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Increased incidence of pediatric type 1 diabetes during the pandemic in Biscay, Spain

Concepción Fernández-Ramos[a,*], **Eunate Arana-Arri**[b], **Amaia Vela**[c], **Inés Urrutia**[d], **Borja Santos Zorrozua**[e], **Itxaso Rica**[f]

[a] *Pediatric Endocrinology Unit, Biobizkaia Health Research Institute, Basurto University Hospital, University of the Basque Country (UPV/EHU), Avenida Montevideo 18, 48013 Bilbao, Bizkaia, Spain*
[b] *Clinical Epidemiology Unit, Biobizkaia Health Research Institute, Cruces University Hospital, Plaza de Cruces s/n, 48903 Barakaldo, Bizkaia, Spain*
[c] *Pediatric Endocrinology Unit, Biobizkaia Health Research Institute, Cruces University Hospital, University of the Basque Country (UPV/EHU), CIBERDEM, Plaza de Cruces s/n, 48903 Barakaldo, Bizkaia, Spain*
[d] *Biobizkaia Health Research Institute, CIBERDEM, CIBERER, University of the Basque Country (UPV/EHU), Endo-ERN, Plaza de Cruces s/n, 48903 Barakaldo, Bizkaia, Spain*
[e] *Bioinformatics, Biostatistics and Information Systems Unit, Biobizkaia Health Research Institute, Plaza de Cruces s/n, 48903 Barakaldo, Bizkaia, Spain*
[f] *Pediatric Endocrinology Unit, Biobizkaia Health Research Institute, Cruces University Hospital, CIBERDEM, CIBERER, Plaza de Cruces s/n, 48903 Barakaldo, Bizkaia, Spain*

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KEYWORDS
Epidemiology;
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Abstract
Objective: To update the incidence rate (IR) and trends of type 1 diabetes mellitus (T1DM) in children aged 0–14 years from 2003 to 2022, in Biscay, Spain.
Subjects and method: We used the capture–recapture method: primary cases were prospectively extracted from the hospital registry and a secondary independent data source was obtained from diabetes associations and a public health database. The IRs standardized by age and sex were calculated using the direct method, assuming an equal distribution in each age/sex group. The IR occurring during the various COVID-19 waves was compared with the pre-pandemic IR.
Results: A total of 378 new cases were identified. The mean age at diagnosis was 9.7 years (5.8–11.9). The completeness of ascertainment was 99.1%. The mean annual age-standardized IR was 12.92 (95%CI, 11.35–13.91). The mean IRs for the 0–4, 5–9, and 10–14 age groups were 7.67, 13.41 and 17.83 cases/100,000 children/year, respectively. The IR trend was statistically significant in the entire group and in the 5–9 year-old group with a mean annual increase of 1.9% (95%CI, 0.1–3.8) and 3.3% (95%CI, 1.002–1.065); $p = 0.039$.

* Corresponding author.
E-mail address: conchi.fernandezramos@osakidetza.eus (C. Fernández-Ramos).

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The 5-year period analysis confirmed that the increase was significant only in the last 5 years (20%). When 2020−2022 (pandemic) and 2017−2019 (pre-pandemic) periods were compared this difference goes up to 44.5%; $p = 0.029$.
Conclusions: After a long period of stability in the IR of T1DM in children younger than 15 years of age in Biscay, Spain, an increase in recent years has been reported, which is consistent with the SARS-CoV2 pandemic, with the largest increase being reported in the 5-to 9-year-old age group.

PALABRAS CLAVE
Epidemiologia;
Incidencia;
Tendencia en incidencia;
Diabetes mellitus tipo 1;
COVID-19

Aumento de la incidencia de diabetes tipo 1 pediátrica durante la pandemia en Bizkaia

