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## Congenital and acquired hypothyroidism: Temporal and spatial trends in France from 2014 to 2019

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### ABSTRACT

**Purpose:** To assess the incidence of congenital hypothyroidism (CH) and acquired hypothyroidism (AH) between 2014 and 2019 in continental France.

**Methods:** New cases of CH and AH were identified using the French National Health Data System (*Système Nationale des Données de Santé*, SNDS). Temporal trends were studied using linear regression models. Spatial distributions were studied using Moran's global index (I) and the statistical method and local indicators of spatial association.

**Results:** The incidence of permanent CH in females increased by 8.9 % per year (2014: 36.9 [31.1–43.7] per 100,000 birth-years vs. 2019: 51 [43.9–59.3] per 100,000 birth-years,  $p < 0.01$ ). The incidence of AH decreased between 2014 and 2019 for both females (2014: 535.7 [533.2–538.2] per 100,000 person-years vs 2019: 335.5 [333.6–337.4] per 100,000 person-years,  $p < 0.01$ ) and males (2014: 197.5 [195.9–199] per 100,000 person-years vs 2019: 141.7 [140.4–142.9] per 100,000 person-years,  $p < 0.01$ ). The incidence of hypothyroidism was high in the Nord-Pas-De-Calais and Lorraine regions (CH and AH).

**Conclusions:** The incidence of permanent CH in females has increased over time. AH incidence decreased. It seems necessary to investigate environmental factors in the disparity of incidence distribution.

### Introduction

Hypothyroidism is among the most common of endocrine disorders and has major public health implications. However, data describing the epidemiology of hypothyroidism in France and its progression over time

are lacking.

Thyroid hormones are essential for the regulation of metabolic processes and neurodevelopment [1,2]. Subtle variations in thyroid function can affect glucose and lipid homeostasis, increasing the risk of atheromatosis and metabolic syndrome [3–5]. In adults,

**Abbreviations:** AH, acquired hypothyroidism, defined as primary (not central) non-iatrogenic and non-congenital hypothyroidism; ATC classification, Anatomical Therapeutic Chemical (ATC) Classification System; CH, congenital primary (not central) hypothyroidism; F4L, Free thyroxine; GIS, Gland-in-situ; HH, "hot spots", high values amongst high values; INSEE, French National Institute of Statistics and Economic Studies; LISA, local indicators of spatial association; LL, "cold spots", low values amongst low values; PCB, polychlorinated biphenyls; PFAAs, perfluorinated-alkyl-acids; PM<sub>2.5</sub>, particulate matter with a diameter of 2.5 μm or less; PM<sub>10</sub>, particulate matter with a diameter of 10 μm or less; SNDS, Système Nationale des Données de Santé, the French National Health Data System; SU.VI.MAX study, SUpplementation in Vitamines and Anti-oxidant Minerals study; TSH, thyroid-stimulating hormone.

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hypothyroidism is linked to atherosclerosis, coronary heart disease, anemia and Parkinson's disease [6–9]. Congenital primary (not central) hypothyroidism (CH) in children leads to neurodevelopmental disorders, such as reduced IQ, due to the crucial role played by thyroid hormones in neuronal development, cretinism due to iodine deficiency being a historical example [10]. This has led to systematic screening for this disease in France since 1979.

Several explanations for CH are being explored. Around two-thirds of CH can be attributed to thyroid dysgenesis or agenesis, with genetic abnormalities identified in only 5 % of cases [11]. The other forms are CH with gland-in-situ (GIS), and may be permanent or transient. Permanent causes include hormone synthesis disorders and iodide organification abnormalities, with a genetic origin in 50 % of cases. Transient CH, accounting for half of CH GIS, may be due to iodine overload or deficiency, maternal antibodies, maternal treatment for Graves' disease, and some genetic abnormalities. Being female is also a risk factor CH [12,13].

In adults in France, the main cause of acquired hypothyroidism (AH), defined as primary (not central) non-iatrogenic and non-congenital, is Hashimoto's thyroiditis, an autoimmune disease, iodine deficiency being rare. Risk factors for Hashimoto's include genetic susceptibility, excessive iodine intake, stress, sexual dimorphism (more common in women), low selenium intake and certain viral infections [14]. No study has yet jointly examined CH and AH, whose causes are not all known, leaving open the question of the possible influence of common environmental factors, such as endocrine disruptors.

