Cyclical variation in the incidence of childhood-onset type 1 diabetes during 40 years in Navarra (Spain)

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Objective: To trace the evolution of type 1 diabetes (T1D) in Navarre in children under 15, between 1977 and 2016, and their characteristics at onset regarding age and sex.

Subjects and methods: We performed a descriptive analysis, using prospective-retrospective information. The study included all cases of T1D diagnosed in Navarre in children aged 0 to 14 years old from 1 January 1977 until 31 December 2016. The capture-recapture method was used, retrieving information from three independent sources: the five hospitals in Navarre as a primary source, and the Navarre Association of Diabetics (ANADI) and the primary healthcare system as the secondary source. Estimates and confidence intervals were calculated assuming a subjacent Poisson distribution. Chi square test was used to compare incidence between groups. The analysis of changes in incidence since 1977, adjusted for age group, sex and year of diagnosis, were evaluated with a multivariate Poisson regression model and joinpoint regression.

Results: A total of 577 cases were registered resulting in a crude incidence rate of 14.99/100 000 inhabitants-year (95% confidence interval [CI]: 13.79-16.26). From 1977, the incidence has increased in cycles, reaching an incidence rate of 22.98 (95% CI: 18.52-28.21) in 2016. The relative annual increase is 3% (95% CI: 2.3-3.8). The highest incidence is in the 10 to 14 age group (P < 0.001). No differences in sex were found. The mean age at onset in children under 15 years has not changed significantly (P = 0.572).

Conclusions: The incidence of T1D in Navarre has increased 4-fold in the last four decades but is stable since 2001.

KEYWORDS
epidemiology, incidence, type 1 diabetes

INTRODUCTION
Type 1 diabetes (T1D) is the most frequent endocrinological disease in childhood. It is a chronic disease that requires lifelong treatment, so it has an important socio-economical and healthcare impact. The current lack of knowledge of the genetic, environmental, and physiopathological factors responsible for the development of the disease impedes its cure. Epidemiologic studies have tried to identify the triggers of T1D, linking nutritional, chemical, infectious, and toxin-derived factors to its pathogenesis. However, the clinical hypotheses derived from these studies haven’t prevented the development of the disease, so further epidemiologic studies are still needed. There is general agreement that T1D incidence rates have increased since the 1980s, although the increment is neither linear nor equal in intensity over different countries. Moreover, the incidence seems to have stabilized over the last decade. In order to have a broad vision of the incidence of the disease, it should be required long periods of follow-up; however, papers with follow-up times over 30 years are not frequent. The incidence of T1D is highest at the age of 10 to 14 years. Studies from Sweden and Belgium have suggested that the disease may be developing earlier, but without a real increase in the incidence rates. Regarding sex-related differences, T1D shows a similar incidence in both
sexes in children under 15 years.\textsuperscript{12,15} However, in some studies, T1D is more frequent in boys between 10 and 14 years.\textsuperscript{16,17} As a general rule, it has been noted that in countries with a high incidence of T1D, the disease predominates in boys, while in low incidence countries it is in girls where it prevails.\textsuperscript{14} Therefore, it is important to bring up the following questions: Is the T1D incidence in childhood and adolescence still increasing or has stabilized? Is the onset of T1D happening in earlier age? What are the differences in the incidence of T1D for age groups? Regarding sex, is there a sex-related difference in incidence?

With the goal of helping to address these questions, we provide data for the incidence in children under 15 years over a period of 40 years in the registry of T1D in Navarre, an autonomous community in northern Spain of 642,797 inhabitants. Additionally we describe the characteristics of patients at onset with regard to age and sex.

