Spatial analysis of hypospadias cases in northern France: Taking clinical data into account.

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Abstract

Background Strong evidence for a causal role of environmental factors in a congenital anomaly is still difficult to produce. The collection of statistical data is crucial for gaining a better understanding of the epidemiology and pathophysiology of these anomalies. We aimed to evaluate spatial variations in hypospadias in our region, taking into account of clinical data, and evaluate association to socio-economic and ecological data. **Methods** All boys with hypospadias born in northern France and seen in Lille University Medical Center (Lille, France) between 1999 and 2012 were included in the analysis. We retrospectively collected geographic data, clinical data (especially known confounding factors associated with an elevated risk of hypospadias), and demographic, socio-economic and ecological data. We analyzed the whole study population and then the subset of boys lacking confounding factors. **Results** The study sample of 975 cases of hypospadias was characterized by significant spatial heterogeneity ($p < 0.005$) and autocorrelation ($p < 0.001$). We detected two high-incidence clusters that differed with regard to their land use. After the exclusion of 221 patients with confounding factors, two high-incidence clusters with significant disease risks (1.65 and 1.75, respectively; $p < 0.001$) and a significant difference in land use ($p < 0.001$) again appeared. The first cluster contained a higher median [interquartile range] proportion of artificialized land (0.40 [0.22;0.47]) than the remaining “neutral areas” (0.19 [0.08;0.53]) did ($p < 0.001$). Conversely, the second cluster contained a higher median proportion of rural land (0.90 [0.78;0.96]) than the “neutral areas” (0.81 [0.47;0.92]) did ($p < 0.001$). The median deprivation index was significantly lower in the urban cluster (0.47 [0.42;0.55]) and significantly higher in the rural cluster (0.69 [0.56;0.73]) ($p < 0.001$). **Conclusions** Our results evidenced the heterogeneous spatial distribution of cases of hypospadias in northern France. We identified two clusters with different environmental and social patterns – even after the exclusion of known confounding factors.

1 Background

Hypospadias is one of the most frequent malformations of the genital organs in boys, with a prevalence of 18/10,000 births in Europe, and a significant variation from one country to another, and also over time; [1, 2] it appeared to rise in the 1970s and 1980s but has remained stable since then.[3]

The observation of familial or syndromic forms of hypospadias suggested the existence of genetic causal factors, such as subsequently characterized causal mutations.[4] However, known genetic causes are only found in about 10–30% of cases – leading researchers to suspect that hypospadias has a multifactorial etiology.[5–7] The suspected causal factors include iatrogenic factors (e.g. medications taken during pregnancy[8–10] or conception via assisted reproductive technologies (ART)[11, 12]) and environmental factors (e.g. fetal exposure to endocrine-disrupting chemicals or other chemical hazards). [13–17] Hence, the collection of statistical data on all the potential genetic and environmental causal factors is crucial for gaining a better understanding of the epidemiology and pathophysiology of hypospadias and, ultimately, for guiding public health measures capable of mitigating exogenous risk factors to the greatest extent possible.[18, 19] Given that many environmental factors are ubiquitous and

not easily measurable, strong evidence for a causal role in a congenital anomaly is still difficult to produce. To date, various methodologies have been used to gather scientific evidence.

Thanks to the ever-increasing amount of geographical information in administrative and medical databases and the simultaneous development of statistical tools and computational power, spatial analysis has emerged as a relevant, efficient tool for epidemiological research.[20–23] Spatial analysis has already been used to describe and evaluate spatial disparities in the occurrence of birth defects and to explore potential associations with environmental factors. Most of the literature studies in this field focused on congenital neural tube defects,[24] gastroschisis[25] or congenital heart defects.[26]

To the best of our knowledge, only seven studies have analyzed the spatial distribution of cases of hypospadias. The statistical methodology varies, and the results remain inconsistent, with spatial cluster detection in three studies, ecological pattern association in three studies (with three different definitions of rural/urban areas), and association to socio-economic status in one article.[16, 27–32] Most of the studies involving spatial analysis used massive administrative datasets from national registries; the latter did not contain much clinical information.

The aim of the present study was to (i) evaluate spatial variations in hypospadias incidence in northern France, (ii) evaluate potential associations between hypospadias and ecological variables, and (iii) compare spatial clusters of hypospadias from 1999 to 2012. The study was designed to take into account of medical information about possible confounding factors (such as a family history of hypospadias, syndromic presentation, medication during pregnancy, and professional exposure) that could potentially introduce bias into spatial analyses of hypospadias.