Resumen
Objetivo: Actualizar la tasa de incidencia (TI) y la tendencia de diabetes mellitus tipo 1 en niños de 0 a 14 años desde 2003 hasta 2022 en Bizkaia.
Sujetos y método: Se utilizó el método de captura-recaptura: los casos primarios se extrajeron de forma prospectiva del registro hospitalario, y la fuente de datos secundaria independiente fueron las asociaciones de diabetes y la base de datos de salud pública. Las tasas de incidencia estandarizadas por edad y sexo se calcularon mediante el método directo, suponiendo una distribución equitativa en cada grupo de edad/sexo. Se comparó la incidencia que se produjo durante las distintas oleadas de COVID con la del período prepandémico.
Resultados: Se identificaron 378 nuevos casos. La edad media al diagnóstico fue de 9,7 años (5,8-11,9). La exhaustividad fue del 99,1%. La TI media anual estandarizada por edad fue de 12,92 (IC 95%: 11,35-13,91). La incidencia media para los grupos de edad de 0 a 4, 5 a 9 y 10 a 14 años fue de 7,67, 13,41 y 17,83 casos/100.000 niños/año, respectivamente. La tendencia de la tasa de incidencia fue estadísticamente significativa, en el grupo total y en el grupo de 5 a 9 años, con un aumento promedio anual del 1,9% (IC 95%: 0,1-3,8) y del 3,3% (IC 95%: 1,002-1,065), $p = 0,039$.

Analizando por quinquenios el incremento es significativo solo en los últimos 5 años, siendo del 20%. Al comparar el periodo 2020-2022 (pandemia) respecto al 2017-2019 (prepandemia), esta diferencia es del 44,5% ($p = 0,029$).
Conclusiones: Tras un largo periodo de estabilidad en la incidencia de diabetes mellitus tipo 1 en menores de 15 años en Bizkaia, se ha producido en los últimos años un aumento que coincidió con la pandemia de SARS-CoV-2, siendo el mayor incremento en el grupo de 5 a 9 años.

Introduction

Type 1 diabetes mellitus (T1DM) is a common chronic disease in children. The epidemiological studies conducted to determine its incidence rate (IR) are a priority because they facilitate the data necessary to estimate the resources that will be eventually required, both in the mid- and short-term, and also because they provide knowledge on the disease etiology and possible risk factors. The global IR of T1DM varies greatly between populations, with the highest rates being reported in Nordic countries and the lowest ones in countries such as Japan, Colombia, and Pakistan.[1] The explanation for the wide disparities in the IR between populations and ethnic groups could have to do with differences reported in the distribution of genetic susceptibility markers, differences in the distribution of environmental disease determinants, or a combination of the two.[2] Variations within the same ethnic group when the geographical location varies suggest the existence of environmental factors.

Coronavirus disease 19 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), has impacted all countries with varying IRs.[3–11] Understanding the impact that this new environmental factor may have had on the incidence of diabetes, or its mode of presentation is an opportunity to study the etiopathogenesis of the disease. For this reason, several studies have been published within the last 3 years, with great heterogeneity in methodology and objectives. Not all studies report the same trend in the incidence of diabetes and no clear conclusion can be drawn in this regard.

In Biscay, Spain we have been keeping a prospective registry of the incidence of diabetes mellitus in children younger than 15 years for decades following the same standardized methodology used for studies like this. In 2016, we published the IRs found in children younger than 15 years from 1990 to 2013 (10.7 cases/100,000 children/year) without a significant increase during that period.[12]

The aim of this study was to update the incidence of T1DM in recent years including the pandemic period, and analyze trends from 2003 to 2022 in patients younger than 15 years in Biscay, northern Spain.

Material and methods

Data collection

We conducted a prospective collection of pediatric patients younger than 15 years diagnosed with T1DM in full compliance with the criteria established by the World Health Organization (WHO)[13] from January 2003 to December 2022. The criteria for the diagnosis of T1DM were kept uniform throughout the study.

Data included children younger than 15 years, diagnosed with T1DM and living in Biscay, Spain for, at least, 6 months prior to disease onset. Other types of diabetes (T2DM, cystic fibrosis or drug-induced diabetes, and monogenic diabetes) were excluded.

