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Trends and cyclic variation in the incidence of childhood type 1 diabetes in two Italian regions over 33 years and during the COVID-19 pandemic

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Abstract

Aim: There is conflicting evidence about the impact of the COVID-19 pandemic on the incidence of type 1 diabetes. Here, we analysed long-term trends in the incidence of type 1 diabetes in Italian children and adolescents from 1989 to 2019 and compared the incidence observed during the COVID-19 pandemic with that estimated from long-term data.

Materials and Methods: This was a population-based incidence study using longitudinal data from two diabetes registries in mainland Italy. Trends in the incidence of type 1 diabetes from 1 January 1989 to 31 December 2019 were estimated using Poisson and segmented regression models.

Results: There was a significant increasing trend in the incidence of type 1 diabetes of 3.6% per year [95% confidence interval (CI): 2.4-4.8] between 1989 and 2003, a breakpoint in 2003, and then a constant incidence until 2019 (0.5%, 95% CI: -1.3 to 2.4). There was a significant 4-year cycle in incidence over the entire study period. The rate observed in 2021 (26.7, 95% CI: 23.0-30.9) was significantly higher than expected (19.5, 95% CI: 17.6-21.4; $p = .010$).

Conclusion: Long-term incidence analysis showed an unexpected increase in new cases of type 1 diabetes in 2021. The incidence of type 1 diabetes now needs continuous monitoring using population registries to understand better the impact of COVID-19 on new-onset type 1 diabetes in children.

KEYWORDS
COVID-19, incidence, paediatric type 1 diabetes, population

1 | INTRODUCTION

The incidence of type 1 diabetes has increased worldwide over the past 30 years, with annual growth rates estimated at 3%-4%.[1] However, there have also been more recent reports of non-linear trends in growth rates, with a tendency to a stabilization or even slight reductions in incidence.[2] For example, in Finland, there was a steady increase in incidence between 2003 and 2006 followed by a slightly decreasing trend between 2007 and 2018.[3] The increased incidence in type 1 diabetes previously observed in Sweden[4] and Norway[5] stabilized from 2005 and 2004 onwards, respectively. Type 1 diabetes is a multifactorial autoimmune disease caused by interactions between genes, environment and lifestyle.[6] As genetic changes in populations occur over a long period, environmental changes would probably play a major role in short-term changes in incidence. However, no definitive exogenous causal factor has yet been identified. Viral infections might trigger autoimmunity, as suggested by the temporal association between coxsackie B virus infections and the appearance of the first β-cell autoantibodies.[7] The SARS-CoV-2 virus, with its clinical manifestations termed COVID-19, spread rapidly through Italy from March 2020 as in other parts of the world and persists today with repeated waves of reduced clinical severity.

It has been widely reported that there was a marked increase in the frequency of diabetic ketoacidosis at the time of diagnosis of childhood diabetes during the COVID-19 pandemic.[8,9] However, it is still unclear whether the incidence of type 1 diabetes changed during the pandemic. Results from early published reports were conflicting, with some suggesting an increase in new cases of type 1 diabetes[10,11] and others no change from the pre-pandemic period.[12] More recently, a large population study from Germany over a longer period confirmed an increased incidence of childhood type 1 diabetes during the COVID-19 pandemic.[13] No information is currently available on the long-term changes in incidence of childhood type 1 diabetes in Italy. Therefore, the aims of this study were (a) to analyse long-term trends in the incidence of type 1 diabetes in Italian children and adolescents from 1989 to 2019 using the population registries in two regions of Italy, and (b) to compare the incidence of type 1 diabetes observed during the COVID-19 pandemic (2020-2021) with that estimated from the calculated long-term incidence.

2 | MATERIALS AND METHODS

2.1 | Data source and study population

This report follows the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines for longitudinal studies (Figure S1 and STROBE Checklist).

Data were obtained from the population-based incidence registry of type 1 diabetes in two regions in Central and Northern Italy (Marche and Piedmont). Type 1 diabetes surveillance registries were established in both regions in January 1990, which have since prospectively collected data on all new cases of type 1 diabetes occurring in children between 6 months and 14 years of age.[14] Both registries retrospectively included 1989 incidence data. The two regions covered a geographical area of 34 731 km^2 (Piedmont 25 387 km^2; Marche 9344 km^2) and a total population of children and adolescents under 15 years of 687 429 (Piedmont 507 623; Marche 179 806) in 2021. The children's parents or guardians provide verbal or written informed consent for participation in the registries.