2 | METHODS

In this report, a transversal descriptive analysis with prospective information gathering is presented. The study included all cases of T1D (according to World Health Organization criteria)\textsuperscript{18} diagnosed in Navarra from 1 January 1977 until 31 December 2016. Patients with other types of primary or secondary diabetes were excluded. Since 1992, blood samples from all patients with T1D diagnosis were tested for anti-GAD (Glutamic Acid Decarboxylase), anti-IAA (Insulin Autoantibodies), and anti-IA2 (Insulinoma-associated protein 2) antibodies. IAA were determined using a competitive fluid-phase radioassay which uses $[^{125}\text{I}]$-labeled recombinant human insulin (Amersham) as antigen and polyethylene glycol for precipitation of immune complexes. GADA (glutamic acid decarboxylase antibodies) and IA2 antibodies were detected using standard radiobinding assay with $[^{35}\text{S}]$-labeled recombinant human GAD\textsubscript{65} and IA2 antigens obtained by in vitro translation using cDNA clones provided by Dr A. Lernmark (University of Washington, Seattle, WA) and Dr E Bonifacio (Istituto Scientifico San Raffaele, University of Milan, Milan, Italy), respectively.\textsuperscript{19}

The population at risk comprised all residents in Navarra younger than 15 years of age that lived in the autonomous community for a period greater than 6 months. In order to estimate the completeness of the record, the capture-recapture method was used, retrieving information about diagnosis from three independent sources: the three public and the two private hospitals in Navarre as a primary source, and the Navarre Association of Diabetics (ANADI) and the primary healthcare system as the secondary source. Paper-based information was substituted with electronic health records as technology became available. The global integration that included the identification of potential duplication of data and the statistical analysis, were carried out by a data manager. In compliance with legislation, safety, and confidentiality of obtained data was reinforced by a Regional Order. Additionally, the study was approved by the Ethical Committee for Research of Navarre and it was in accordance with the Declaration of Helsinki.

2.1 | Local and environmental information

Navarre is an autonomous community that administers its own public health service. It is located in the northern region of Spain, and has a surface area of 10.391 km\textsuperscript{2}. It has a mainly Caucasian population with relatively low to mid immigration rates that ranged from 2.7% of the inhabitants of Navarre in the year 2000 to 13.4% in 2016 (Spanish National Institute of Statistics). The wide geographic, climatic, and demographic variety of the region can be divided into three subregions: the northern valleys of the Pyrenees, the central area, and the southern Ebro riverside valley. The northern area has a temperate, rainy climate (average annual 15°C and 1400 mm/m\textsuperscript{2}), with a low density population. The central area has a drier climate (500-700 mm/m\textsuperscript{2} annual rainfall and hot summers). The southern region climate is continental/Mediterranean, with dry summers, wide temperature variations, and low rainfall rates.

2.2 | Statistical analysis

Population data classified by sex and age for each year was obtained from the census and the register of inhabitants of the autonomous community of Navarre provided by the Spanish Office of National Statistics. Estimates of incidence rates in units of 100,000 person-years and confidence intervals were calculated assuming a subjacent Poisson distribution. Chi square test was used to compare incidence between groups (independence test). The analysis of changes in incidence since 1977, adjusted for age group, sex, and year of diagnosis, were evaluated with a multivariate Poisson regression model. In order to allow the comparison of the calculated incidence rates with those from other populations that potentially differ in their age and sex distributions, the rates were adjusted to a standard population comprising the same number of individuals in the analyzed subgroups (age [0-4 years; 5-9 years; 10-14 years]) for each sex [male; female]).

For statistical analysis, IBM \texttt{SPSS} statistics 20.0 and \texttt{R} statistical software v.3.4.0 were used.

