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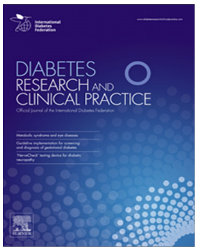

Trends in childhood type 1 diabetes incidence in France, 2010–2015

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ABSTRACT

Aims: To estimate type 1 diabetes incidence in children in France and its evolution between 2010 and 2015, based on comprehensive medico-administrative databases.

Methods: The algorithm built to identify new cases of type 1 diabetes selected children aged between 6 months and 14 years who had at least one hospital stay for diabetes, followed by their first insulin treatment, excluding children suffering from another form of diabetes.

Age and sex specific annual incidence rates were estimated and time trend was analyzed using Poisson regression.

Results: A total of 12 067 children were identified as newly diagnosed with type 1 diabetes and the annual incidence rates increased between 2010 and 2015 (from 15.4 [95% Confidence Interval: 14.7; 16.1] to 19.1 [18.3; 19.9] per 100 000 person-years), among boys and girls, and in each age group (4 and under, 5–9, 10–14 year olds). The annual rate of increase was 4.0% [3.4; 4.6]. This trend was not significantly different between each gender, and each age group.

Conclusions: Valid database information on disease incidence is essential for healthcare planning and provides a valuable resource for health research. An increase of the incidence rate of type 1 diabetes in children was highlighted in both sexes and in all age groups.

1. Introduction

Type 1 diabetes is an auto-immune disease that is most often discovered in young people [1]. Treatment with insulin is required at diagnosis and for life. In France, treatment initiation is systematically and exclusively performed in hospitalized individuals. Inpatients and their families are educated about diabetes management during their stay [2,3]. A diagnosis of diabetes in young people is suspected when characteristic symptoms such as polydipsia, nocturia, enuresis and weight loss are present. Late diagnosis can result in ketoacidosis, which in turn can lead to stupor, coma and death [1]. The frequency of ketoacidosis at type 1 diabetes onset varies from country to country [4] with an inverse correlation

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between the frequency of ketoacidosis and the incidence rate of type 1 diabetes: the highest rates of ketoacidosis are observed in countries where incidence rates are lowest. Studies suggest that ketoacidosis at type 1 diabetes onset is frequent and often severe in France [5]. With respect to disease evolution, children and adolescents diagnosed with type 1 diabetes may develop complications during adolescence or young adulthood, such as diabetic kidney disease, retinopathy, peripheral neuropathy, cardiovascular autonomic neuropathy, arterial stiffness and hypertension [6].

Furthermore, even before the onset of late complications due to diabetes, there is a significant excess mortality of children and young adults diagnosed with type 1 diabetes in childhood compared with the general population in Europe [7] that is largely attributed to acute metabolic complications of diabetes, i.e. ketoacidosis and hypoglycemia [8].

Worldwide, almost 500,000 children under 15 years of age are estimated to have type 1 diabetes and almost 80,000 developed the disease annually in 2013 [9]. A large variation is observed in terms of incidence of type 1 diabetes across the world [9–11]. Based on 1990s data, France is described as a country with an intermediate incidence rate [11].

Type 1 diabetes registries are used as a reference (“gold standard”) to estimate disease incidence. In France, a registry based on four regions reflecting the diversity of the French population was used to estimate national incidence trends between 1988 and 1997 [2,12,13]. Since that date, only 3 regional registries have recorded children with newly diagnosed type 1 diabetes. Although regional incidence values [3,14,15] and clinical information exist, no national incidence figures for childhood type 1 diabetes are currently available.

The aim of our study was to estimate the incidence of type 1 diabetes in children in France, and its evolution between 2010 and 2015, using national medico-administrative databases.

2. Subjects, material and methods

2.1. Data source

The national medico-administrative databases used in this study were the French national health insurance information system SNIIRAM (*Système national d’information inter-régimes de l’assurance maladie*) and the French national hospital discharge register PMSI (*Programme de médicalisation des systèmes d’information*).