For adults, the latest published data for France dates back to the SU.VI.MAX study (SUPplementation in Vitamines and Anti-oxidant Minerals) carried out between 1994 and 2002 [15]. SU.VI.MAX was a randomized controlled study in which a cohort was created ( $n = 5166$ ) to retrospectively estimate the incidence of thyroid diseases. Free thyroxine (F4L) and thyroid-stimulating hormone (TSH) measurements were taken at inclusion and during the follow-up. The annual incidence rate of biological hypothyroidism was estimated to be 310 and 20 cases per 1000 person-years for females and males, respectively. Geographical distribution did not appear to be uniform across France.

All newborns in France are screened for CH on the basis of TSH determinations. The national newborn screening program is conducted at a regional scale by regional newborn screening centers. Descriptive multicenter studies have been carried out over periods ranging from 1982 to 2012 [16,17]. The overall incidence rate was 33.0 cases per 100,000 birth-years for 2002–2012, with a mean annual increase in the incidence of 7.7 % ( $p < 0.0001$ ) observed for GIS CH [16]. Here too, geographical distribution does not appear to be uniform across France [16].

The aim of this study was to describe the spatial and temporal trends in the incidence of CH and AH, defined as primary (not central) non-iatrogenic and non-congenital hypothyroidism, between 2014 and 2019. Data from the French National Health Data System (*Système Nationale des Données de Santé*, SNDS) were used.

## Methods

### Data source

The French National Health Data System (*Système National des Données de Santé*, SNDS) aggregates various healthcare-related databases, including reimbursement data for hospital and ambulatory services, as well as data concerning causes of death [18,19]. This system is the primary source of data concerning healthcare expenditures, as it records all health insurance claims for each individual. This comprehensive database includes patient-specific information, such as age, sex, place of residence, chronic diseases, date of birth and date of death. The database also contains information on drug reimbursements. It allows the identification of individuals based on their city of residence at the time of delivery. SNDS data is considered to cover the entire French

population from 2013 onwards [19,20]. Data beyond 2020 were considered incomplete at the time of the study. This study only covered continental France.

### Study population and outcome

Individuals with primary hypothyroidism were identified using SNDS data from 2014 to 2019 based on published and validated algorithms from the French Health Insurance [21]. This algorithm is based on thyroid hormone drug deliveries with ATC classification H03AA01 (levothyroxine sodium), H03AA02 (liothyronine sodium), or H03AA03 (combinations of levothyroxine and liothyronine) (inclusion criteria), hydrocortisone delivery, and a history of thyroidectomy or radioactive iodine delivery to identify specific thyroid disease groups (exclusion criteria) (Fig. S1). Three groups were studied according to patient age and the nature of delivery: permanent CH, transient CH, and AH. Cases of CH were defined as any delivery of thyroid hormones in the first three months of life. Transient CH was defined as CH without the delivery of thyroid hormones within six months of death or before 12/31/2020.

The reference population consisted of the entire French population of the year in question between 2014 and 2019 using open access data from the French National Institute of Statistics and Economic Studies (INSEE).

### Data analysis

The incidence of CH and AH were estimated for the entire French territory as well as for various geographical entities (administrative regions and non-administrative subdivisions) to examine potential geographical disparities and identify potential clusters. Because of the very low incidence of CH relative to the number of births (approximately 700,000 per year), regions (21 administrative geographical areas) were chosen as the geographical unit for CH [22]. For AH, a finer geographical scale was chosen. French cities were not used as geographical units because most (2013: 54 % and 2022: 52.5 %) had fewer than 500 inhabitants [23,24]. Instead, we chose population basins as the geographical unit because it refers to the smallest area in which inhabitants have access to the most common facilities and services [25]. A population basin is an intermediate geographic unit based on cities and defined on the basis of population indicators, not administrative or electoral boundaries (1659 in continental France). In 2022, the mean number of inhabitants for the least populated population basins, i.e., rural areas, was 14,980. The national mean of inhabitants by population basin was 39,495. The number of cases per city was extracted from the SNDS secure space using SAS Enterprise Guide 8.3 and R 4.3.1. The DEMEX\_CIB\_MEDICAMENT.sas program, created by the French national health insurance fund, was used. Incidence calculations and spatio-temporal analyses were performed outside the SNDS using R 4.3.1. Maps were generated using QGIS 3.32.2.