3 | RESULTS

A total of 577 cases of T1D in children under 15 years were registered (277 female and 300 male) resulting in a crude incidence rate of 14.99 cases per 100,000 people-years (95% confidence interval [CI]: 13.79-16.26). Given the wide period analyzed, the completeness of ascertainment ranged from 94.6% to 98.8%. The age at onset (mean = 3.83 years, (boys = 8.82 ± 3.77; girls = 9.36 ± 3.88). The distribution by age groups and sex is shown in Table 1. The highest incidence rate was found in the 10 to 14 age group (P < 0.001). The overall incidence of boys under 15 years was 15.14 (95% CI: 13.49-16.69), while in girls under 15 years the incidence was 14.83 (95% CI: 13.13-16.68). The differences between the sexes were not statistically significant. Crude and adjusted quadrennial incidence of T1D in Navarre (1977-2016) is shown in Table 2. The incidence has increased over the years, peaking at an incidence rate of 22.98 (95% CI: 18.52-28.21) at the end of the analyzed period. However the increment has not been linear. The incidence increases in the first 12 years, stabilizes between the periods of 1985 to 1988 and 1997 to 2000, and then increases again reaching a rate of 20 cases per 100,000 inhabitants under 15 years, being stable in the current century.
Joinpoint regression was used in order to detect significant variations in incidence, with the most significant changes taking place in 1990, 1996, and 2002 (Figure 1).

The results of Poisson regression showed an annual increase of 3.0% (95% CI: 2.3-3.8) of the incidence. While comparing the youngest age group with the rate ratio of the 5 to 9 age group, is 1.53 (95% CI: 1.21-1.94) \((P < 0.001)\), comparing with the 10 to 14 group, results in a rate ratio of 2.36 (95% CI: 1.90-2.93) \((P < 0.001)\) (Figure 2).

Another data extracted from the same model is that the incidence is not significantly different among sexes in the analyzed period and region \((P = 0.788)\). The mean onset age does seem to have a lowering trend in children, but it is not statistically significant \((P = 0.572)\).

### 4 | DISCUSSION

The incidence of T1D has experienced a 4-fold increase over the last four decades. This has been a staggered increase and the incidence is stable from 2001.8,20 The annual relative increase according to our data is in consonance with the data from EURODIAB that place this increase at 3% to 4% in the last 20 years,7 and it is identical to the estimations made by the International Diabetes Federation (IDF Diabetes Atlas)21 at global level (3.0%). The mean incidence in Navarre through the study is high (14.99/100 000 inhabitants-year) and, in the last years, very high (>20/100 000 inhabitants-year). Currently, the incidence of T1D in Navarre is higher than most of the autonomous communities of northern Spain, but at a similar level to “Castilla y Leon” and the regions of the south of Spain.22 Compared to other countries, it is higher than Central European nations and the United States, and closer to the incidence rates of Norway and Canada.5

In recent years, there has been a debate about whether the incidence of T1D is increasing,2 decreasing,4 or has stabilized.19 On the other hand, some authors believe that the incidence seems to be higher because of an earlier onset.13,14 Our results show that the incidence has increased and that the differences with other studies might depend on the analyzed period. In Navarre, in the last 20 years, the incidence is steady. However, if we increase the period to the last 40 years, an annual increase of 3% of the incidence can be seen. The country where the study takes place influences the results20 because in countries with high incidence the trend is to stabilize, while in low incidence countries, as in Eastern Europe12 or developing countries23 there is a tendency to increase. In Navarre, our group has previously published that, taken together children and adults, their onset age table 1

**TABLE 1** Incidence in Navarre of T1D by age group and sex (1977-2016)

| Group  | Cases | People/year | Incidence (95% CI) | P-value* |
|--------|-------|-------------|---------------------|---------|
| 0-4 years | Global | 113 | 2 120 618 | 9.33 (7.69-11.22) | 0.2395 |
|        | Female | 61 | 586 269 | 10.40 (7.95-13.37) | 0.3226 |
|        | Male | 52 | 624 349 | 8.32 (6.22-10.92) | 0.8726 |
| 5-10 years | Global | 179 | 1 283 108 | 13.95 (11.98-16.15) | 0.7782 |
|        | Female | 85 | 622 874 | 13.65 (10.90-16.87) | 0.2673 |
|        | Male | 94 | 660 234 | 14.24 (11.51-17.42) | 0.3782 |
| 10-14 years | Global | 285 | 1 355 467 | 21.03 (18.66-23.61) | 0.3712 |
|        | Female | 131 | 658 994 | 19.88 (16.62-23.59) | 0.1253 |
|        | Male | 154 | 696 473 | 22.11 (18.76-25.89) | 0.8008 |
| <15 years | Global | 577 | 3 849 193 | 14.99 (13.79-16.26) | 0.8008 |
|        | Female | 277 | 1 868 137 | 14.83 (13.13-16.68) | 0.8008 |
|        | Male | 300 | 1 981 056 | 15.14 (13.48-16.69) | 0.8008 |

Abbreviations: CI, confidence interval; T1D, type 1 diabetes.