We conceived this study as a new way of consolidating previous findings on the association between hypospadias and environmental factors.

2 Methods

2.1 Study area and data sources

The former *Nord - Pas-de-Calais* region of northern France comprises around 4,100,000 inhabitants over 12,414 km² (326 inhabitants/km²). The region is distributed into 170 rural, industrial or urban *cantons* (a French local administrative unit). Lille University Medical Center (Lille, France) is the region's reference center for pediatric surgery; and all referred cases of hypospadias are seen and treated by a single pediatric urologist in our team. Furthermore, hypospadias consultations are organized in three different general hospitals across the region. Based on this surgical registry, we collected data about all consecutive cases of hypospadias between January 1999 and December 2012. All types of hypospadias were included - even those not requiring surgery. The study's data collection procedures were registered with and validated by our University Medical Center's Data Protection Officer (reference: DEC19-084).

All the data were retrospectively collected by manually reviewing each patient's health records:

- The zip code at birth was collected when the patient was born in Lille University Medical Center; otherwise the zip code noted during the first medical consultation was used. Patient were excluded if they had been adopted or had been born outside our region.
- The type of hypospadias was evaluated.
- We collected information about potential confounding factors (CFs) associated with a higher risk of hypospadias: family history of hypospadias,[4, 33] syndromic association, consanguinity, known genetic defect,[6] ART,[11, 12, 34] vegetarian diet,[35] and known exposure for endocrine disrupting chemicals. Based on the French reference center for teratogenic agents,[36] and data from the literature we also considered the following medication -taken during pregnancy- as associated with a higher risk of hypospadias: anti-epileptic such as valproate, gabapentin, clonazepam, primidone, topiramate,[8–10] diethylstilbestrol,[37] and thyroxine.[38]
- We also gathered information about the pregnancy, such as intrauterine growth retardation, preterm delivery, and multiple pregnancy.

As a reference, the number of male births in each *canton* during the study period was extracted from data provided by the French National Institute of Statistics and Economic Studies (*Institut National de la Statistique et des Etudes Economiques, INSEE*).

Land use data were obtained from the European CORINE Land Cover database.[39] The proportion of artificial surfaces (level 1) and rural areas were calculated for each *canton*. In the rural land use category, we also considered agricultural surfaces in more detail (level 2).

The French Ecological Deprivation Index (EDI) was computed for each *canton*.[40] This deprivation index is composed of 10 variables: overcrowding, no access to central or electric heating, non-homeowner, unemployment, foreign nationality, no access to a car, unskilled work/farm work, a household with more than 6 people, a low educational level, and a single-parent household. The higher the *canton's* EDI, the higher the level of deprivation. Socioeconomic data were extracted from the 2009 French national census (*INSEE*). Lastly, the EDI was considered in quartiles for ecological regression, as described in the “statistical analysis” section below.

Distance to the CWIP. Data from the French National Environmental Agency (*Agence de l'Environnement et de la Maîtrise de l'Energie*) were used to identify the region's waste incineration plants operating before and during the study period. The Euclidian distance (in km) between each *canton's* centroid and the CWIP was computed and considered in quartiles for the ecological regression.

2.2 Statistical analysis

Quantitative variables were described as the mean (standard deviation) when normally distributed or as the median [interquartile range (IQR)] if not. The normality of distribution was assessed using histograms, a normal probability plot, and the Shapiro-Wilk test. Qualitative variables were described as the frequency (percentage).

We used the Potthoff-Whittinghill test to test for the presence of spatial heterogeneity in the incidence of hypospadias between spatial units.[41] The presence of spatial autocorrelation among spatial units was quantified using Moran's index (with a value above 0 indicating the presence of autocorrelation) and probed using Moran's test.[42, 43]

The spatial distribution of hypospadias incidence was assessed by calculating the standardized incidence ratio (SIR). For each spatial unit, the SIR was defined as ratio between the observed number of cases and the expected number of cases. Given that the SIRs were unstable (due to low frequencies and spatial autocorrelation), the ratios were smoothed using the Bayesian Poisson regression model developed by Besag *et al.*[44]

Associations between the incidence of hypospadias and ecological variables (considered in quartiles) were assessed using an extension of the previous model, namely ecological regression (*i.e.* the inclusion of ecological covariates as fixed effects). For each covariate, the relative risk (RR) of hypospadias incidence and its 95% Bayesian credibility interval (BCI) were computed.