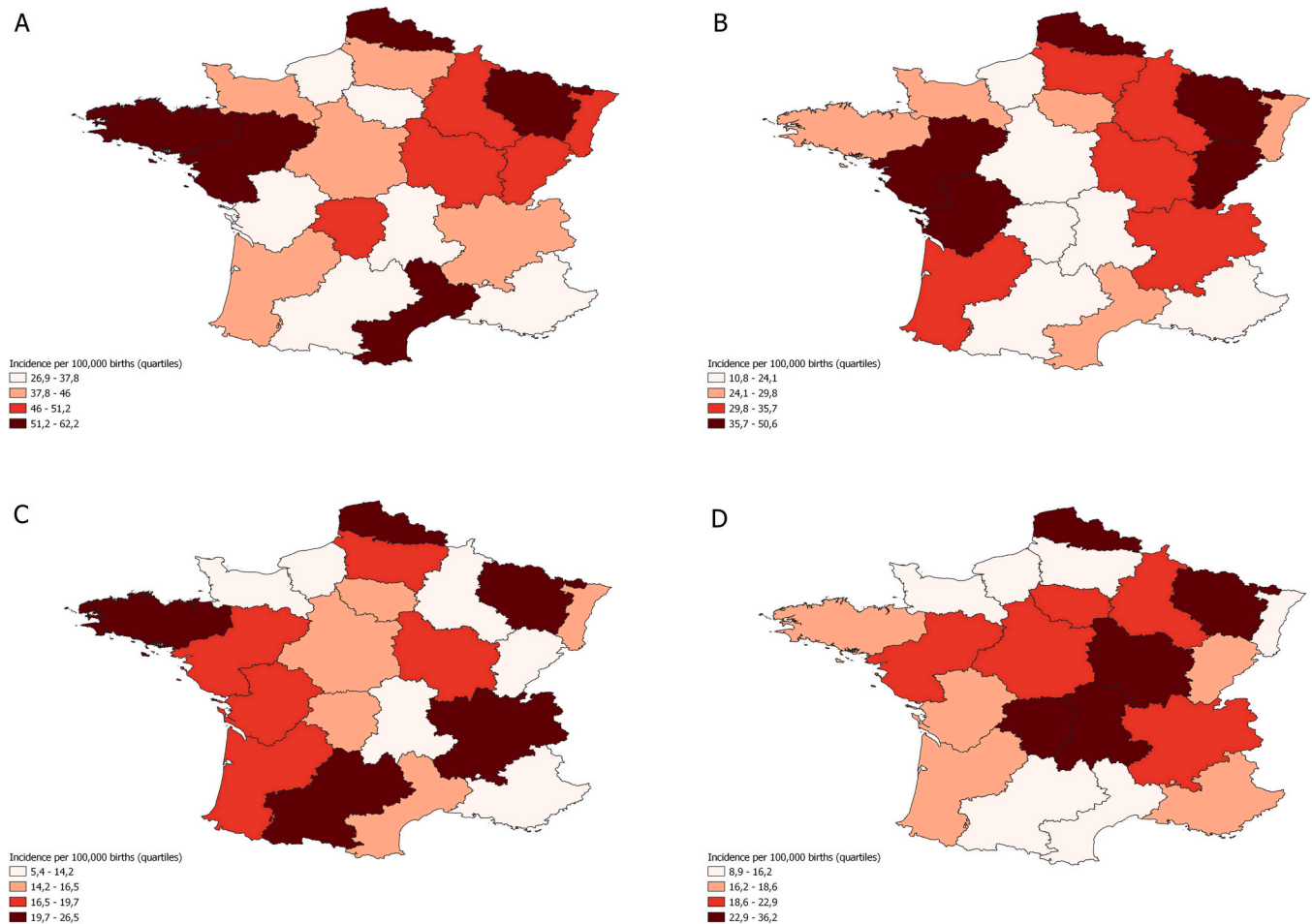
Using INSEE open-access data as a reference, we calculated age-standardized incidence rates for AH and CH as a whole, as well as by age category. January 1, 2014, was defined as the baseline time point at which we considered a case to be an incident, bearing in mind that we studied drug deliveries in 2013 to ensure that they were not false incidents). December 31, 2019 was defined as the date of the end of follow-up because census data were available and geographically projectable to 2019 at the time of the study. The incidence was then expressed as the number of cases per 100,000 person-years. The temporal analysis was carried out using a linear regression model. The conditions of validity for the linear regression of each model were investigated by checking the independence of model residuals (Durbin-Watson test), the normality of the distribution of residuals (Shapiro-Wilk test), and the homogeneity of residual variances (Breusch-Pagan test). We considered  $P$  values  $< 0.05$  in two-tailed tests to be statistically significant for all models.

For the spatial analysis, the spatial distribution and autocorrelation of AH were determined using the *spdep* [26,27] and *sf* [28] packages.

**Table 1**

Incidence of transient or permanent CH in France by sex on 2014–2019 and temporal trend (per 100,000 birth-years).