Case definitions were as previously described.[14] Briefly, each regional registry collects hospital discharge data from local paediatric and adult diabetes centres verified locally using at least two sources of assessment data. Regional registries of insulin prescriptions, personal codes for the free prescription of syringes, devices and drugs by the national health system, and registers of patient associations are used as independent secondary sources. The data flow is continuously checked by reviewing local logs, and inconsistent data are verified via a report sent to the detection source so that corrections can be made and the data validated. For both the Marche and Piedmont registries, the completeness of the assessment was >95% for the entire 1989-2021 study period. All data were completely anonymized and centralized for analysis.

2.2 | Statistical analysis

The crude and age- and sex-specific incidence rates for each year of study (1989-2021) were calculated using point estimates and 95% confidence interval (95% CI). Incidence rates were obtained by dividing the number of registered cases by the annual population resident in the two regions according to the Italian National Institute of Statistics. The population was considered in three age-group ranges: 0.5-4, 5-9 and 10-14 years. Age-standardized incidence rates for males and females were estimated using the direct method with the standard European population. All rates were expressed in 100 000 person-years.

Poisson regression models were applied to estimate the overall trend in incidence rates, adjusted for sex and age, and the trend in incidence rates stratified by age and sex, between 1989 and 2019. The annual population was included in the model as an off-set to consider any possible demographic variations over time. Following previously reported results of 4-, 5- and 6-year cycles in incidence rates, sine and cosine terms were included in the Poisson regression models to detect cyclical variations in annual rates. A possible breakpoint in the long-term trend was assessed by fitting the segmented regression to the estimates obtained from the Poisson regression models. The overall and age- and sex-specific incidence rates observed in 2020 and 2021 were compared with those predicted by the segmented regression models. All analyses were performed in R version 4.0.4. A probability of 5% was used to assess statistical significance.

3 | RESULTS

Overall, 4009 new cases of type 1 diabetes were recorded between 1989 and 2021, 53.5% of whom were male.

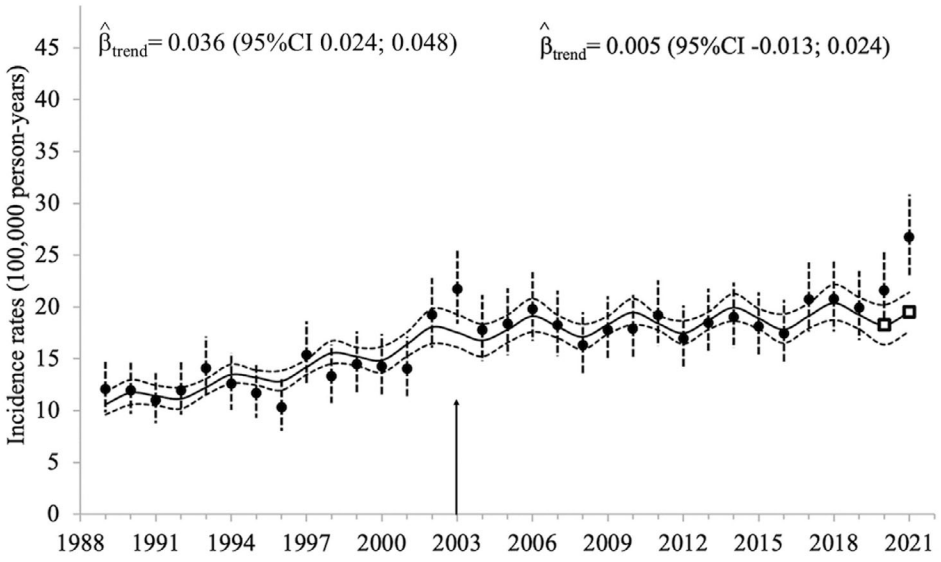

FIGURE 1 Trend analysis of type 1 diabetes incidence rates in children aged 0.5-14 years in two Italian regions, 1989-2021. Circles and vertical dotted lines: observed rates and 95% confidence interval (CI) per year, 1989-2021. Solid lines: incidence trend estimated by the regression model adjusted by sex and age classes with a 4-year cyclic component during the period 1989-2019. Dotted lines: 95% CIs of the estimated incidence trend. Squares: expected rates for 2020-2021 estimated by the regression model. Arrow: breakpoint year detected by the segmented regression model.