The SNIIRAM anonymously collects individualized and comprehensive data concerning beneficiaries’ health care reimbursements [16,17], in particular reimbursed medications identified by codes of the ATC (Anatomical Therapeutic Chemical) classification and the health care service dispensing date. It does not contain any information about clinical results related to prescriptions or examinations. However, it does include information on patients with certified long-term illness status (who are eligible for 100% reimbursement of health care expenditure) and on the associated diagnosis (such as sickle cell disease, cystic fibrosis or malignant tumor), coded according to the International Classification of Diseases 10th revision (ICD-10).

The PMSI contains individualized anonymous data concerning hospital stays, in particular patient characteristics, such as age at the beginning of the hospital stay and sex, duration of stay and diagnosis, coded according to the ICD-10, and town of residence.

Record linkage between the SNIIRAM and the PMSI provides detailed information on medical services and medicine consumption for more than 98% of the population living in France, i.e. more than 66 million people.

The study population for the present work included residents of metropolitan France and its overseas departments, excluding Mayotte. Same-sex twins were excluded from the study population for technical reasons inherent to the use of the medico-administrative databases. Their frequency was estimated at 2% throughout the study. Before 2010, the specific date of the beginning of hospital stays was not registered so we could only apply the algorithm from 2010 onwards.

2.2. Algorithm

Children newly diagnosed with type 1 diabetes were identified based on a selection algorithm. For a given calendar year *n*, this algorithm selected children aged between 6 months and 14 years who had the following characteristics: (a) at least one hospital stay longer than 2 days, during year *n*, with a primary, related or associated diagnosis for diabetes (ICD-10 codes: E10-E14); (b) at least one reimbursement for insulin treatment during the 12 months following the beginning of the selected first hospital stay in the year *n*.

Children were excluded from the study if they were classified as having another form of diabetes: iatrogenic diabetes or diabetes related to other chronic diseases. Iatrogenic diabetes was defined as follows: (1) more than 3 reimbursements per year for immunosuppressant treatments or more than 6 reimbursements per year for corticosteroid treatments, at different dispensing dates, and preceding first hospital stay previously selected; (2) diagnosis of terminal renal disease (diabetes while on corticosteroid therapy or after a renal transplant); (3) leukemia. Children with specific severe chronic diseases related to insulin-dependent and non-autoimmune diabetes (i.e., cystic fibrosis and sickle cell disease) were also excluded. Details about the methods used to select children who met exclusion criteria are presented in the Support Table 1. These methods draw on algorithms previously developed by the French national health insurance fund [18].

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Children were also excluded if reimbursement for insulin treatment or oral anti-diabetic drugs had been made at least once prior to the beginning of first selected hospital stay previously selected.

2.3. Analysis

The distribution of the number of newly diagnosed children was recorded according to age group (6 months–4 years old, 5–9 years old and 10–14 years old) and sex, for the six years of the study period.

Age and sex-specific incidence rates and their 95% confidence intervals (CI) were derived from the number of children newly diagnosed with type 1 diabetes divided by the number of person-years, for each year during 2010–2015. The number of person-years at risk was estimated by the mean of the January 1st populations of year n and $n + 1$, aged between 6 months and 14 years. The January 1st populations were provided by Insee (the French National Institute of Statistics and Economic Studies) statistics [19].

Poisson regression was used to estimate the time trends in incidence rates between 2010 and 2015. The model included the calendar year, the age group and sex as covariates. In order to assess if the time trend was statistically different between age groups and between sexes, we tested for an interaction between age group and year and an interaction between sex and year.

To compare our results with the Eurodiab standardized incidence rates [20], age and sex standardized incidence rates were obtained using the same method [10,20–22], i.e. the direct method which assumes that the standard population is distributed in groups of equal size and defined by age and gender.

Analyses were performed using SAS Enterprise Guide® (version 4.3, SAS, Cary, USA), and R (version 3.4.3) for Poisson regression analysis.

3. Results

3.1. *Incidence of type 1 diabetes in 2015*

In 2015, 2 286 cases were identified in France as children newly diagnosed with type 1 diabetes between 6 months and 14 years old. The boys/girls ratio was 1.10. The flow chart of the selection process of the new cases of type 1 diabetes in 2015 is presented in Fig. 1.