Sex	Type	2014	2015	2016	2017	2018	2019	$\beta$	<i>p</i>
Females	Permanent	36.9 [31.1 –43.7]	35.5 [29.8 –42.3]	43.8 [37.3 –51.3]	45.2 [38.6 –52.9]	49.7 [42.7 –57.8]	51 [43.9 –59.3]	<b>3.27</b>	<b>&lt; 0.01</b>
	Transient	17.9 [14 –22.9]	18.4 [14.4 –23.5]	19.7 [15.5 –25]	19.5 [15.3 –24.8]	20.1 [15.8 –25.5]	12.4 [9.1 –16.9]	–0.65	0.40
Males	Permanent	28.5 [23.6 –34.4]	24.3 [19.8 –29.9]	27.2 [22.3 –33.1]	29.6 [24.5 –35.9]	28.1 [23 –34.2]	38.3 [32.3 –45.4]	1.80	0.11
	Transient	18.4 [14.5 –23.3]	21 [16.7 –26.2]	23 [18.5 –28.5]	23.2 [18.6 –28.8]	17.2 [13.3 –22.1]	14.6 [11.1 –19.3]	–0.86	0.35

CH: congenital hypothyroidism.  $\beta$ : regression coefficient in a linear regression model. Bold indicates statistically significant time trends ( $p < 0.05$ ).**Fig. 1.** Spatial distribution of the mean incidence of CH in France over 2014–2019 (per 100,000 birth-year). CH: congenital hypothyroidism. From left to right and bottom to top, A: Permanent congenital hypothyroidism in females, B: Permanent congenital hypothyroidism in males, C: Transient congenital hypothyroidism in females, D: Transient congenital hypothyroidism in males. Values are the mean incidences over the whole period 2014–2019 for the region considered.

Spatial autocorrelation was studied using Moran's global index ( $I$ ), a widely recognized measure that evaluates the degree of spatial clustering of a variable, by calculating a global average of the similarity between neighbouring observations over the entire study area. The statistical method and local indicators of spatial association (LISA) were then used to identify and visualize clusters and spatial outliers, providing a more detailed understanding of the spatial patterns present in the data. Here, we used the LISA most commonly used in scientific studies: the local Moran's  $I$ . The significance of these indicators was tested. A queen-like  $W$  adjacency matrix was used for both analyses, and neighboring population basins were considered to share boundaries and nodes.

The  $I$  index varies from  $-1$  to  $1$ , where  $1$  indicates a direct correlation,  $0$  indicates random variation, and  $-1$  indicates an inverse correlation. Two types of clusters, with high or low incidence values unexplained by random variation (cut-off: median of the year), can be identified on the LISA map: "hot spots" (high values amongst high values, HH) and "cold

spots" (low values amongst low values, LL).

#### Data availability and ethics statement

The data generated in this study are not publicly available. Research teams at Amiens-Picardie University Hospital have permanent regulatory access to data in the SNDS. This permanent access is given in accordance to French Decree no. 2021–848 of June 29, 2021 related to the processing of personal data known as the "National Health Data System" [29]. All data were deidentified. Thus, informed consent was not necessary.