The province of Biscay is a small geographical area with a population of f 1,142,396 inhabitants with 146,047 inhabitants younger than 15 years (6% of these are not Caucasians).[14]

Data collected at diagnosis included sex, age, insulin therapy data, place of residence, and date of birth. Insulin autoantibodies (IAA), autoantibodies to glutamate decarboxylase (GADA), tyrosine phosphatase-related islet antigen 2 (IA2A), and zinc transporter-8 autoantibodies (ZnT8A) were determined in serum at diagnosis using previously described standardized radioassays.[15] IAA were determined using a competitive fluid phase radioassay, which uses [125I]-labeled recombinant human insulin (PerkinElmer Inc, Waltham, MA, United States) as antigen. GADA, IA2A, and ZnT8A were determined using standardized radiobinding assays using recombinant human full-length glutamate decarboxylase labeled [35S] in vitro, IA2ic (amino acids 605-979), and ZnT8 antigens. The ZnT8A assay simultaneously measures autoantibodies for both variants of the COOH-terminal domain (Arg325/Trp325). Our lab has participated in various islet autoantibody standardization program workshops, the latest one held in 2020. The specificity rate was 100% for all 4 antibody assays and the sensitivity rate was 65% for IAA, 80% for GADA, and 72% for IA2A and ZnT8A. In cases in which autoantibodies were not detected, HLA and monogenic diabetes studies were performed. The rate of negativity is approximately 5.7%.[16]

We use the capture−recapture method with data records from 2 independent sources. As a primary source, we used the hospital electronic health records of patients from the 4 tertiary referral centers that take care of this population in Biscay, Spain. As a secondary source, health records from patient associations and computer diagnostic coding health records from primary health care programs were used. Matching was performed between these 2 sources to identify any potential duplicate records. The completeness of the percentage of ascertainment was taken as the number of observed cases and divided by the number estimated from the capture−recapture method. All denominators for the incidence calculations were provided annually by the Spanish Office of National Statistics.[14] The study was approved by the hospitals research and ethics committees. The information was processed anonymously with absolute data confidentiality and in full compliance with the Spanish current legislation and ethics regulations on the processing of information (the Spanish Organic Data Protection Law 3/2018 of 5 December).

Data on the incidence of COVID in the Basque Country, Spain were obtained from official sources from the Department of Health of the Basque Government published in weekly epidemiological bulletins on the advances made by COVID-19 in the Basque Country.[17]

Six different periods where the incidence of COVID-19 increased called ''waves'' were identified from March to June 2020 (wave #1), June to December 2020 (wave #2), December 2020 to March 2021 (wave #3), March to June 2021 (wave #4), June to October 2021 (wave #5), and October 2021 to March 2022 (wave #6).

Statistical methods

Age- and sex-specific IRs were calculated from the number of new cases divided by the number of persons-year at risk per 100,000 for the 2003-2022 period. Age- and sex-standardized incidence rates were obtained for the 0-14 year age group using the direct method according to the global population (WHO World Standard), consisting of equal numbers of children in each of the 6 subgroups defined by age (0−4, 5−9, and 10−14 years) and sex.[18] The 95% confidence interval (CI) for the IRs and their odd ratios (OR) was estimated using Poisson distribution.

Time was subdivided into 5-year periods to study data. For the analysis of the pre- and post-pandemic periods, data have been incorporated into 3-year periods.

Poisson regression models were used to analyze IRs by sex, age, and time period included in the model, and estimate the temporal trend in the overall IRs. Results are reported as OR (95% CI). p values < 0.05 were used to assess statistical significance.

The number of incident cases and the size of the study population during the 36 months preceding the start of the pandemic and within the first 24 months following the start of the pandemic period were used to calculate the incidence rate ratio (IRR), pooled IRR, and corresponding 95%CIs.

Differences in sex and age were analyzed using a 2-sample t-test. Seasonal variation was evaluated using the Chi-square test. Seasons were classified as spring: April−June; summer: July−September; autumn: October−December; and winter: January−March.

Statistical analysis was performed using Stata® 16 software.

Results

During the study period (2003−2022), a total of 378 children with newly diagnosed T1DM met the inclusion criteria (204 boys and 174 girls). The median age at diagnosis was 9.7

Table 1 Mean annual age and sex-specific IR of T1DM in Biscay split across 5-year periods.