The crude annual incidence rate of type 1 diabetes in children between 6 months and 14 years old in France in 2015 was 19.1 per 100 000 person-years [95%CI: 18.3; 19.9]: 19.6 [18.5; 20.7] in boys and 18.7 [17.5; 19.8] in girls. According to the 3 age groups, 6 months–4 years, 5–9 years and 10–14 years old, the crude annual incidence rates were 14.2 [12.9; 15.4], 19.4 [18.1; 20.8] and 23.1 [21.7; 24.6] per 100,000 person-years, respectively (14.5 [12.8; 16.2], 20.2 [18.3; 22.1] and 23.4 [21.4; 25.5] per 100,000 person-years in boys; 13.8 [12.1; 15.5], 18.7 [16.8; 20.5] and 22.8 [20.8; 24.9] per 100 000 person-years in girls).

3.2. *Trends in type 1 diabetes incidence from 2010 to 2015*

A total of 12 067 newly diagnosed children with type 1 diabetes were identified between 2010 and 2015: 1788 in 2010, 1916 in 2011, 1 939 in 2012, 2008 in 2013, 2130 in 2014 and 2286 in 2015. Over the study period, the boys/girls ratio was 1.12. Median age at diagnosis was 8.0 years (interquartile range (IQR) [Q1 = 5 years; Q3 = 11 years]) and was stable across the years of the study. It was 9 years (IQR [5; 12 years]) in boys and 8 years (IQR [5; 11 years]) in girls.

The number of cases are presented by year, age group and sex in Support Table 2 with the population at risk and the incidence rates.

As shown in Fig. 2, the crude annual incidence rate of type 1 diabetes in children between 6 months and 14 years old in France increased from 15.4 in 2010 to 19.1 per 100,000