#### Results

##### Congenital hypothyroidism

Among females, the incidence of permanent CH in 2014 was 36.9

**Table 2**  
Mean incidence of CH in France by sex region over the period 2014–2019 (per 100,000 birth-years).

Region	Females		Males	
	Permanent CH	Transient CH	Permanent CH	Transient CH
Alsace	51.2 [35.4–73.7]	16.5 [8.4–31.5]	29.7 [18.4–47.3]	14.1 [6.9–27.8]
Aquitaine	45.6 [33.6–61.9]	18.7 [11.4–30.2]	31.6 [22–45.2]	17.8 [10.9–28.7]
Auvergne	26.9 [13.7–51.3]	5.4 [0.9–21.7]	23.1 [11.3–45.6]	23.1 [11.3–45.6]
Basse-Normandie	46 [28.5–73.3]	9.7 [3.1–26.6]	27.8 [15.1–50.1]	16.2 [7.1–35]
Bourgogne	46.1 [29.3–71.7]	19.7 [9.6–38.8]	35.7 [21.5–58.5]	35.7 [21.5–58.5]
Bretagne	53.3 [40.1–70.6]	24 [15.6–36.7]	29.8 [20.4–43.1]	16.9 [10.2–27.6]
Centre	39.1 [27–56.2]	16.4 [9.1–28.8]	24.1 [15.1–38]	22.9 [14.2–36.5]
Champagne-Ardenne	48.9 [30.7–77]	7.3 [1.9–23.4]	35.2 [20.5–59.6]	18.8 [8.7–38.6]
Franche-Comté	49.2 [30.1–79.4]	13.7 [5–33.9]	41.6 [24.6–69.2]	18.2 [8–39.3]
Haute-Normandie	33.5 [21.3–52.1]	9.6 [3.9–21.9]	10.8 [4.7–23.2]	15.4 [7.8–29.3]
Ile-de-France	37.6 [32.6–43.4]	16.5 [13.3–20.5]	25.6 [21.6–30.3]	19.3 [15.9–23.5]
Languedoc-Roussillon	51.8 [38.1–70.1]	15.3 [8.5–26.9]	25.8 [16.7–39.3]	13.4 [7.3–24.2]
Limousin	49.4 [24.1–97.5]	16.5 [4.3–52.5]	20.7 [6.6–56.9]	36.2 [15.9–78.2]
Lorraine	60.4 [43.9–82.8]	26.5 [16.2–42.8]	37.5 [25.2–55.4]	32 [20.7–48.8]
Midi-Pyrénées	37.8 [26.6–53.5]	24.5 [15.7–37.7]	11.7 [6.1–21.6]	14.9 [8.5–25.6]
Nord-Pas-de-Calais	62.2 [50.4–76.8]	20.5 [14.1–29.7]	50.6 [40.3–63.5]	24.7 [17.7–34.2]
Pays de la Loire	52.5 [40.7–67.6]	17.5 [11.1–27.3]	41.3 [31.1–54.5]	21.4 [14.4–31.6]
Picardie	40.3 [26.9–60]	18.6 [10.1–33.5]	33.9 [22–51.8]	8.9 [3.6–20.3]
Poitou-Charentes	37.4 [22.8–60.3]	18.7 [9.1–36.9]	38.4 [23.8–61.1]	18.2 [8.9–35.9]
Provence-Alpes-Côte d'Azur	35.6 [27.4–46.1]	14.2 [9.3–21.5]	20.3 [14.4–28.4]	18.6 [13–26.4]
Rhône-Alpes	39.1 [31.7–48.3]	24.9 [19.1–32.5]	29.9 [23.6–37.8]	19.7 [14.7–26.3]

CH: congenital hypothyroidism.

[31.1–43.7] per 100,000 birth-years versus 51 [43.9–59.3] per 100,000 birth-years in 2019. The increasing trend over time was significant ( $p < 0.01$ ). The incidence of transient CH was 17.9 [14–22.9] per 100,000 birth-years in 2014 and remained stable over time ( $p = 0.4$ ) (Table 1). Among males, the incidence of permanent CH in 2014 was 28.5 [23.6–34.4] per 100,000 birth-years and that of transient CH 18.4 [14.5–23.3] per 100,000 birth-years, with no change over time ( $p = 0.11$  and  $p = 0.35$ , respectively). There was geographical disparity in the distribution of CH, regardless of the type (Figure 1 and Table 2).

#### Acquired hypothyroidism

For females, the incidence of AH in 2014 was 535.7 [533.2–538.2] per 100,000 person-years versus 335.5 [333.6–337.4] per 100,000 person-years in 2019. For males, the incidence of AH in 2014 was 197.5 [195.9–199] per 100,000 person-years versus 141.7 [140.4–142.9] per 100,000 person-years in 2019. The decreasing trend in the incidence over time was significant for both sexes ( $p < 0.01$ ) (Table 3). The annual incidence of AH was 2 to 3 times lower among males than females but was similar for people aged under 15 and over 75.

Spatial analysis showed the presence of a significant positive spatial

autocorrelation (global Moran's  $I > 0$ ) for the incidence of AH for all years studied, confirming the presence of a spatial structure (Fig. S2). However, the spatial dependence of the incidence of AH was much greater for females than males.

The incidence of AH by sex, calculated by direct standardization, showed a uniform decrease across France (Figs. 2 and S3). There was one exception among females in a set of population basins in the Lorraine region where the incidence remained high and relatively stable over time.

LISA analysis showed "hot spots" of AH incidence among females in the Midi-Pyrénées, Auvergne, and Languedoc-Roussillon regions (Fig. 3). From 2017 onwards, we also observed hot spots in north-eastern France, in the Nord-Pas-De-Calais, Picardie, and Lorraine regions. A "hot spot" located in Basse Normandie in 2014 was no longer found in subsequent years. Female cold spots were also found in the Pays de la Loire region since 2017, and in Brittany in 2019. Among males, there were no important "hot spots" or "cold spots", confirming the trend towards a random geographical distribution of incident cases among males (Fig. S4).

#### Discussion

We found that the incidence of permanent CH among females increased between 2014 and 2019 in France, whereas the incidence of AH decreased for all age groups over 15 years of age. There were geographical disparities, in particular, among females, for whom several hot spots and cold spots were identified.