	2003–2007			2008–2012			2013–2017			2018–2022		
	Cases	IR	Incidence rate (95%CI)	Cases	IR	Incidence rate (95%CI)	Cases	IR	Incidence rate (95%CI)	Cases	IR	Incidence rate (95%CI)
Boys												
0–4	12	10.13	5.23–17.7	7	5.102	2.05–10.51	8	6.406	2.76–12.62	13	11.55	6.14–19.74
5–9	14	12.78	6.98–21.45	9	7.055	3.22–13.39	16	11.48	6.56–18.64	28	21.2	14.09–30.64
10–14	21	19.18	11.87–29.32	21	18.46	11.43–28.22	27	20.51	13.51–29.84	28	20.25	13.46–29.27
0–14	47	13.93	10.23–18.52	37	9.775	6.88–13.47	51	12.88	9.59–16.94	69	18.02	14.02–22.81
Girls												
0–4	6	5.158	1.89–11.23	10	7.699	3.69–14.16	4	3.297	0.89–8.44.	14	13.49	7.37–22.63
5–9	13	12.58	6.69–21.52	17	14.06	8.19–22.52	19	14.36	8.64–22.42	17	13.44	7.83–21.52
10- 14	20	19.27	11.77–29.76	15	13.93	7.79–22.97	21	16.88	10.45–25.81	18	13.83	8.19–21.85
0–14	39	12.06	8.57–16.48	42	11.72	8.44–15.84	44	11.64	8.45–15.62	49	13.59	10.06–17.97
Total												
0–4	18	7.667	4.54–12.12	17	6.365	3.70–10.19	12	4.874	2.51–8.51.	27	12.48	8.22–18.15
5–9	27	12.69	8.36–18.46	26	10.46	6.83–15.33	35	12.88	8.97–17.91	45	17.41	12.7–23.29
10–14	41	19.22	13.79–26.08	36	16.26	11.39–22.51	48	18.75	13.82–24.85	46	17.13	12.54–22.86
0–14	86	13.01	10.41–16.07	79	10.72	8.48–13.36	95	12.27	9.93–15.01	118	15.87	13.14–19.01

years (IQR, 5.8–11.9 years). There were no statistically significant differences between the age of onset in boys (9.8 years [IQR, 5.9–12.3 years]) and in girls (9.4 years [IQR, 5.7–11.5 years]) for any of the study periods.

The degree of completeness in the primary source is 95%, and the safety of both sources, 99.1%.

The rate of positivity for antipancreatic autoantibodies at the beginning of the study did not differ across the study period (94% up to 95%).

Incidence rates

The overall IR observed during the 2003–2022 period was 12.97/100,000/year (95%CI, 11.37–13.94).

The age-standardized IR was 12.92/100,000/year (95%CI, 11.35–13.91) without significant differences between sexes (boys, 13.65; girls, 12.25).

The mean IRs for the 0–4, 5–9, and 10–14 age groups were 7.67, 13.41 and 17.83 per 100,000 children/year, respectively.

The age- and sex-category-specific rate for the 5-year periods is shown in Table 1.

Over the past 5-year period, the IR for the 5–9 year-old group (17.41) is even higher vs the IR for the 10–14 year-old group (17.13). The IR for the 0–4 year-old age group for girls over the past 5 years was very similar to the IR of the 5–9 or 10–14 year-old age groups, which was not seen in any other period or sex.

Incidence trends

The change in IR over a 20-year span showed an annual mean increase of 1.9% (95%CI, 0.10–3.8; *p*: 0.038) (Fig. 1).

Trends based on period, sex, and age groups are reported in Table 2.

We saw a 20% increase over the past 5 years (2018–2022); $p = 0.006$.

This trend is significant in the 5–9 age group for the entire period with a yearly mean increase of 3.3% (95%CI, 1.002–1.065); $p = 0.039$.

Broken down by sexes, trend is significance for the group of boys both as a whole with a 2.9% increase (95%CI, 1.004–1.055); $p = 0.023$ and in the subgroup of 5–9 year-olds, with a 5.6% increase (95%CI, 1.010–1.104); $p = 0.016$.

Seasonality of onset

There were no differences in the diagnosis of T1DM among the 4 seasons (spring, 24.1%; winter, 25.4%; autumn, 26.4%, and summer, 24.1%) in all the study years.

Incidence of new cases of diabetes in relation to waves of COVID

The IR of COVID 19 fluctuated with periods of ups and downs known as waves. We compared the IR of diabetes from the beginning of the pandemic (March 2020) to wave #6 (October 2021) with similar periods in the preceding 3 years.

When comparing the IR in the 2020–2022 period (pandemic period) vs the 2017–2019 IR (pre-pandemic period), the IRR is 1.445 (95%CI, 1.036–2.017), which is a significant difference; $p = 0.029$. We also found significance when comparing the specific period of wave #6, as detailed in Fig. 2, which compares the period of each wave peak during the COVID pandemic with a similar pre-pandemic period. We can observe increases in most periods, being significant in wave #6.