*P-value female vs male.

**TABLE 2** Crude and adjusted quadrennial incidence of T1D in Navarre (1977-2016)

| Period | Cases | People/year | Crude incidence Rate | 95% CI | Adjusted incidence Rate | 95% CI |
|--------|-------|-------------|----------------------|------|--------------------------|------|
| 1977-1980 | 27 | 502 084 | 5.38 | 3.54 | 7.82 | 5.32 | 3.50 | 7.77 |
| 1981-1984 | 47 | 474 563 | 9.90 | 7.27 | 13.17 | 9.79 | 7.18 | 13.09 |
| 1985-1988 | 56 | 428 338 | 13.07 | 9.87 | 16.98 | 12.29 | 9.26 | 16.13 |
| 1989-1992 | 56 | 370 085 | 15.13 | 11.42 | 19.66 | 13.93 | 10.47 | 18.32 |
| 1993-1996 | 39 | 324 337 | 12.02 | 8.55 | 16.45 | 11.76 | 8.33 | 16.25 |
| 1997-2000 | 46 | 301 776 | 15.24 | 11.16 | 20.33 | 14.82 | 10.84 | 19.84 |
| 2001-2004 | 63 | 311 370 | 20.23 | 15.54 | 25.90 | 20.53 | 15.77 | 26.31 |
| 2005-2008 | 75 | 342 684 | 21.89 | 17.20 | 27.45 | 22.25 | 17.49 | 27.94 |
| 2009-2012 | 76 | 391 154 | 19.43 | 15.29 | 24.33 | 19.76 | 15.56 | 24.77 |
| 2013-2016 | 92 | 402 802 | 22.84 | 18.41 | 28.02 | 22.98 | 18.52 | 28.21 |

Abbreviations: CI, confidence interval; T1D, type 1 diabetes.
does not take place earlier. Navarre possesses a public Health system that covers the whole population and that has not changed in the last 40 years. The population, however, has increased 22.4% in the last four decades. The non-Spanish population has shifted from 1% to 13.4% in this period of time. Remaining external increase in population is derived from the population of other Spanish autonomous communities. There is not enough volume of patients with onset of T1D that come from the other 16 autonomous communities of Spain or from other countries to know the relative contribution of each group to the observed incidence increase. Therefore, we cannot confirm or dismiss that the population from areas with higher T1D have contributed to the increase in Navarre. The increase of the standard of living in our community could also have impacted the increase of T1D, because the per capita incomes in Navarre has risen from €16 300 in 1997 to €29 807 in 2016 (above the European mean) (data from Institute for statistics of Navarre), which represents an increase of 82.8%. However, over the last 20 years, the incidence of T1D has stabilized, while the per capita income has increased, a fact that works against this hypothesis.

By age group, the highest incidence in Navarre is observed in the 10 to 14 age group, as in most of the countries; however, countries like Finland, Italy, Estonia, and some autonomous communities of Spain, have described peak incidence in the 5 to 9 age group. At follow-up, in Navarre, an increase in the three age groups can be observed, increasing as the group age increases. A higher increase of the disease was described in the final years of the past century and the first years of the current century, in the younger children, that raised the hypothesis of the advance of age at diagnosis. This trend has disappeared in the last 10 years. With regard to the differences by sex, contrary to what is seen in Navarre, it is frequent to
observe an early peak of incidence in girls that has been attributed to their earlier puberty.28
In our study we do not find differences in sex, either in absolute terms or in the speed of incidence increase. This data is consistent with what has been published for Germany12 Belgium,14 Poland,16 and Brazil23 but differs from what has been published for United States,2 Australia,9 Finland,16 Sweden,13 Hungary,17 United Kingdom,29 and Italy,30 that finds a higher incidence in boys than in girls. Thus, while in adults there is a unanimous consensus about the predominance of the disease in adult males14,29,31,32 the results in children are more controversial.