The detection of significant spatial clusters of a high hypospadias incidence was performed with isotonic spatial scan statistics based on a Poisson model.[22, 45] An isotonic regression function is used to model the potential cluster; the risk decreases as with distance from the cluster center to its boundaries increases, and the function takes a step down (isotonic levels) at several locations. The risk function is fitted with an isotonic regression, and no *a priori* assumptions about the number of steps are made. The significance of each detected cluster was been evaluated in 9,999 Monte-Carlo replications under the null hypothesis of the absence of clusters. The RR was calculated for each significant cluster and each isotonic level, and was interpreted as the risk of observing hypospadias inside the cluster, relative to the risk outside the cluster.

In order to compare clusters based on ecological data, the *cantons* were categorized by cluster (*i.e.* the *cantons* composing each identified cluster). A "neutral" group of cantons comprised those which do not fall inside a cluster. For the comparison of clusters on the basis of clinical data at the individual patient level, the same groups were considered but with regard to the patient's *canton* of residence.

Intergroup comparisons of quantitative variables were performed with a one-way ANOVA (if appropriate) or a non-parametric Kruskal-Wallis' test. Chi-square tests were used for qualitative variables. The Potthoff-Whittinghill test, Moran's test, SIR smoothing, ecological regressions, and comparisons were carried out using R software (version 3.4.3) and the latter's DCluster and R-INLA packages.[46] Maps were produced using QGIS software (version 2.18).[47] The threshold for statistical significance was set to $p < 0.05$.

We performed spatial analyses on two distinct layers. Layer #1 comprised the whole study population (*i.e.* all boys with hypospadias born within our region, excluding those born outside the region or who had been adopted). Layer #2 comprised the subset of boys with hypospadias and no known potential causal factors (or potential confounding factors) for hypospadias, which might otherwise have biased our

analysis of environmental factors The exclusion criteria for the layer #2 analysis was the presence of at least one CF as described in 2.1.

The clusters comparison is only described for the second layer in this article (for the first layer of the spatial analysis, see the Additional file 2).

3 Results

Of the 983 patients seen in our hospital between January 1999 and December 2012, 8 were excluded for geographical reasons (1 adopted patient, 3 patients born in another region of France, 3 born outside France, and 1 seen at the age of 11 years after referral from another hospital, and for whom zip code at birth was not available) (Figure 1). The incidence of hypospadias over the 13-year period was 25.4/10,000 male births, and mean annual incidence was 17.67/10,000 male births. Of the 975 included patients, 548 (56.2%) had anterior hypospadias, 319 (32.7%) had middle hypospadias, and 108 (11.1%) had posterior hypospadias. Other data on clinical presentations are summarized in Table 1. We found 221 patients with at least one CF typically associated with a greater risk of hypospadias (as described in section 5.2). These 221 patients were included in layer #1 of our analysis but excluded from layer #2 (Figure 1).

The age-smoothed SIR ranged from 0.2 (95% BCI 0.04, 0.55) to 2.4 (95% BCI 1.29, 3.84) over all cases (layer #1), and from 0.2 (95% BCI 0.04, 0.67) to 2.2 (95% BCI 0.97, 4.15) after exclusion of 221 cases with potential CFs (layer#2) (Figure 2). In both layer #1 and #2, a Potthoff-Whittinghill test confirmed the spatial variation over the region in the incidence of hypospadias ($p=0.005$ and 0.008 , respectively), and Moran's test confirmed the spatial correlation (Moran's index = 0.34 , $p<0.001$ and 0.26 , $p<0.001$, respectively).

The associations between the hypospadias risk and the ecological variables (the French EDI, the proportion of artificialized surface area, the proportion of rural surface area, the proportion of agricultural surface area, and the CWIP) were tested in an ecological regression as shown in the additional figures [see Additional file 1]. None of the associations were statistically significant.