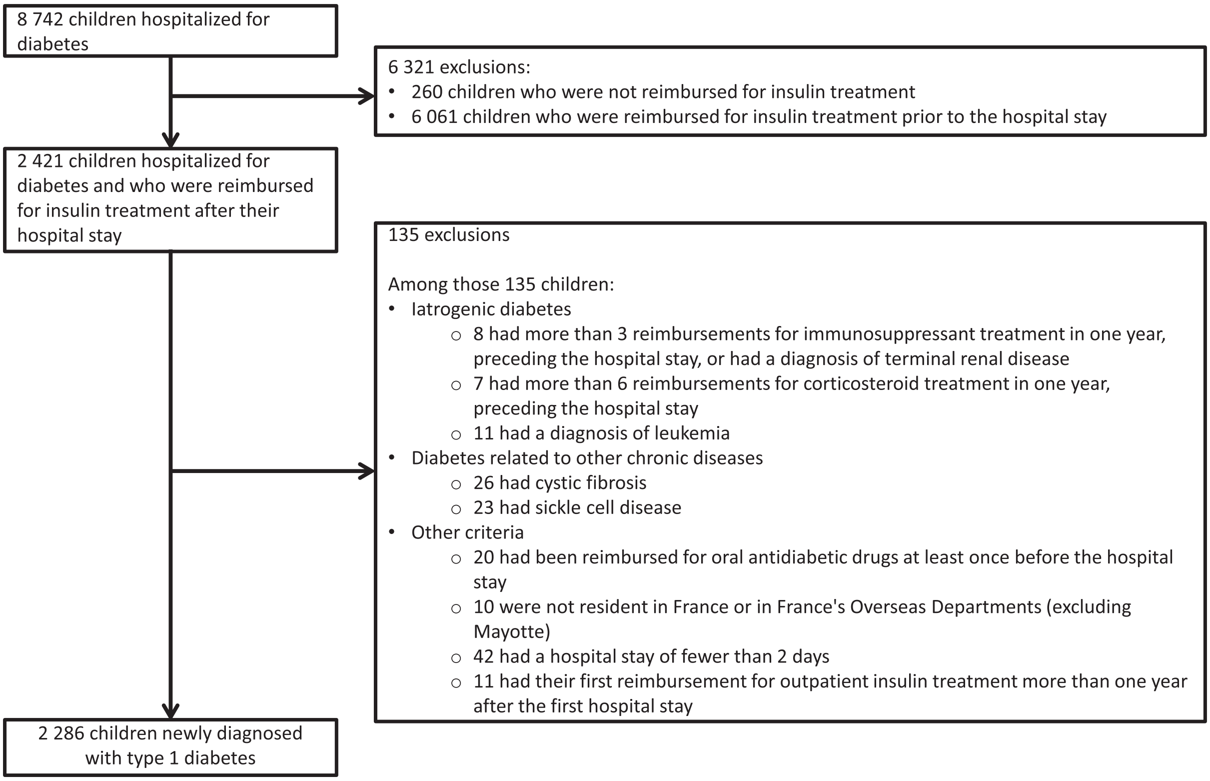
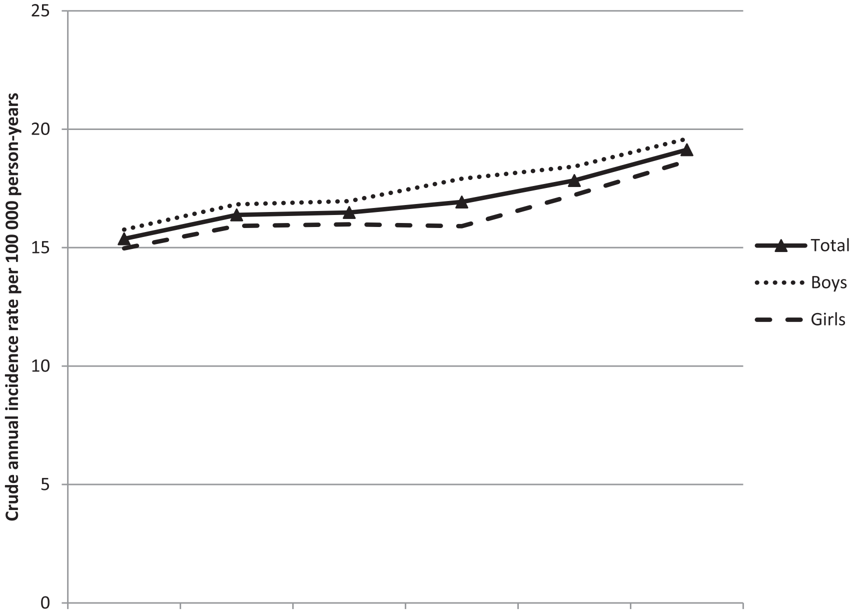


Fig. 1 – Flow chart of the year 2015.

person-years in 2015. This increase was observed in both sexes (from 15.8 to 19.6 among boys and from 15.0 to 18.7 among girls) and with standardized incidence rates (Fig. 2). It was also observed in all 3 age groups, from 11.7 to 14.2 among 6 months–4 years, from 15.9 to 19.4 among 5–9 years and from 18.2 to 23.1 among 10–14 years old (Fig. 3).



Year Per 100 000 person-years	2010	2011	2012	2013	2014	2015
Crude rates	15.4 [14.7;16.1]	16.4 [15.7;17.1]	16.5 [15.8;17.2]	16.9 [16.2;17.7]	17.8 [17.1;18.6]	19.1 [18.3;19.9]
Standardized rates	15.4 [14.7;16.1]	16.4 [15.6;17.1]	16.4 [15.7;17.2]	16.9 [16.1;17.6]	17.8 [17.0;18.5]	19.1 [18.3;19.8]

Fig. 2 – Crude and standardized annual incidence rate.