The main strengths of the study are its length (four decades) and the homogeneity of the data gathering. The limitation might reside in the fact that despite the completeness of the capture-recapture method, some cases could be unrecorded, mainly in the first years of the follow-up, where data was gathered on paper.

In conclusion, Navarre currently displays a high incidence of T1D. In the last 40 years the incidence has multiplied by four. It is important to continue researching the factors that can influence this increase in order to prevent the development of the disease.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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REFERENCES

1. Compés ML, Feja C, Niño de Guzmán E, et al. Bayesian analysis of the geographical variation of type 1 diabetes mellitus in under 15 yr olds in northeast Spain, 1991-2009. Pediatr Diabetes. 2013;14:66-76.
2. Mayer-Davis EJ, Lawrence JM, Dabelea D, et al. Incidence trends of type 1 and type 2 diabetes among youths, 2002-2012. N Engl J Med. 2017;376:1419-1429.
3. Katsumoto A, Gudbjörnssottir S, Ravshani A, et al. Type 1 diabetes mellitus. Nat Rev Dis Primers. 2017;30(3):17016. https://doi.org/10.1038/nrdp.2017.16.
4. Di Ciaula A. Type 1 diabetes in paediatric age in Apulia (Italy): incidence and associations with outdoor air pollutants. Diabetes Res Clin Pract. 2016:111:36-42.
5. Songini M, Mannu C, Targhetta C, Bruno G. Type 1 diabetes in Sar- dinia: facts and hypotheses in the context of worldwide epidemiologi- cal data. Acta Diabetol. 2017;54:9-17.
6. The DIAMOND Project Group. Incidence and trends of childhood type 1 diabetes worldwide 1990-1999. Diabet Med. 2006;23:857-866.
7. Patterson C, Gyürüs E, Rosenbauer J, et al. Trends in childhood type 1 diabetes incidence in Europe during 1989-2008: evidence of non-uniformity over time in rates of increase. Diabetologia. 2012:55: 2141-2147.
8. Forga L, Goñi MJ, Cambra K, Ibáñez B, Chueca M, Berrade S. Incidence and temporal trends of childhood type 1 diabetes between 1975 and 2012 in Navarre (Spain). Gac Sanit. 2015;29:51-54.
9. Haynes A, Bulsara MK, Bower C, Jones TW, Davis EA. Cyclical variation in the incidence of childhood type 1 diabetes in Western Australia (1985–2010). Diabetes Care. 2012;35:2300-2302.
10. Berhan Y, Waernbaum I, Lind T, Möllsten A, Dahlquist G, Swedish Childhood Diabetes Study Group. Thirty years of prospective nationwide incidence of childhood type 1 diabetes. The accelerating increase by time trends to level off in Sweden. Diabetes. 2011;60:577-581.
11. Skrivarhaus T, Stene LC, Drivvoll AK, Strom H, Joner G, Norwegian Childhood Diabetes Study Group. Incidence of type 1 diabetes in Norway among children aged 0-14 years between 1989 and 2012: has the incidence stopped rising? Results from the Norwegian Childhood Diabetes Register. Diabetologia. 2014;57:57-62.
12. Manuwal U, Heinke P, Salzieder E, et al. Incidence trends of type 1 diabetes before and after the reunification in children up to 14 years of age in Saxony, Eastern Germany. PLoS One. 2017;12(9):e0183665 https://doi.org/10.1371/journal.pone.0183665.
13. Dahlquist GG, Nyström L, Patterson C, The Swedish Childhood Diabetes Study Group, Diabetes Incidence in Sweden Study Group. Incidence of type 1 diabetes in Sweden among individuals aged 0-34 years, 1983-2007. An analysis of time trends. Diabetes Care. 2011;34: 1754-1759.
14. Weets I, De Leeuw IH, Du Caju MVL, Belgian Diabetes Registry, et al. The incidence of type 1 diabetes in the age group 0-39 years has not increased in Antwerp (Belgium) between 1989 and 2000. Evi- dence for earlier disease manifestation. Diabetes Care. 2002;25: 840-846.
15. Wojcik M, Sudacka M, Wasył B, et al. Incidence of type 1 diabetes mellitus during 26 years of observation and prevalence of diabetic ketoacidosis in the later years. Eur J Pediatr. 2015;174:1319-1324.
16. Harjutsalo V, Sjöberg L, Tuomilehto J. Time trends in the incidence of type 1 diabetes in Finnish children: a cohort study. Lancet. 2008;371: 1777-1782.
17. Gyürüs EK, Patterson C, Soltesz G, Hungarian Childhood Diabetes Epidemiology Group. Twenty-one years of prospective incidence of childhood type 1 diabetes in Hungary - the rising trend continues (or peaks and highlands?). Pediatr Diabetes. 2012;13:21-25.
18. World Health organization. Diabetes Mellitus: Report of a WHO Study group. Technical Report Series Number 727. Geneva: World Health Organization; 1985
19. Fernández-Ramos C, Arana-Arri E, Jiménez-Huertas P, Vela A, Ria I. Incidence of childhood-onset type 1 diabetes in Biscay, Spain, 1990-2013. Pediatr Diabetes. 2017;18:71-76.
20. International Diabetes Federation. IDF Diabetes Atlas. 8th ed. Brussels, Belgium: International Diabetes Federation; 2017.
21. Chueca M, Oyarzabal M, Reparaz F, García G. Type 1 diabetes in Navarre (Spain) during the last two decades. Gac Sanit. 2013;27:566-568.
25. Valent F, Candido R, Faleschini E, et al. The incidence rate and prevalence of pediatric type 1 diabetes mellitus (age 0-18) in the Italian region Friuli Venezia Giulia: population-based estimates through the analysis of health administrative databases. *Acta Diabetol*. 2016;53:629-635.