A spatial scan statistic detected two significant isotonic clusters of hypospadias incidence in layer #1 (RR 1.79 and 1.65, $p<0.001$) and again in layer #2 (RR 1.65 and 1.75, $p<0.001$) (Table 2, Figure 2). The clusters characteristics are here described as determined in layer #2 (*i.e.* after the exclusion of 221 cases with potential CFs). For the cluster characteristics of the first spatial analysis see Additional tables [see Additional file 2].

The most significant Cluster (#1, "*North-West*") comprised 24 *cantons* and a total of 37,368 inhabitants, and had an RR of hypospadias of 1.75 ($p<0.0001$). The second cluster (#2, "*Center-East*") comprised 19 *cantons* and a total of 37,369 inhabitants, and had an RR of hypospadias of 1.65 ($p<0.0001$) (Table 2). It

should be kept in mind that the clusters were numbered here in decreasing order of statistical significance; hence, Cluster #1 (*North-West*) determined in layer #2 corresponds to Cluster #2 (*North-West*) determined in layer #1 (Figure 2).

We also compared clusters with regard to ecological variables and found significant differences for each variable ($p \leq 0.001$) (Table 3). Cluster #1 (*North-West*) had high proportion of rural surface area (0.90 [0.78; 0.96]), and a high proportion of agricultural surface area (0.85 [0.66, 0.92]), relative to the neutral *cantons* (0.83 [0.52, 0.93] and 0.56 [0.23, 0.70], respectively) and Cluster #2 (*Center-East*) (0.47 [0.36, 0.62] and 0.47 [0.34, 0.54] respectively). In contrast, Cluster #2 (*Center-East*) had a higher proportion of artificialized surface area (0.53 [0.38, 0.64]) and a higher French EDI (*i.e.* greater deprivation) (0.69 [0.56, 0.73]) than the neutral *cantons* (0.17 [0.07, 0.48] and 0.52 [0.44, 0.65] respectively) and Cluster #1 (*North-West*) (0.10 [0.04, 0.22] and 0.47 [0.42, 0.55] respectively) ($p < 0.001$) did. Lastly, we found a lower distance to the CWIP in Cluster #2 (*Center-East*) (4.92 [2.85, 9.62]).

With regard to clinical data, we found a significant difference in the preterm rate: the value was 12.2% in neutral *cantons*, 3.42% in Cluster #1 (*North-West*), and 8.93% in Cluster #2 (*Center-East*) ($p = 0.016$) (Table 4).

4 Discussion

Our results revealed significant spatial heterogeneity in the incidence of hypospadias in a region of northern France during the period from 1999 to 2012. We identified two spatial clusters. These results are consistent with previous research performed in northern England, North Carolina, and Nova Scotia.[27–29] When comparing the detected spatial clusters, we found a significant difference in their socio-ecological pattern. Lastly, these findings remained significant after exclusion of patients with a known potential confounding factor (*i.e.* potential bias for spatial analysis).

Strengths of the study. Because most of the spatial analysis studies are based on massive administrative datasets, they usually lack clinical information, especially specific information related to the disease of interest such as – in our situation – familial history of hypospadias. In our work, we took into account of clinical information about potential confounding factors associated with a higher risk of hypospadias, and we performed a systematic approach for spatial analysis.

Furthermore, the registry included all types of hypospadias - even minor types not requiring surgery (not listed in hospital episodes statistics) and those diagnosed after the child had left the maternity unit (not listed in maternity based birth defect monitoring system).

The geographical unit is an important parameter in spatial analysis. We used a French local administrative unit called a *canton* (170 *cantons* over 12,414 km²); this is quite small, relative to the literature studies. Other studies have used larger geographical units, such as the location of the referring hospital (159 hospitals across six South American countries),[32] the county (18 Canadian counties over

55,284 km²),[27] and the region (four Chinese regions over 9,500,000 km²),[30] which limits the ability to interpret environmental factors.

Limitations of the data. In the absence of a French national registry of hypospadias cases, we chose to perform a single-center registry study based on a single referral surgeon for hypospadias in our region's university hospital. However, the fact that surgeon also consulted in three general hospitals across the region broadened our study's coverage.