#### Congenital hypothyroidism

Consistent with the results of other studies, we also observed a temporal increase in the incidence of CH. A role for the change in screening thresholds and the ethnic composition of populations has been suggested to explain this variation in certain studies [17,30–36]. The incidence we report is similar to that reported in these studies. No study in France has yet been able to accurately track the incidence of transient CH over time [37]. Until recently, the question had been raised as to whether an increase in these forms could explain, at least in part, the increase in the incidence rate of patients with GIS CH. We show that the incidence of transient CH did not vary significantly from 2014 to 2019, regardless of sex, throughout France. In contrast, permanent CH in females has increased between 2014 and 2019.

Our study showed the incidence of permanent CH to be 1.5 to 2 times higher among females than males. The reasons why the incidence of hypothyroidism is higher in females than in males are still unclear. For permanent CH, this difference seems similar between forms with and without thyroid dysgenesis [13]. A recent meta-analysis of genome-wide association studies found no differences between males and females in genetic variants for TSH and FT4, although some genetic factors are associated with a higher risk of hypothyroidism [38]. Non-genetic factors may also be involved [39].

In our study, we found that the incidence of CH varied between different regions of France. An environmental origin of the increased incidence of CH has been suggested and highlighted in a recent Scottish study of thyroid dysgenesis [40]. Our teams recently demonstrated that neonatal TSH was also correlate with the contamination of tap water by nitrate and perchlorate ions in the mother's zip code of residence, in addition to PM [41], but other pollutants have also been described [42–51]. Further studies are needed to determine whether these environmental factors could explain at least part of the heterogeneous distribution or this increase in incidence of CH in France.

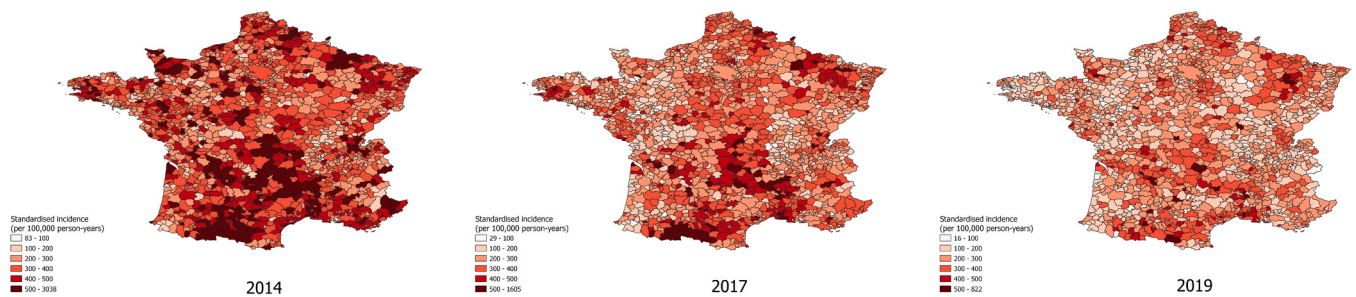
#### Acquired hypothyroidism

The incidence of AH was consistent with that observed in most countries [39,52], as well as its distribution according to age [53]. The

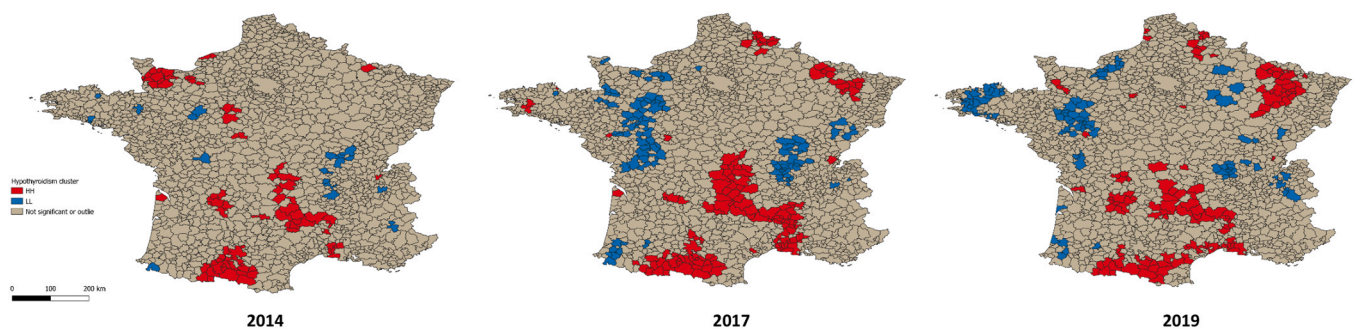
**Table 3**  
Incidence of AH in France by sex and age group over the period 2014–2019 and temporal trend (per 100,000 person-years).