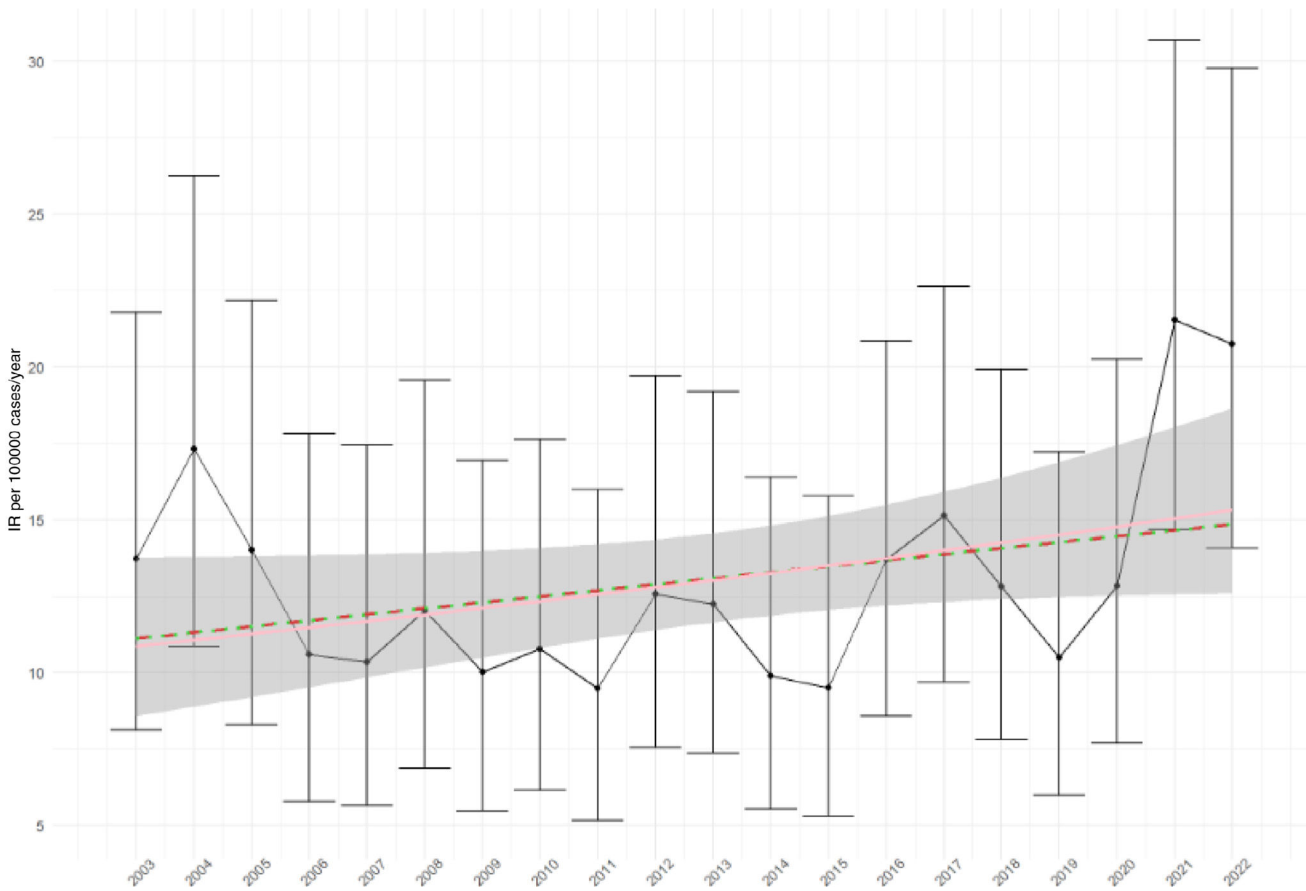

Figure 1 Age-standardized IR (with 95% confidence intervals) for T1DM in 0–14 year-old children in Biscay for each year from 2003 to 2022 with a fitted log-linear trend. Dotted line: estimated trend from the Poisson model.

Table 2 Incidence rate ratio (IRR) and 95%CI based on period, sex, and age groups.