Our data showed that 975 cases of hypospadias were observed among the 393,341 male newborns recorded over the 13-year study period. Thus, the calculated prevalence and annual incidence rate were 24/10,000 male births, and 17.67/10,000 male births, respective. According to the literature, the estimated overall prevalence of hypospadias is around 18.61/10,000 total births (i.e. male and female births) in Europe and 15.41/10,000 total births (i.e. male and female births) in France.[2] These values suggest that we might have underestimated the regional prevalence of hypospadias; some patients might have been seen by a urologist in a general hospital elsewhere in the region. However, the breakdown in the types of hypospadias was in line with the literature data.[48]

With regard to the statistical methodology, we chose to study high-incidence areas only because our objective was to find ecological factors associated with a higher risk of hypospadias. In principle, missing patients could produce "false positive" low-incidence areas or "false negative" high-incidence areas. Hence, the analysis of high-risk area is less biased by missing patients than the analysis of low-risk areas. Unfortunately, missing patients will inevitably constitute a source of bias in spatial analysis unless the data come from a truly exhaustive registry in a geographically isolated region.

With regard to geographical data, we used the zip code at the time of delivery or at the time of the first consultation in our hospital (usually within 12 months of birth for patients with hypospadias) (Table 1). Ideally, we would have analyzed the mother's zip code before pregnancy and during the first trimester of pregnancy; however, this information was not available retrospectively. Miller *et al.* recently evaluated birth defects and residential mobility during pregnancy in the USA. They found that 22% of pregnant women moved during pregnancy, and that 51% of these women moved within the same county. There was no difference in residential mobility between mothers of children with a birth defect and control mothers.[49] In their review of mobility during pregnancy, Bell *et al.* reported that pregnant women typically moved a short distance only (less than 10 km), which would tend not to greatly change their environmental exposure.[50]

Interpretation. Our results evidenced spatial heterogeneity, spatial autocorrelation, and presence of spatial clusters of hypospadias incidence that remained statistically significant after the exclusion of cases with potential confounding factors. This result reinforces the conclusions of previous spatial analyses of hypospadias - none of which took account of potential confounding factors.[27–29, 32]

In 2007, Abdullah *et al.* reported on significant spatial clustering among 577 cases of hypospadias in northern England (based on hospital episode statistics).[29] Using data from a birth defect monitoring

program, Winston *et al.* showed significant spatial clustering among 995 cases of hypospadias in North Carolina; the researchers took account of data on maternal age, maternal race/ethnicity, maternal educational level, smoking status, parity, and diabetes but not the family history and other potential confounding factors.[28] Recently, Lane *et al.* published a comparison of the spatial distribution of four different congenital anomalies, of which two were endocrine-mediated (hypospadias and cryptorchidism) and two were not (clubfoot and gastroschisis). Lane *et al.* detected significant spatial autocorrelation and clustering for hypospadias and cryptorchidism congenital anomalies but none for clubfoot and gastroschisis.[27]

Our comparisons of spatial cluster with regard to ecological variables revealed significant differences between high-incidence *cantons* and neutral *cantons*. The first spatial cluster was characterized by a rural land use pattern, with a higher proportion of rural (and agricultural) land cover, and a lower deprivation index than neutral *cantons* (*i.e.* less deprived). The second cluster had a more urban and industrial pattern, with higher proportion of artificialized land cover and a higher deprivation index (*i.e.* more deprived) than neutral *cantons*. It should be noted that the region's main city (Lille, where our university hospital) fell outside this "urban" cluster.

Abdullah *et al.* showed an association between hypospadias and a lower deprivation index but not with the UK wards' urban/rural status.[29] In their study of North Carolina, Winston *et al.* found a high-risk area with > 5% crop cover.[28] Lane *et al.* also mentioned that their hotspots in Canada were associated with intense agricultural activity but did not underpin this comment with statistical results.[27] In China, Li *et al.* assessed 3,426 cases of hypospadias recorded in a hospital-based birth defect monitoring system. The researchers found that the prevalence rate was higher in urban areas than in rural areas but that it was increasing more rapidly in rural areas. However, Li *et al.* did not specify how each area had been classified as either rural or urban.[30]

In the present study, there were few differences between the spatial clusters with regard to clinical data. The proportion of preterm births was lower for hypospadias cases from the "rural" cluster (*North-West*) than for cases in the "urban" and most deprived cluster (*Center-East*) and the neutral *cantons*.

5 Conclusions

Our results revealed significant spatial clustering in the incidence of hypospadias across our region – even after the exclusion of potential confounding factors – and thus strengthen the findings of previous spatial analyses of this disease. The two identified spatial clusters had significantly different ecological patterns. Our results thus emphasize the complexity of the link between environmental exposure and the incidence of hypospadias; one cannot simply hypothesize that the highest risk occurs in rural areas because of exposure to pesticides.