Sex	Age range	2014	2015	2016	2017	2018	2019	$\beta$	<i>p</i>
<b>Females</b>	Overall	535.7 [533.2 – 538.2]	495.7 [493.3 – 498.1]	448.3 [446 – 450.5]	405.4 [403.3 – 407.5]	351.4 [349.5 – 353.4]	335.5 [333.6 – 337.4]	-42.19	<b>&lt; 0.01</b>
	0 – 14	47.2 [45.5 – 49]	48.3 [46.6 – 50.2]	48.3 [46.6 – 50.1]	47.1 [45.4 – 48.9]	43.4 [41.7 – 45.1]	36.2 [34.7 – 37.8]	-2.03	0.05
	15 – 29	331.9 [327.2 – 336.7]	315.4 [310.8 – 320.1]	302.4 [298.1 – 306.9]	276.7 [272.5 – 280.9]	250.9 [246.9 – 254.9]	234.2 [230.3 – 238.1]	-20.22	<b>&lt; 0.01</b>
	30 – 44	565.4 [559.6 – 571.4]	545.1 [539.3 – 550.9]	510.5 [505.1 – 516]	478 [472.7 – 483.3]	428.3 [423.3 – 433.4]	422.9 [417.9 – 427.9]	-31.30	<b>&lt; 0.01</b>
	45 – 59	699.8 [693.4 – 706.3]	644.5 [638.3 – 650.7]	568.7 [563.1 – 574.4]	504.5 [499.2 – 509.8]	429.8 [424.9 – 434.7]	414.3 [409.6 – 419.2]	-61.02	<b>&lt; 0.01</b>
	60 – 74	760.9 [753.4 – 768.5]	702.1 [695 – 709.3]	613.7 [607.3 – 620.2]	531.1 [525.2 – 537]	435.6 [430.3 – 440.9]	418.3 [413.1 – 423.5]	-74.16	<b>&lt; 0.01</b>
	75 – 89	889.6 [879.3 – 900]	770.4 [760.8 – 780.1]	684.4 [675.6 – 693.4]	617.2 [608.8 – 625.7]	536.3 [528.5 – 544.3]	491.5 [484 – 499.1]	-78.86	<b>&lt; 0.01</b>
	≥ 90	1340.3 [1308.9 – 1372.5]	1125.2 [1097.2 – 1154]	976.7 [951.8 – 1002.1]	926.5 [902.8 – 950.9]	787.1 [765.6 – 809.2]	728.7 [708 – 749.9]	-117.79	<b>&lt; 0.01</b>
	<b>Males</b>	Overall	197.5 [195.9 – 199]	194.8 [193.2 – 196.4]	191.5 [190–193]	173.1 [171.7 – 174.5]	152.4 [151.1 – 153.8]	141.7 [140.4 – 142.9]	-12.02
0 – 14		34.7 [33.2 – 36.2]	35.5 [34 – 37.1]	35.6 [34.1 – 37.1]	36.7 [35.2 – 38.2]	32.8 [31.4 – 34.2]	24.5 [23.3 – 25.8]	-1.65	0.13
15 – 29		57.7 [55.7 – 59.7]	57.1 [55.2 – 59.1]	54.1 [52.2 – 55.9]	51.9 [50.1 – 53.7]	45.2 [43.6 – 47]	41.8 [40.2 – 43.4]	-3.35	<b>&lt; 0.01</b>
30 – 44		114.1 [111.4 – 116.8]	110 [107.4 – 112.7]	103.7 [101.2 – 106.2]	90.3 [88 – 92.7]	84.2 [81.9 – 86.5]	81.5 [79.3 – 83.7]	-7.25	<b>&lt; 0.01</b>
45 – 59		205.4 [201.8 – 209]	200.1 [196.7 – 203.7]	190.8 [187.5 – 194.2]	168.3 [165.2 – 171.5]	147.2 [144.3 – 150.1]	138.2 [135.4 – 141]	-14.79	<b>&lt; 0.01</b>
60 – 74		395.4 [389.7 – 401.2]	394.8 [389.2 – 400.5]	396.9 [391.5 – 402.4]	349.3 [344.3 – 354.5]	288.3 [283.8 – 292.9]	272.8 [268.4 – 277.3]	-28.00	<b>0.01</b>
75 – 89		739.3 [727.6 – 751.1]	713.3 [701.9 – 724.9]	707.4 [696.3 – 718.6]	643.1 [632.6 – 653.8]	576.7 [566.8 – 586.7]	521 [511.6 – 530.5]	-44.73	<b>&lt; 0.01</b>
≥ 90		1363.2 [1309.7 – 1419]	1237.2 [1187.8 – 1288.6]	1177.8 [1132.2 – 1225.3]	1045 [1002.9 – 1088.7]	1001.2 [960.9 – 1043.2]	959.8 [920.5 – 1000.8]	-81.65	<b>&lt; 0.01</b>

AH: acquired hypothyroidism.  $\beta$ : regression coefficient in a linear regression model. Bold indicates statistically significant time trends ( $p < 0.05$ ).