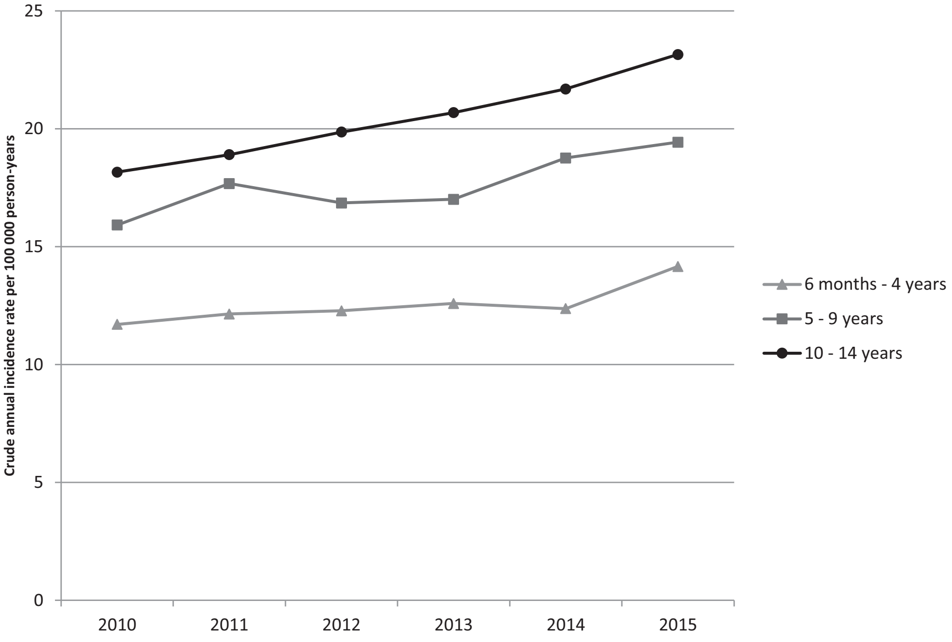


Fig. 3 – Crude annual incidence rate by age group.

The annual increase of incidence rates between 2010 and 2015 was 4.0% [95%CI: 3.4; 4.6] ($p < 0.001$), using the Poisson regression model. In this model, the relative risk (RR) was higher for boys compared to girls (RR = 1.07 [1.05; 1.09], $p < 0.01$). This risk was also higher for the 5–9 years old group (RR = 1.40 [1.37; 1.44], $p < 0.001$) and for the 10–14 years old group (RR = 1.63[1.59; 1.67], $p < 0.001$) compared to the 6 months–4 years old group. The interactions between year and sex, and between year and age groups were not significant.

4. Discussion

A crude incidence rate of 19.1 for 100 000 children was found in our study in France in 2015. In addition, an increase in the incidence of type 1 diabetes in children was highlighted between 2010 and 2015 with a 4.0% increase per year. During the study period, the risk of developing type 1 diabetes was significantly higher in boys than in girls and among 5–9 years old and 10–14 years old than among 6 months–4 years old, with a risk gradient increasing with age. However, the annual increase trend was not significantly different between the two sexes, or between each age group.

It is known [11,23] that the age-standardized incidence of type 1 diabetes in children under 14 years of age differs greatly between countries and regions worldwide, varying from 0.1 per 100 000 persons per year in China in 1990–1994 to 62.4 in Finland in 2006–2011. The various Eurodiab study centers' standardized incidence rates in 2004–2008 varied between 5.8 per 100,000 person-years in Former Yugoslav Republic of Macedonia (FYROM) and 36.6 in Stockholm county in Sweden [20]. The standardized incidence rate of type 1 diabetes in children between 6 months and 14 years old in France in our study (19.3 per 100,000 person-years in 2015) was situated between those two Eurodiab centers values but it was a high level according to the Diamond project group classification of 2000 [11].

In addition, the Eurodiab study of 1989–2003 trends predicted that the number of European children under 15 years old newly diagnosed with type 1 diabetes would increase by 63% between 2005 and 2020 [10]. Consistent with those predictions, our study highlighted an increase of the number of newly diagnosed children with type 1 diabetes in 6 months–14 years children in France (28% increase between 2010 and 2015).