Our spatial analysis was intended to generate additional medical data on environmental factors and hypospadias. We also think that spatial analysis and spatial cluster identification could be better used to

guide local and regional health policies and to design guide further observational epidemiological studies on the individual patient level.

Abbreviations

CWIP: closest waste incineration plant; EDI: European deprivation index; INSEE: *Institut national de la statistique et des études économiques*; IUGR: intrauterine growth retardation; SIR: standardized incidence ratio ;

Declarations

Ethics approval and consent to participate

Our work fitted a standard methodology (MR004) as defined by the french *Comité National Informatique et Liberté* (CNIL), and the study's data collection procedures were registered with and validated by our University Medical Center's Data Protection Officer (reference: DEC19-084). Since our work was non-interventional and retrospective, no further specific ethics approval was needed.

Consent for publication

Not applicable

Availability of data and materials

The medical datasets analyzed during the current study are not publicly available due to the sensitiveness of geo-spatial information on each clinical cases, but are available from the corresponding author on reasonable request.

National datasets are available on request:

CORINE Land Cover: <https://www.data.gouv.fr/>

Institut National de la Statistique et des Études Économiques : <https://www.insee.fr>

Agence de l'environnement et de la Maîtrise de l'Énergie : <https://www.ademe.fr>

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ALDP: Conceptualization, methodology, investigation, data curation, writing - original draft, writing - review & editing, supervision

MG: Conceptualization, methodology, validation, formal analysis, data curation, writing - review & editing, visualization

FO: Conceptualization, methodology, formal analysis, data curation, visualization

RHP: Validation, writing - review & editing

RB: Conceptualization, resources, validation, writing - review & editing

CL: Conceptualization, methodology, validation, writing - review & editing

DS: Conceptualization, methodology, writing - review & editing, supervision, project administration

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Tables

Table 1. Clinical data of all 975 cases included in the spatial analysis. Overall, and stratified on hypospadias form.

	Overall	Anterior	Middle	Posterior
n	975	548	319	108
Type (%)				
Anterior	548 (56.2)	-	-	-
Middle	319 (32.7)	-	-	-
Posterior	108 (11.1)	-	-	-
Chordee (%)				
Normal	555 (56.9)	421 (76.8)	127 (39.8)	7 (6.5)
<45°	202 (20.7)	77 (14.1)	105 (32.9)	20 (18.5)
>45°	212 (21.7)	49 (8.9)	84 (26.3)	79 (73.1)
NA	6 (0.6)	1 (0.2)	3 (0.9)	2 (1.9)
Hormone treatment (%)				
No treatment	902 (92.5)	537 (98.0)	303 (95.0)	62 (57.4)
Treatment	64 (6.6)	6 (1.1)	13 (4.1)	45 (41.7)
NA	9 (0.9)	5 (0.9)	3 (0.9)	1 (0.9)
Family history (%)				
None	848 (87.0)	488 (89.1)	270 (84.6)	90 (83.3)
1 st degree relative	79 (8.1)	39 (7.1)	26 (8.2)	14 (13.0)
2 nd degree relative	29 (3.0)	13 (2.4)	13 (4.1)	3 (2.8)
3 rd degree relative	19 (1.9)	8 (1.5)	10 (3.1)	1 (0.9)
IUGR (%)	93 (9.5)	33 (6.0)	18 (5.6)	42 (38.9)
Term of delivery (%)				
Term delivery	860 (88.2)	502 (91.6)	295 (92.5)	63 (58.3)
Preterm delivery	113 (11.6)	45 (8.2)	23 (7.2)	45 (41.7)
NA	2 (0.2)	1 (0.2)	1 (0.3)	0 (0.0)
Multiple pregnancy (%)				
Singleton	927 (95.1)	522 (95.3)	308 (96.6)	97 (89.8)
Twins	47 (4.8)	25 (4.6)	11 (3.4)	11 (10.2)
Triplets	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)
Age at 1 st consultation (months) Median [IQR]	9.48 [4.52;18.69]	11.67 [5.30;23.54]	8.43 [3.98;16.39]	6.64 [3.88;12.47]

IQR: interquartile range. IUGR: intrauterine growth retardation. NA: information not available.

