664 (24.0)	31 (25.6)	1 (Ref)	—	290 (22.5)	1 (Ref)	—	327 (23.4)	1 (Ref)	—
No vines but other crops[c]	26,517 (66.0)	76 (62.8)	0.96 (0.63, 1.46)	—	873 (67.7)	1.14 (0.99, 1.30)	—	938 (67.1)	1.04 (0.92, 1.19)	—
Presence of vines[d]	4,015 (10.0)	14 (11.6)	1.19 (0.63, 2.24)	—	127 (9.8)	1.12 (0.91, 1.39)	—	132 (9.4)	0.97 (0.79, 1.20)	—
Density of vines within 1,000 m[e]										
RPG and CLC (sensible indicator)	—	—	1.13 (0.94, 1.35)	0.09	—	1.04 (0.97, 1.11)	0.16	—	1.03 (0.96, 1.10)	0.23
RPG only (specific indicator)	—	—	1.39 (0.92, 2.11)	0.06	—	1.13 (0.94, 1.36)	0.10	—	1.10 (0.92, 1.31)	0.14

Note: 280 (9%) cases were excluded because cytogenetic information was missing. —, no data; ALL, acute lymphoblastic leukemia; CI, confidence interval; CLC, Corine Land Cover; OR, odds ratio; Ref, reference; RPG, Graphic Parcel Register.

[a] OR and 95% CI estimated by unconditional logistic regression adjusted for age.

[b] One-sided p-values for the slope parameter in the quantitative analyses with the density of vines within 1,000 m.

[c] At least one plot identified by RPG or CLC with a crop different from viticulture.

[d] At least one vine plot identified by RPG or CLC.

[e] OR associated with a 10% increase in viticulture density.

Table 4. Sensitivity analyses of the association between childhood acute leukemia and density of vines within 1,000 m of the geocoded address (GEOCAP, inclusions 2006–2013, GIS-based assessment of exposure based on RPG and CLC).

	Controls	All acute leukemia					Acute lymphoblastic leukemia					Acute myeloid leukemia				
			RPG and CLC		RPG alone			RPG and CLC		RPG alone			RPG and CLC		RPG alone	
Density within 1,000 m	n	n	OR (95% CI)[a]	p^a	OR (95% CI)[a]	p^a	n	OR (95% CI)[a]	p^a	OR (95% CI)[a]	p^a	n	OR (95% CI)[a]	p^a	OR (95% CI)[a]	p^a
Main analyses	40,196	3,711	1.04 (0.99, 1.08)	0.05	1.07 (0.95, 1.20)	0.15	3,088	1.05 (1.00, 1.09)	0.03	1.12 (0.99, 1.26)	0.04	552	0.95 (0.84, 1.08)	0.77	0.73 (0.47, 1.13)	0.92
Adjustment for density of other crops[b]	40,196	3,711	1.04 (1.00, 1.08)	0.04	1.07 (0.95,1.20)	0.14	3,088	1.05 (1.00,1.10)	0.02	1.12 (0.99,1.26)	0.04	552	0.95 (0.84,1.08)	0.79	0.73 (0.47,1.13)	0.92
Only the best geocoded addresses[c]	33,235	3,015	1.05 (0.99, 1.10)	0.05	1.07 (0.92, 1.24)	0.21	2,506	1.06 (1.01, 1.12)	0.02	1.13 (0.97, 1.32)	0.06	446	0.94 (0.80, 1.11)	0.78	0.58 (0.29, 1.18)	0.93
Only the 8 most intensive wine-growing regions[d]	23,643	2,231	1.03 (0.99, 1.08)	0.07	1.05 (0.94, 1.19)	0.20	1,877	1.04 (0.99, 1.09)	0.05	1.10 (0.97, 1.24)	0.07	309	0.97 (0.85, 1.10)	0.70	0.75 (0.49, 1.17)	0.90
Only children with crops within 1,000 m	30,532	2,814	1.04 (0.99, 1.08)	0.05	1.06 (0.95, 1.20)	0.15	2,380	1.04 (1.00, 1.09)	0.04	1.10 (0.98, 1.25)	0.06	379	0.98 (0.87, 1.11)	0.63	0.79 (0.51, 1.21)	0.86
Adjustment for potential confounders																
Size of urban unit[e]	40,196	3,711	1.03 (0.99, 1.08)	0.08	1.05 (0.93, 1.18)	0.22	3,088	1.04 (0.99, 1.08)	0.07	1.08 (0.96, 1.23)	0.10	552	0.97 (0.86, 1.10)	0.68	0.76 (0.49, 1.18)	0.89
Municipality deprivation index[f]	40,196	3,711	1.04 (1.00, 1.08)	0.04	1.07 (0.95, 1.20)	0.14	3,088	1.05 (1.00, 1.09)	0.03	1.12 (0.99, 1.26)	0.04	552	0.96 (0.85, 1.08)	0.76	0.73 (0.47, 1.14)	0.92
Length of major roads within 150 m[g]	40,196	3,711	1.04 (1.00, 1.08)	0.04	1.07 (0.95, 1.20)	0.14	3,088	1.05 (1.00, 1.09)	0.03	1.11 (0.99, 1.26)	0.04	552	0.96 (0.85, 1.09)	0.75	0.74 (0.48, 1.14)	0.91
Average UV radiation in the municipality[h]	40,196	3,711	1.04 (1.00, 1.09)	0.04	1.07 (0.95, 1.21)	0.13	3,088	1.05 (1.00, 1.10)	0.02	1.12 (0.99, 1.27)	0.04	552	0.96 (0.84, 1.09)	0.75	0.73 (0.47, 1.15)	0.91
All above potential confounders	40,196	3,711	1.03 (0.99, 1.08)	0.07	1.05 (0.93, 1.19)	0.20	3,088	1.04 (0.99, 1.09)	0.07	1.09 (0.96, 1.23)	0.10	552	0.98 (0.86, 1.12)	0.61	0.78 (0.51, 1.22)	0.86