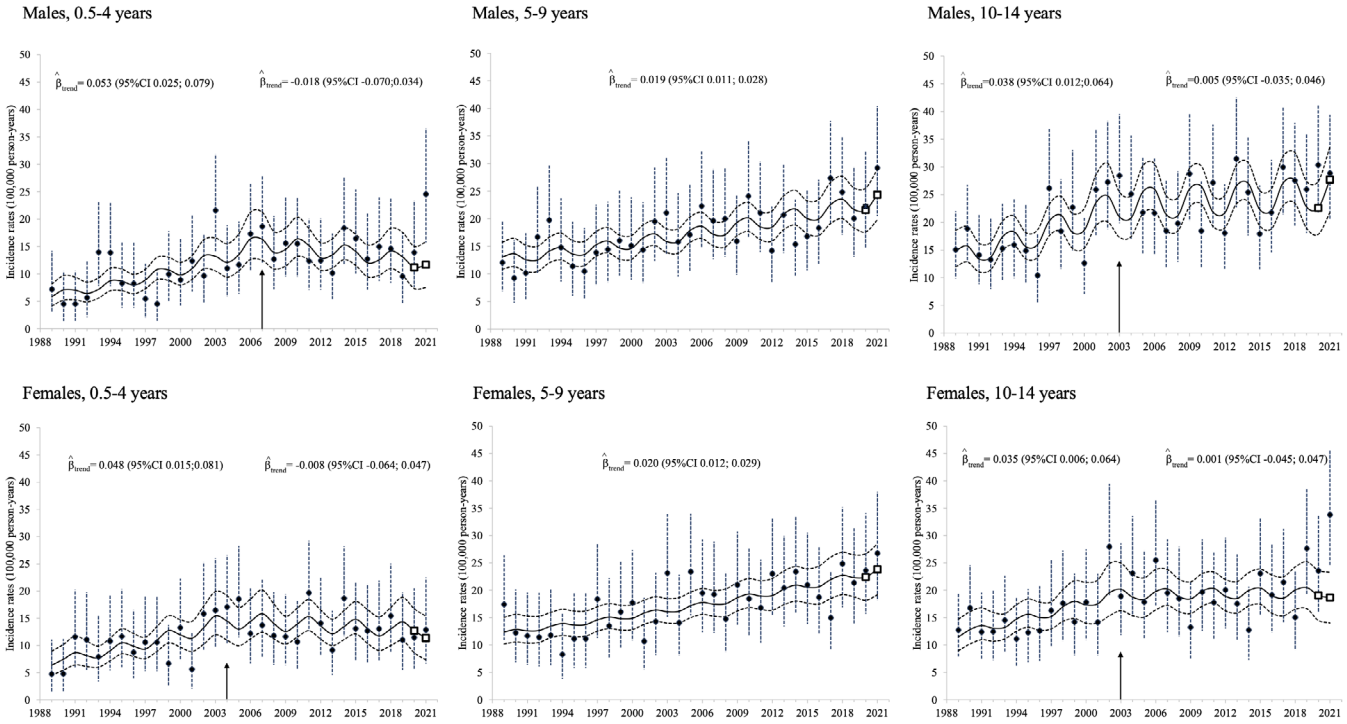

FIGURE 2 Trend analysis of type 1 diabetes incidence rates in males and females aged 0.5-14 years in two Italian regions according to age subgroups, 1989-2021. Circles and vertical dotted lines: observed rates and 95% confidence interval (CI) per year, 1989-2021. Solid lines: incidence trend estimated by the regression model with a 4-year cyclic component during the period 1989-2019. Dotted lines: 95% CIs of the estimated incidence trend. Squares: expected rates for 2020-2021 estimated by the regression model. Arrow: breakpoint year detected by the segmented regression model.

The overall standardized incidence rate was 16.9, increasing from 12.0 in 1989 to 26.6 in 2021. Total numbers of children with a new diagnosis of type 1 diabetes over the 33-year period and the crude and age-standardized incidence rates with 95% CI for males and females are shown in Table S1. The crude and standardized incidence rates estimated for the entire period were similar in males and females.

The incidence rate for the 0.5-4-year age group (12.2, 95% CI: 11.4-13.0) over the entire period was significantly lower than in the two older age groups (17.7, 95% CI: 16.8-18.6 and 19.9, 95% CI: 19.0-20.9, respectively, for the 5-9- and 10-14-year groups; $p < .001$) (Table S2).