	IRR	95%CI	*p*
2003–2007	0.893	0.768–1.039	0.140
2008–2012	1.017	0.870–1.190	0.829
2013–2017	1.089	0.945–1.258	0.240
2018–2022	1.200	1.055–1.368	0.006
From 2003 to 2022	1.019	0.001–2.077	0.038
0–4 yr	1.035	0.993–1.079	0.105
5–9 yr	1.033	1.002–1.065	0.039
10–14 yr	0.996	0.971–1.023	0.786
Boys	1.029	1.004–1.055	0.023
0–4 yr	1.013	0.958–1.071	0.650
5–9 yr	1.056	1.010–1.104	0.016
10–14 yr	1.011	0.977–1.047	0.520
Girls	1.008	0.982–1.035	0.551
0–4 yr	1.061	0.997–1.128	0.060
5–9 yr	1.011	0.968–1.055	0.629
10–14 yr	0.977	0.939–1.016	0.250

Discussion

The mean IR of T1DM in Biscay for 2003–2022 was 12.97/100,000/year. The results of this study show that there was a significant change in the IR throughout the entire period. This IR is lower than the one reported by most European studies[19] and Spanish territories.[20] In the work conducted by Rodriguez[21] in Asturias, also in northern

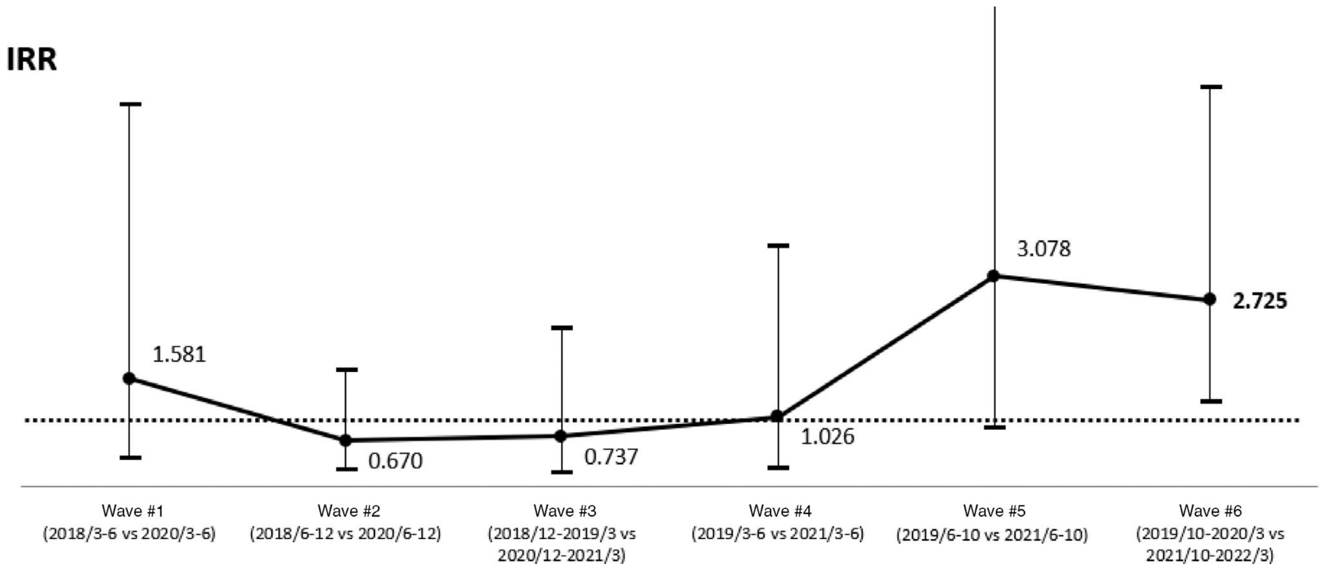

Figure 2 Trends of IRR in the onset of T1DM in children younger than 15 years comparing COVID wave periods with a similar pre-pandemic period.

Spain, an IR of 19.6 cases/100,000/year in children younger than 15 years was reported in the period 2011–2020. Regarding our data from the previous report,[12] the mean age has increased by 0.8 years globally and the age standard IR has increased by 1.92 points remaining as a low IR.[22]

Regarding changes to IR in different age groups, in Finland, Parviainen[23] reports an increase of 0.45 years in the mean age at diagnosis with a decrease in IR in the younger group. Others, however, show an increase in their IR affecting more the 10–14 year age group such as Canterbury.[24] In our work, a significant increase was observed in the group of children aged 5–9 years.