Note: CI, confidence interval; CLC, Corine Land Cover; OR, odds ratio; RPG, Graphic Parcel Register.

[a] OR for a 10% increase in viticulture density (based on RPG and CLC sources and RPG alone) and 95% CI estimated by unconditional logistic regression adjusted for age. *p*-values are one-sided.

[b] Inclusion in the model of the proportion of buffer area allocated to crops other than vines.

[c] Analyses based on children with the best geocoded addresses: geocoding incertitude <100 m.

[d] Exclusion of the Bretagne, Hauts-de-France, Ile-de-France and Normandie regions.

[e] Adjustment for urban unit size using 4 population categories: <5,000, 5,000–19,999, 20,000–99,999, ≥100,000 inhabitants.

[f] Adjustment for the 2006 Fdep deprivation index.

[g] Adjustment for the length of major roads within 150 m (OR for a 300 m increase in road length).

[h] Adjustment for the average daily UV radiation level in the municipality (OR for an increase of 25 J/cm^2).

Table 5. Association between childhood acute leukemia and density of vines within 1,000 m of the geocoded address, stratifying by region (GEOCAP, inclusions 2006–2013, exposure assessment based on RPG and CLC, and on RPG only).

	Controls	All acute leukemia							Acute lymphoblastic leukemia							Acute myeloid leukemia						
			RPG and CLC			RPG only		—		RPG and CLC			RPG only				RPG and CLC			RPG only		
	n	*n*	OR[a]	(95% CI)	*p*[b]	OR[a]	(95% CI)	*p*[b]	*n*	OR[a]	(95% CI)	*p*[b]	OR[a]	(95% CI)	*p*[b]	*n*	OR[a]	(95% CI)	*p*[b]	OR[a]	(95% CI)	*p*[b]
Region[c]					<0.01			<0.01				<0.01			<0.01				0.12			0.17
Occitanie	3,223	297	1.04	(0.97, 1.12)	—	1.17	(0.98, 1.40)	—	251	1.06	(0.99, 1.15)	—	1.24	(1.03, 1.48)	—	38	0.90	(0.71, 1.16)	—	0.71	(0.32, 1.58)	—
Nouvelle-Aquitaine	3,251	319	0.97	(0.87, 1.07)	—	0.80	(0.59, 1.09)	—	268	0.99	(0.89, 1.10)	—	0.85	(0.63, 1.16)	—	49	0.83	(0.58, 1.19)	—	0.46	(0.12, 1.74)	—
PACA-Corse	3,078	293	1.10	(0.97, 1.24)	—	1.30	(0.90, 1.87)	—	241	1.09	(0.95, 1.25)	—	1.30	(0.86, 1.96)	—	48	1.14	(0.88, 1.47)	—	1.44	(0.70, 2.98)	—
Auvergne-Rhône-Alpes	4,942	455	0.75	(0.56, 0.99)	—	0.50	(0.24, 1.07)	—	373	0.56	(0.33, 0.94)	—	0.46	(0.19, 1.12)	—	70	1.07	(0.80, 1.44)	—	0.77	(0.21, 2.81)	—
Bourgogne-Franche-Comté	1,706	168	1.00	(0.80, 1.27)	—	0.90	(0.32, 2.52)	—	141	0.91	(0.67, 1.24)	—	0.58	(0.13, 2.54)	—	20	1.34	(0.95, 1.88)	—	2.16	(0.63, 7.38)	—
Centre-Val-de-Loire	1,615	156	1.09	(0.82, 1.45)	—	1.33	(0.56, 3.14)	—	132	1.15	(0.86, 1.52)	—	1.57	(0.67, 3.66)	—	—	—	—	—	—	—	—
Grand Est	3,381	337	1.12	(0.99, 1.28)	—	1.08	(0.67, 1.73)	—	291	1.15	(1.00, 1.31)	—	1.17	(0.73, 1.87)	—	—	—	—	—	—	—	—