The trend analysis adjusted for age and sex is shown in Figure 1, which shows the observed annual incidence rates for 1989-2021 with

95% CIs, the incidence rate trend with 95% CI estimated by the regression model for 1989-2019, and the expected incidence rates for the pandemic years. A significant increasing trend of 3.6% per year was observed between 1989 and 2003 (95% CI: 2.4-4.8). Segmented regression revealed a breakpoint in 2003, followed by a constant trend until 2019 (0.5%, 95% CI: -1.3 to 2.4). A significant 4-year cycle was found over the entire study period that allowed for more accurate prediction of the incidence rate over time. From the comparison between the observed and expected rates, it emerged that the rate in 2020 (21.6, 95% CI: 18.3-25.3) followed the trend estimated by the model for 2004-2019 (18.3, 95% CI: 16.3-20.2), while the rate observed in 2021 (26.7, 95% CI: 23.0-30.9) was significantly higher than expected (19.5, 95% CI: 17.6-21.4; $p = .010$). No significant differences were found in the frequencies of β-cell autoantibody negativity from 2017 to 2021 (Table S3), with the highest observed value in 2018 and the lowest in 2021.

The trend analysis of sex- and age-specific incidence rates is shown in Figure 2. Age- and sex-stratified analyses showed that rates followed the general trend but with different breakpoints. In the 0.5-4-year subgroup, the breakpoint was in 2007 in males and in 2004 in females; in the 5-9-year subgroup, there were no breakpoints; while in the 10-14-year subgroup, there was a breakpoint in 2003 for both sexes. Incidence rates increased significantly up to the breakpoint year, while in the subsequent period up to 2019 the rate trend remained constant for the 0.5-4- and 10-14-year subgroups for males and females. Rates in the 5-9-year subgroup significantly increased for both sexes over the 31-year period by about 2% per year. The 4-year cycle was statistically significant for males in the 10-14-year age group. Comparison of the observed and expected rates was statistically significant for males aged 0.5-4 years and females aged 10-14 years in the second year of the pandemic.

4 | DISCUSSION

This study reports incidence data of type 1 diabetes in Italian children and adolescents under 15 years of age based on data collected over 33 years from two population registries. Our results confirm the presence of a 4-year cycle in the incidence of type 1 diabetes and an increasing annual trend in the incidence from 1989 to 2003 of 3.6% per year, a breakpoint in 2003, followed by a stable period from 2004 to 2019. During the second year of the COVID-19 pandemic, there was a huge increase in the incidence of type 1 diabetes, reaching an unprecedented rate of 26.7 per 100 000 person-years. These increases were statistically significant in 0.5-4-year-old boys and 10-14-year-old girls. Because of the descriptive nature of the study, it is not possible to explain the mechanism underlying the observed differences, with further analytical studies required to explain fully these differences.

This analysis over such a long observation period highlighted two subperiods of considerable length, separated by a breakpoint year, and characterized by two different trends in incidence rates. Our results are consistent with the stabilization in incidence observed in Sweden from 2005 to 2007[4] and in Norway from 2004 to 2012.[5] In the present study, the breakpoint was in the same period but the subsequent stability in incidence was observed over a much longer period. Recent data from Austria,[15] also based on a long observation period (1989-2017), showed an increasing trend until 2012 followed by a high-level plateau. This contrasts with Germany,[13] where the incidence was reported to increase between 2011 and 2019, while data from Finland suggested a decreasing incidence between 2003 and 2018.[3] These differences in the patterns of incidence rates observed in various countries might be because of different exposures to yet unidentified environmental factors that trigger autoimmune destruction of β-cells.

A recent systematic review and meta-analysis of 24 studies estimated an overall increase in the incidence of paediatric type 1 diabetes from 19.73 per 100 000 person-years in 2019 to 32.39 in 2020.[16] This short-term analysis did not allow for the analysis of a cyclical variation, so it cannot be excluded that these observed variations were linked to periodicity in incidence. It has been suggested that SARS-CoV-2 infection might pre-date the clinical onset of type 1 diabetes by triggering autoimmune β-cell damage. There have been published reports[8,9] of an increase in diabetic ketoacidosis at the diagnosis of type 1 diabetes during the pandemic, suggesting that this period was associated with delays in diagnosis, but the impact of the pandemic on the incidence of type 1 diabetes remained unclear. Although our study now provides more data supporting an association between COVID-19 and increased incidence of type 1 diabetes, further studies with long observation periods before and after the pandemic are needed to evaluate further the effect of COVID-19 on the incidence of the disease.

In Italy, the SARS-CoV-2 pandemic has been characterized by several waves of different variants, but the total number of infections in 2021 were almost double those recorded in 2020 (Figure S2). It cannot be excluded that the dramatic increase in the incidence of type 1 diabetes observed in 2021 may be because of COVID-19, although the stability observed in the frequency of β-cell autoantibodies during 2017-2021 does not suggest that SARS-CoV-2 has a direct effect. Nested case-control studies in cohorts of interest will be needed to analyse the association between SARS-CoV-2 infection and the onset of type 1 diabetes. Furthermore, the continuous surveillance of the incidence will allow us to observe whether the dramatic increase in COVID-19 cases observed between January and September 2022 will be accompanied by a further increase in the incidence of type 1 diabetes in the third year of the pandemic.