The trend of IR increases significantly in the period 2018–2022 after previous years of plateau. In this work, we presented data from a 20-year period to analyze the trend thoroughly, avoiding fluctuations of analysis over a short period. Pre-pandemic reports identified a plateau or even a decline in the IR according to data from Ireland,[25] Sweden,[26] Finland,[27] and Norway.[28] The pandemic caused by SARS-CoV2 has given epidemiologists a new opportunity to study changes in the way diabetes shows up. In 2020, the first studies ever conducted on the effect of COVID 19 on T1DM were published, and they were uneven: some of them reported an increase in wave#1 of the pandemic vs previous years[3]; in others the increases were not significant compared to what would have been expected,[4] or even for the same country, as it occurred in Italy, where some authors reported lower IR,[5] and others reported significant increases in 2021 of up to 31%.[6] The limitation of these studies is that they cannot establish IR since data were collected from a single hospital or were not part of registries. In all of them, we should remember that the periods analyzed are short because the objective of the studies was to see the effect the pandemic had on the IR.[3–7]

In Czechia, Cinek revealed the IR from 2005 to 2021 showing a greater-than-expected increase over the past 2 years, with an IRR of 1.16. Within the first few months of the strictest lockdown, new diagnoses decreased, but then went up what would have been expected for the summer months.[8]

In Germany in 2022, after the first study that reported no increases whatoever,[4] the DPV registry published a 15% increase (from January 2020 to June 2021) in the observed vs the expected IR of T1DM.[9] A cohort study conducted in the Finnish Pediatric Diabetes Registry reported that the annual IR had increased from 39 cases in 2016–2019 up to 56 per 100,000 inhabitants from April to October 2020,[10] while in Scotland a 20% increase was also reported from 2020 to 2021 vs the previous 7 years,[11] while in Ireland the increase was 21% in the pandemic years.[29]

We know that the IR of T1DM does not follow a pattern of constant increase, but a cyclical variation that reveals the influence of external factors.[30] The relationship between periodicity or IR increases and infectious epidemics such as flu has been sought.[31] Some environmental factors may act, even at birth, while others are more likely to play a role in precipitating clinical diagnosis in patients whose pancreatic insulin production is already compromised.[32]

The hypothesis proposed by studies that have seen IR increases, such as the one that occurs in our region with a 44.5% increase in the relative risk is that the transition from stage 2 to stage 3 of the natural progression of diabetes has accelerated. This would suggest an advanced age of onset, increasing the number of patients in the 5–9 and 0–4 year-old groups, subtracting from the 10-to-14 year-old group. Different factors may have contributed to the acceleration of the disease, such as the fact that a viral infection affected the entire population in a short period of time, or the psychological stress due to confinement or social distancing. For Craig[33] the host immune response to infection plays a key role in susceptibility, yet we cannot specify when the autoimmune process begins or, for that matter, symptom onset.

Studies that looked at the IR of diabetes in patients with positive or negative SARS-CoV2 serology did not find any differences. We haven't been able to demonstrate a higher incidence of SARS-CoV2 antibody positivity in patients with new-onset T1DM during the pandemic, or the direct relationship between infection and diabetes, suggesting that there are other causes in populations that have seen IR peaks.[11,23,24,29–34] The association between SARS-CoV2 infection and the development of new-onset T1DM is still to be elucidated.

The strength of this study is that it was a registry conducted over a long period of time with homogeneous methodology, avoiding the fluctuation biases that can occur in short periods of time. Our study does not include data on previous SARS-CoV2 infection or SARS-CoV2 antibodies in the study population which is, therefore, a limitation to establish a relationship.

In conclusion, after a long period of stability in Biscay in the IR of T1DM in children younger than 15 years, we have seen an increase in recent years consistent with the SARS-CoV2 pandemic, with the highest increase being reported in the 5–9 year-old age group.

Monitoring the IR of T1DM based on periodic records is highly significant in determining epidemiological trends. Whether the increase still remains or has been the result of the natural course of the disease in susceptible subjects will need to be analyzed.

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Conflict of interest

The authors declare that they have no conflict of interest.

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