Pays de la Loire	2,447	206	1.24	(1.07, 1.42)	—	1.76	(1.16, 2.67)	—	180	1.21	(1.03, 1.42)	—	1.82	(1.18, 2.81)	—	—	—	—	—	—	—	—

Note: —, no data; CI, confidence interval; CLC, Corine Land Cover; OR, odds ratio; PACA, Provence-Alpes-Côte d'Azur; RPG, Graphic Parcel Register.

[a] OR for a 10% increase in viticulture density and its 95% CI estimated by unconditional logistic regression adjusted for age.

[b] *p*-value of the test for heterogeneity between regions (test for an interaction between viticulture density and region).

[c] The analyses could not be carried out in the Hauts-de-France, Île-de-France, Normandie, and Bretagne regions due to an insufficient number of children living near the vines.

residence was associated with a greater risk of childhood ALL. However, the viticulture density at the municipality scale explained only part of the variability in viticulture density around residences ($R^2 = 0.62$).

Our cartographic method combining information from the RPG, CLC, and VV sources enabled precise description of viticultural areas on the national scale, overcoming the main limitations of each source considered independently.[25] It is noteworthy that RPG is used to apply for European financial subsidies for specific crops. Farmers who want to benefit from the subsidies are required to report all of their crop areas, including those of crops not covered by the subsidies, such as grape vines. While there may be some imprecision in those reports, RPG affords marked overall precision (1:5,000). Using RPG alone underestimates the total viticulture area by 35% in comparison to the 2010 agricultural census, the main reason being that viticulture-only farmers do not apply for subsidies. CLC satellite images are not precise enough to detect crops covering <25 ha; the plots are roughly localized, and confusion of vineyards and orchards is possible. Using CLC alone overestimates the total viticulture area by 23% in comparison to the agricultural census. Lastly, the VV database is as precise as RPG (1:5,000); the total viticultural area is very well estimated compared to the agricultural census, but the database does not cover the whole study period. The distribution of regional viticultural areas was highly heterogeneous. Combining the RPG and CLC sources in the 2012 map resulted in a total estimate of viticulture area closer to that of the agricultural census than that with RPG alone in all regions except Occitanie, for which the viticultural area was the most overestimated by CLC and the least underestimated by RPG. It might reflect a smaller part of monocultures in the Occitanie region, but we cannot explain this regional difference with certainty.