**Fig. 2.** Spatiotemporal trends in annual incidence of AH in females in France in 2014, 2017 and 2019 (per 100,000 person-years). AH: acquired hypothyroidism. The same scale was used for each population basin between years. Six incidence brackets, the first of which ranges from the lowest observed incidence in the population for a given population basin to 100 cases per 100,000 persons, followed by brackets increasing by 100 cases per 100,000 persons each time until the last, which ranges from 500 per 100,000 persons to the highest observed incidence in the population for a given population basin.



**Fig. 3.** Spatio-temporal patterns of hot and cold spots of AH incidence in females in 2014, 2017 and 2019. AH: acquired hypothyroidism. HH: High-high hot spot (clustering of population basins with a high incidence of AH). LL: Low-Low cold spot (clustering of population basins with low incidence of AH).

decrease in incidence could be explained by, the guidelines of 2007 to combat the overdiagnosis of hypothyroidism by basing the diagnostic strategy on a decision algorithm based on TSH, which was previously routinely not performed before treatment initiation [54]. These practice guidelines were proposed in order to encourage physicians to stop over replacement with levothyroxine, and their impact required several years to become apparent. According to a survey of levothyroxine prescribing practices based on reimbursement data for the period January 1, 2006, to December 31, 2012, approximately 30 % of levothyroxine initiations had not been preceded by a TSH measurement [55]. Patients were therefore given thyroid substitution therapy on the basis of unspecific symptoms (asthenia, weight gain, constipation, muscle weakness, etc.), which undoubtedly led to numerous diagnostic errors and an overall overtreatment of the population. The trend of overtreatment is greater in adults. It is therefore logical that the impact of these recommendations was not reflected in the youngest population in our study. The decrease in the AH incidence has also very recently been observed in the United Kingdom [53].

Nevertheless, there were marked geographical disparities in the incidence of AH among females, which were relatively stable over time, with hot spots in regions with a high incidence of CH (Lorraine, Nord-Pas-De-Calais) questioning again the impact of the environment, given that these are regions heavily affected by water contamination with perchlorate ions, recognized thyroid disruptors, from weapons buried during the First World War. Two mountainous regions were also affected by a high incidence: Midi-Pyrénées and Auvergne. These regions may be more affected by iodine deficiencies, but precise French data on this subject are dated. [56].

### Limitations

The distinction between secondary and primary hypothyroidism for AH and CH was based on the administration of hydrocortisone, which may be questionable, given that certain rare forms of secondary hypothyroidism are not accompanied by a corticotropin deficiency. Similarly, we were unable to obtain more precise information on the origin of AH, although we were careful not to include iatrogenic origins linked to thyroidectomy or internal irradiation. Some patients with both primary hypothyroidism and primary adrenal insufficiency may have been erroneously excluded because they were considered to have central hypothyroidism. The distinction between transient and permanent forms of CH was based on the administration of thyroid-replacement therapy after July 1, 2020, or within six months of death. The age of thyroid function reassessment in newborns is left to the clinician's discretion and can vary, with reassessment in some cases being carried out in the third year of life. Thus, it is logical that the incidence of permanent CH was higher in the years closest to the end of the study than that of transient CH, as revalidation and the cessation of treatment would not have occurred for some of the CH cases that would subsequently be classified as transient. However, this does not explain the increase in the incidence of permanent CH among females, as this was clear even for the incidence at the beginning of the period studied and there was no statistically significant variation among males.

### Conclusion

The results of this study suggest that the incidence of permanent CH among females is increasing in France, whereas the incidence of AH is decreasing for all sexes and all age groups over the age of 15 years. There are wide regional disparities within France for both AH and CH and further studies are needed to assess whether environmental factors are involved in this distribution.

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### CRedit authorship contribution statement

**Vincent Bonneterre:** Writing – review & editing, Validation, Supervision, Methodology. **Christophe Cancé:** Writing – review & editing, Validation, Supervision, Methodology. **Thibaut Balcaen:** Writing – review & editing, Validation, Supervision, Methodology. **Pascal Petit:** Writing – review & editing, Validation, Supervision, Methodology. **Abdallah Al-Salameh:** Writing – review & editing, Validation, Supervision, Methodology. **Sylvain Chamot:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rachel Desailoud:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

### Declaration of Competing Interest

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

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### Supporting information

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