Furthermore, over the past three decades, an increase in the incidence of type 1 diabetes in children has been observed in most countries in numerous international studies and reviews [1,9–11,20,23–25]. As expected, the estimation of the national incidence rate in our study, i.e. 19.1 per 100,000 person-years in the 6 months to 14 years old population in 2015, was much higher than that of the national type 1 diabetes registry of 1997, i.e. 9.6 per 100,000 person-years in the 0–19 years old population [13]. It was also higher than the estimation in two regional French registries: 13.4 in 2004 in Aquitaine [3] in the 0–14 years old population and 16.8 in 2005 in Languedoc-Roussillon in the 0–15 years old population [15]. These previous estimations are consistent with the increase of 4.0% [95%CI: 3.4; 4.6] per year estimated in our study. In addition, this mean increase rate is of the same order of magnitude as the previous national estimation, i.e. 4.2% [95%CI: 2.8; 5.5] in the 0–14 years old population in 1988–1997 [13], and the previous French regional estimation, i.e. 3.34% [3.33; 3.34] in Aquitaine between 1988 and 2004 [3]. Moreover, France is one of the European countries with high average annual increases: thus, 50% of European countries have an average annual increase higher than 3.3% (1999–2008, Eurodiab [20]) whereas the increase found in our study was 4.0% (2010–2015).

The increase in the incidence of type 1 diabetes was highlighted in both sexes and in all age groups up to 14 years old, in our study as well as in international [1,9–11,20,24] and other French studies [3,13–15].

According to Diamond (1990–1999) [11], the risk of type 1 diabetes increased with age: the 5–9 year olds had 1.62 [1.57; 1.66] times higher risk, and the 10–14 year olds had 1.94 [1.89; 1.98] times higher risk than that of the 0–4 year olds. In our study, we also found a significantly higher risk in 5–9 year olds and 10–14 year olds than in 6 months–4 year olds. However, we did not find a statistically significant difference between the annual increase in each age group. In other words, we did not find a higher mean increase rate in the youngest children, unlike other European studies [3,10,13–15]. For example, the Eurodiab study in 1989–2003 found different rates of change over time between different age-groups, with increase rates of 5.4% [4.8; 6.1] in the 0–4 years old, 4.3% [3.8; 4.8] in the 5–9 years old and 2.9% [2.5; 3.3] in the 10–14 years old populations. In the Netherlands [26], the incidence of type 1 diabetes is still increasing but seems to have been stable in children under five since the late 1990s. Elsewhere, in Asia, in Africa, in North and South America, according to the Diamond study in 1990–1999 [11], an increase was found among all age groups but there were no significant differences in trends over time between age groups. For instance in Asia [11], the increase was 1.3% [−3.5; 6.2] in the 0–4 years old, 5% [1.4; 8.8] in the 5–9 years old and 5.1% [1.8; 8.5] in the 10–14 years old populations. Finally, an Australian study [27] and the Eurodiab study [20] also highlighted evidence of non-uniformity over time in the rates of increase in many registers (in other words, the existence of periods of less rapid and more rapid increases in incidence).

The ISPAD (International Society for Pediatric and Adolescent Diabetes) clinical practice consensus guidelines [1] of 2014 found that, in some studies, gender differences in the incidence of type 1 diabetes were observed, and that in Europe higher incidence was found in boys, especially in countries with high level of incidence [28]. In our study, we also found higher incidence rates in boys and a significantly higher risk in boys than in girls, although the annual incidence increase was not significantly different between both sexes.

The variability in the incidence of type 1 diabetes between countries and regions worldwide, together with the constantly increasing incidence of type 1 diabetes in recent decades, cannot be explained only by genetic susceptibility and changes to it [29–31]. Current thinking is that the answers are most likely to be found in environmental factors and gene-environment interaction. Indeed, some of these factors may initiate the disease by triggering the beta-cells damaging process. They are poorly known and are numerous to be evoked, such as, viral infections, toxins, hygiene hypothesis and numerous dietary factors. A complex combination of many of these elements, and others that remain to be discovered, is most likely to be responsible for this incidence variability and increase [11,23,25,32]. Novel geographic approaches to the investigation of environmental factors of multifactorial diseases will help researchers obtain a greater understanding of these issues [33].

One of the most important strengths of this study is the large study population, almost 100% of the French population. In France, children are systematically hospitalized for at least two days at diagnosis to initiate insulin treatment [2,3], due to the absence of specialized out-patient care and the fact that day hospital – i.e. without overnight care – cannot achieve all the objectives of the incident hospital stay (such as initiation of treatment and education about diabetes management). Therefore, although outpatient diagnosis and initiation of treatment with insulin is not captured by our selection method, it is unlikely to happen in France. Furthermore, to create our study algorithm we combined hospital admission data with beneficiaries' health care reimbursement data, which ensured that the quality of our selection method was high.