Table 2. Isotonic Cluster characteristics, after exclusion of patients with potential confounding factors

Cluster	p	Cluster RR	Population	Isotonic level	Radius (km)	Number of <i>cantons</i>	Cases	Expected	RR for each level
1	<0.0001	1.75	37 368	1	14.8	7	41	15.52	2.83
				2	19.2	3	9	6.3	1.53
				3	28.9	14	67	49.81	1.44
2	<0.0001	1.65	37 369	1	2.4	2	13	5.39	2.55
				2	6.2	4	37	15.95	2.45
				3	8.3	4	24	19.70	1.29
				4	12.6	9	38	33.99	1.18

RR: relative risk; Expected: expected number of cases

Table 3. Comparison of cantons with regard to ecological data, as a function of presence/absence in each identified high-incidence cluster and after the exclusion of patients with a known potential confounding factor.

	Neutral <i>cantons</i> N=127	Cluster #1 (<i>North-West</i>) N=24	Cluster #2 (<i>Center-East</i>) N=19	p
French EDI	0.52 [0.44;0.65]	0.47 [0.42;0.55]	0.69 [0.56;0.73]	0.001
Percentage of artificialized area	0.17 [0.07;0.48]	0.10 [0.04;0.22]	0.53 [0.38;0.64]	<0.001
Percentage of rural area	0.83 [0.52;0.93]	0.90 [0.78;0.96]	0.47 [0.36;0.62]	<0.001
Percentage of agricultural area	0.56 [0.23;0.70]	0.85 [0.66;0.92]	0.47 [0.34;0.54]	<0.001
Distance to CWIP (km)	14.4 [7.92;23.6]	12.8 [8.55;16.3]	4.92 [2.85;9.62]	<0.001

Note: CWIP = closest waste incineration plant, EDI = Ecological Deprivation Index. Statistical comparisons were performed using the Kruskal Wallis test. All results are quoted as the median [IQR]

Table 4. Comparison of cantons with regard to clinical data, as a function of presence/absence in each identified high-incidence cluster and after the exclusion of patients with a known potential confounding factor.

	Neutral cantons	Cluster #1 North-West	Cluster #2 Center-East	p
	N=525	N=117	N=112	
Clinical presentation				
Form, N (%):				0.406
Anterior	299 (57.0%)	74 (63.2%)	67 (59.8%)	
Middle	166 (31.6%)	35 (29.9%)	37 (33.0%)	
Posterior	60 (11.4%)	8 (6.84%)	8 (7.14%)	
Chordee, N (%):				0.513
None	299 (57.4%)	66 (56.4%)	74 (66.1%)	
<45°	111 (21.3%)	24 (20.5%)	19 (17.0%)	
>45°	111 (21.3%)	27 (23.1%)	19 (17.0%)	
Pregnancy				
IUGR, N (%):				0.452
No	475 (90.5%)	110 (94.0%)	103 (92.0%)	
Yes	50 (9.52%)	7 (5.98%)	9 (8.04%)	
Preterm delivery, N (%):				0.016
No	460 (87.8%)	113 (96.6%)	102 (91.1%)	
Yes	64 (12.2%)	4 (3.42%)	10 (8.93%)	
Multiple pregnancy, N (%):				0.892
No	510 (97.1%)	114 (97.4%)	108 (96.4%)	
Yes	15 (2.86%)	3 (2.56%)	4 (3.57%)	
Medical consultation				
Age at 1 st medical consultation (months) , median [IQR]	10.0 [4.75;20.0]	9.00 [4.00;21.0]	6.00 [3.00;17.0]	0.051
Follow-up (months), median [IQR]	29.0 [20.0;60.5]	29.0 [20.0;63.0]	29.0 [19.0;57.0]	0.75

Note: IUGR = intrauterine growth retardation. Statistical comparisons were performed using the Kruskal Wallis test for quantitative variables and the chi-squared test for qualitative variables.

Figures

Figure 1

Flow chart for spatial analysis.

Figure 2

Spatial distribution of age-smoothed Standardized Incidence Ratios (SIR) for hypospadias (1999-2012) in each canton (A) and isotonic spatial cluster detection (B), for all cases (#1), and after the exclusion of 221 cases with potential confounding factors (#2). NB: The spatial clusters are numbered in order of statistical significance.

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