The study could not avoid exposure misclassifications induced by uncertainties in geocoding, impossibility of perfect identification of vines on the buffer level throughout the study period, and absence of indication of children's space-time budgets regarding their opportunity to be exposed at other places than at their address. However, all of the processes were carried out blind to the case or control status in order to avoid any differential misclassification.

The association between viticulture density and the risk of ALL appeared more marked in 5 of the 12 regions (Centre-Val-de-Loire, Grand-Est, Pays de la Loire, Occitanie, and Provence-Alpes-Côte d'Azur-Corse); no association was found for the other regions, in particular Nouvelle-Aquitaine, where more than 20% of the controls resided in the proximity of viticulture. This may be due to heterogeneity with respect to our indicators' description of viticultural areas in buffers or regional heterogeneity in pesticide use or practices. These hypotheses call for further investigation.

Our previous studies have shown associations between the risk of childhood AL and urbanization, deprivation level in the area of residence, UV radiation, and traffic-related air pollution. Taking those factors into account did not change the results, suggesting that there was no large-scale spatial confounding. In our GIS-based study, it was not possible to take into account the individual factors that are highly suspected of being associated positively (e.g., maternal pesticide use during pregnancy, maternal occupational exposure to pesticides during pregnancy, paternal prenatal smoking, increased fetal growth) or negatively (e.g., breastfeeding, early common infections, maternal folate intake preconception) with childhood AL. Even if those individual factors may be influenced by rural/urban lifestyle, their distribution should be strongly different in viticultural and other rural areas to have a significant impact on the association with viticulture density, which we believe unlikely. The study assessed proximity of

Table 6. Association between childhood acute leukemia and indicators of proximity to vines in the period of 2010 to 2013; exposure assessment based on the 2012-VV map with RPG, CLC, and VV sources.

	Controls ($n = 20,198$)	All acute leukemia ($n = 1,909$)			Acute lymphoblastic leukemia ($n = 1,605$)			Acute myeloid leukemia ($n = 282$)		
	[n (%)]	n (%)	OR[a] (95% CI)	p[b]	n (%)	OR[a] (95% CI)	p[b]	n (%)	OR[a] (95% CI)	p[b]
Presence of vines within 1,000 m										
No vines, no other crops, UU ≥100,000 inhabitants	4,243 (21.0)	423 (22.2)	0.88 (0.64, 1.20)	—	334 (20.8)	0.75 (0.54, 1.04)	—	85 (30.1)	2.25 (0.82, 6.17)	—
No vines, no other crops, UU <100,000 inhabitants	449 (2.2)	50 (2.6)	1 (Ref)	—	46 (2.9)	1 (Ref)	—	4 (1.4)	1 (Ref)	—
No vines, other crops[c] ≤1,000 m but none ≤500 m	2,339 (11.6)	214 (11.2)	0.83 (0.60, 1.14)	—	182 (11.3)	0.76 (0.54, 1.08)	—	29 (10.3)	1.41 (0.49, 4.02)	—
No vines, other crops[c] ≤500 m	9,890 (49.0)	920 (48.2)	0.84 (0.62, 1.14)	—	780 (48.6)	0.78 (0.57, 1.06)	—	131 (46.5)	1.52 (0.56, 4.13)	—
Possible presence of vines ≤1,000 m[d]	21 (0.1)	1 (0.1)	0.44 (0.06, 3.32)	—	1 (0.1)	0.47 (0.06, 3.56)	—	0 (0.0)	—	—
Probable presence of vines ≤1,000 m[e]	3,256 (16.1)	301 (15.8)	0.84 (0.61, 1.16)	—	262 (16.3)	0.80 (0.57, 1.11)	—	33 (11.7)	1.16 (0.41, 3.30)	—
Probable >500 m, not ≤500 m	1,373 (6.8)	121 (6.3)	0.80 (0.56, 1.13)	—	102 (6.4)	0.73 (0.51, 1.06)	—	—	—	—
Probable >500 m, possible ≤500 m	39 (0.2)	8 (0.4)	1.95 (0.86, 4.45)	—	8 (0.5)	2.14 (0.94, 4.92)	—	—	—	—
Probable ≤500 m but not ≤200 m	918 (4.5)	97 (5.1)	0.97 (0.67, 1.39)	—	82 (5.1)	0.89 (0.61, 1.30)	—	—	—	—
Probable ≤500 m, possible ≤200 m	93 (0.5)	6 (0.3)	0.60 (0.25, 1.45)	—	6 (0.4)	0.66 (0.27, 1.59)	—	—	—	—
Probable ≤200 m	833 (4.1)	69 (3.6)	0.76 (0.52, 1.12)	—	64 (4.0)	0.77 (0.52, 1.15)	—	—	—	—
Density of vines within 1,000 m[f]										
VV, RPG, and CLC (sensible indicator)	—	—	1.05 (0.99, 1.11)	0.06	—	1.07 (1.01, 1.13)	0.01	—	0.88 (0.72, 1.08)	0.90
Only VV and RPG (specific indicator)	—	—	1.06 (0.98, 1.15)	0.06	—	1.10 (1.01, 1.18)	0.01	—	0.80 (0.59, 1.09)	0.93
Weighted density of vines within 1,000 m[g]										
VV, RPG, and CLC (sensible indicator)	—	—	1.04 (0.99,1.10)	0.07	—	1.07 (1.00,1.13)	0.02	—	0.87 (0.70, 1.07)	0.90
Only VV and RPG (specific indicator)	—	—	1.05 (0.98, 1.13)	0.07	—	1.08 (1.01, 1.16)	0.01	—	0.80 (0.60, 1.08)	0.93