The principal limitation of this study is the lack of validation by clinic confirmation of the algorithm used to estimate the number of children newly diagnosed with type 1 diabetes. However, our algorithm was built with specially selected and relevant criteria to ensure a good specificity of the selection process: the algorithm included only children, hospitalized for diabetes and treated by insulin only after the hospital stay. Indeed, while insulin treatment reimbursement alone may not be sufficient to identify such children (i.e., duplicate entries and children from other countries who move to France would artificially increase the number of newly diagnosed children), the complementary use of hospital admission data almost guaranties that the selection of newly diagnosed children with type 1 diabetes is accurate. In addition, certain external elements demonstrate the quality of the algorithm: our results are coherent with those of the French registries comprising clinical data and with their projections [3,13–15]. Nevertheless, a validation study would be necessary.

Another limitation is the risk that the number of newly diagnosed children with type 1 diabetes could be slightly overestimated due to some children having another form of diabetes, such as MODY (Maturity-onset diabetes of the young), type 2 diabetes, iatrogenic diabetes, diabetes caused by some specific severe chronic diseases, diseases of the exocrine pancreas, other endocrine diseases and infections. Although these other forms of diabetes are much less frequent in children [1,34], we nonetheless tried to identify them, in order to exclude them from the study population (details in Fig. 1). However, in a small number of cases, the algorithm may mistake children with type 2 diabetes treated with insulin only and those with monogenic diabetes for children with type 1 diabetes, and erroneously include them.

As with all studies using medico-administrative databases, there are also limitations concerning data collection or extraction, data entry and coding [16]. Other limitations are inherent to technical details regarding SNIIRAM and PMSI data, for example the presence of non-detected duplicate entries (estimated in our study at less than 1‰ in 2015) or the exclusion of same-sex twins, both of which have little impact on our study.

Our findings point to an alarming increase in the incidence of type 1 diabetes, especially in the pediatric context of an illness requiring specialized care and treatment for life that can have serious consequences (at the time of the discovery of type 1 diabetes but also during its evolution): incidence continued to increase in the period 2010–2015 across all ages in children between 6 months and 14 years old living in France. Given this result, specific health resources should be made available [10]. Increased incidence is an extra burden for healthcare professionals, especially for toddler care. At this age, the disease is characterized by a more severe mode of revelation, i.e. ketoacidosis, a high risk of complications, fast and large glycemic variability, a very high danger of hypoglycemia, interference of febrile concomitant diseases, child immaturity regarding treatment, and the time consuming care needed in adapted structures with multidisciplinary staff who are trained in diabetes care [35]. Furthermore, information campaigns on symptoms should be promoted to avoid late diagnosis and associated complications, such as ketoacidosis [5].

Finally, although many countries still use specific registries [27,36–38] as the reference ("gold standard"), some countries use medico-administrative databases [39,40] to estimate the incidence of type 1 diabetes. In France, in the absence of a national registry, medico-administrative databases allowed us to estimate the incidence of type 1 diabetes in children in all of the French population since 2010, as well as to highlight its regional variations (*data not shown*). The selection algorithm presented in this paper can also serve as a tool for a long-term surveillance system for type 1 diabetes incidence in children in France. In addition, it could be employed for surveillance of type 1 diabetes complications or to explore the hypothesis of a link between environmental, geographical or nutritional factors and the occurrence of type 1 diabetes, based on a spatio-temporal analysis (using the location of residence of the newly diagnosed children to look for spatial heterogeneity).

5. Conclusions

This study provides recent estimates of the annual incidence of type 1 diabetes in children for all the French population, and highlights an increasing trend, in both sexes and in all age groups during the period 2010–2015. Valid database information on disease incidence is essential for health care planning and provides a valuable resource for health research. In France, medico-administrative data allows us to estimate type 1 diabetes incidence in children in the whole population, as well as an alarming increase of the incidence.

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Duality of interest

The authors declare that they have no conflict of interest.

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