26. Fortunato F, Capelli MG, Vece MM, Childhood-Onset Diabetes Registry Workgroup, et al. Incidence of type 1 diabetes among children and adolescents in Italy between 2009 and 2013: the role of a Regional Childhood Diabetes Registry. *J Diabetes Res*. 2016;2016:7239692-7239697. https://doi.org/10.1155/2016/7239692.

27. Teeäär T, Liivak N, Heilman K, et al. Increasing incidence of childhood-onset type 1 diabetes mellitus among Estonian children in 1999-2006. Time trend analysis 1983-2006. *Pediatr Diabetes*. 2010;11:107-110.

28. Sella T, Shoshan A, Goren I, et al. A retrospective study of the incidence of diagnosed type 1 diabetes among children and adolescents in a large health organization in Israel, 2000-2008. *Diabet Med*. 2011;28:48-53.

29. Ak I, Gulliforg MC. Trends in type 1 diabetes incidence in the UK in 0-to 14-year-olds and in 15- to 34-year-olds, 1991-2008. *Diabet Med*. 2011;28:811-814.

30. Bruno G, Maule M, Merletti F, et al. Age-period-cohort analysis of 1990-2003 incidence time trends of childhood diabetes in Italy: the RIDI study. *Diabetes*. 2010;59:2281-2287.

31. Kyvik KO, Nystrom L, Gorus F, et al. The epidemiology of type 1 diabetes mellitus is not the same in young adults as in children. *Diabetologia*. 2004;47:377-384.

32. Díaz-Valencia P, Bougnères P, Valleron AJ. Global epidemiology of type 1 diabetes in young adults: a systematic review. *BMC Public Health*. 2015;15:255-269.

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