Note: —, no data; CI, confidence interval; CLC, Corine Land Cover; OR, odds ratio; Ref, reference; RPG, Graphic Parcel Register; UU, urban unit; VV, vegetation layer of the BD Topo database.

[a] OR and 95% CI estimated by unconditional logistic regression adjusted for age.

[b] One-sided p-values for the slope parameter in the quantitative analyses with the density of vines within 1,000 m.

[c] At least one plot identified by RPG, VV, or CLC with a crop different from viticulture.

[d] The presence of viticulture was considered "possible" if at least one vine plot was identified by CLC, but no vine plot was identified with RPG or VV.

[e] The presence of viticulture was considered "probable" if at least one vine plot was identified by RPG or VV.

[f] OR associated with a 10% increase in viticulture density within 1,000 m.

[g] OR associated with an increase equal to 10% of the maximum weighted density.

vines to the residence at diagnosis for the cases or at inclusion for the controls. We did not have the ability to access previous residences, particularly during the prenatal period or at birth, which may also have been relevant to childhood cancer risk.

Our study has major strengths. It was registry-based and, therefore, included all of the AL cases diagnosed during the period of 2006 to 2013 with virtually no risk of selection bias, and it included a large number of controls representative of the same-aged population during the same period. The large numbers enabled several analyses by main AL subgroup (AML, ALL, ALL molecular subtype, and age). Furthermore, the use of the 2007 and 2012 crop maps enabled definition of objective exposure indicators on a fine scale, thereby taking into account the changes in viticultural areas that may have occurred between 2007 and 2012. The availability of the gold standard source VV, although limited to the short period of 2010 to 2013, was also a strength of this study. The results of the sensitivity analysis based on this were fully consistent with those of the main analysis and suggested that the combination of RPG and CLC sources was able to provide good estimates of viticulture areas or at least to well describe the contrasts in viticulture density on a small scale.

In conclusion, we evidenced a slight increase in the risk of childhood ALL living in areas with higher viticulture density, with some heterogeneity between regions. This finding reinforces the hypothesis that pesticides used in viticulture may be associated with childhood AL, a hypothesis that we will investigate further using available databases of agricultural uses of pesticides.

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