In a previous international study,[1] periodicity was detected in only six of 26 participating registries. Italy participated with data from the Marche registry, which included 579 new cases of type 1 diabetes and in which no significant cyclical incidence was noted. The detection of a significant cyclical pattern in the present study can reasonably be attributed to the greater power obtained with the inclusion of data from the second registry. The cyclic pattern in type 1 diabetes incidence has been associated with the periodicity of environmental factors, in particular some infectious agents that occur at regular intervals.[1] Enterovirus[17] infections are thought to play a role in the onset

of type 1 diabetes, as have cyclical weather patterns that may modify lifestyles to alter the risk of childhood type 1 diabetes directly or indirectly.[18] We cannot exclude that environmental factors may also protect against type 1 diabetes, which could help explain the levelling of incidence rates observed in many countries after 2000. However, it is difficult to assess a direct relationship between environmental factors and disease onset, as the identification of causative determinants requires measuring exposure at the individual level in the target population, as used to detect the temporal association between infection from coxsackie B virus and the appearance of the first islet autoantibodies.[7]

This study has both strengths and limitations. Our results are obtained from a longitudinal population study with data recorded consecutively from two Italian registries for type 1 diabetes over a long period. Furthermore, the analysis was based on many observations, allowing us to detect an increasing trend followed by a levelling in incidence rates and the presence of a 4-year cycle throughout the observation period. Among the limitations, the data from the disease registries only considered a few potential confounders. Factors such as socio-economic status, environmental exposures and COVID-19 history were not routinely collected. Data analysis was based on an ecological study design and therefore subject to ecological bias. An analysis of the association between COVID-19 and the onset of type 1 diabetes was not possible for data at the individual level, as the COVID-19 status of the patients was only available for a few participants.

In conclusion, this long-term incidence analysis reveals an unexpected increase in new cases of type 1 diabetes in 2021. Further epidemiological observations in the years following the pandemic are now needed to understand better the impact of COVID-19 infection on the incidence of type 1 diabetes in children.

AUTHOR CONTRIBUTIONS

VC had full access to the data used in this article and is the guarantor of this study. VC and RG contributed to the study design and drafting, and gave the final approval for this version to be published. IR, VM, LDS, MM, VT, AI, LF and CG collected data. IR, FC and CG contributed to the discussion and revision of the manuscript. RG performed and was responsible for the integrity of the data and accuracy of the data analysis. VM contributed to the statistical analysis and drafting the manuscript. All authors have read and agreed to the published version of the manuscript.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Valentino Cherubini upon reasonable request.

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REFERENCES

1. Patterson CC, Harjutsalo V, Rosenbauer J, et al. Trends and cyclical variation in the incidence of childhood type 1 diabetes in 26 European centres in the 25 year period 1989–2013: a multicentre prospective registration study. *Diabetologia*. 2019;62(3):408-417. doi:10.1007/s00125-018-4763-3
2. Harjutsalo V, Sund R, Knip M, Groop P-H. Incidence of type 1 diabetes in Finland. *JAMA*. 2013;310(4):427-428. doi:10.1001/jama.2013.8399
3. Parviainen A, But A, Siljander H, Knip M. Decreased incidence of type 1 diabetes in young finnish children. *Diabetes Care*. 2020;43(12):2953-2958. doi:10.2337/dc20-0604
4. Berhan Y, Waernbaum I, Lind T, Möllsten A, Dahlquist G. Thirty years of prospective nationwide incidence of childhood type 1 diabetes: the accelerating increase by time tends to level off in Sweden. *Diabetes*. 2011;60(2):577-581. doi:10.2337/db10-0813
5. Skrivarhaug T, Stene LC, Drivvoll AK, Strøm H, Joner G. 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 registry. *Diabetologia*. 2014;57(1):57-62. doi:10.1007/s00125-013-3090-y
6. Norris JM, Johnson RK, Stene LC. Type 1 diabetes—early life origins and changing epidemiology. *Lancet Diabetes Endocrinol*. 2020;8(3):226-238. doi:10.1016/S2213-8587(19)30412-7
7. Laitinen OH, Honkanen H, Pakkanen O, et al. Coxsackievirus b1 is associated with induction of β-cells autoimmunity that portends type 1 diabetes. *Diabetes*. 2014;63(2):446-455. doi:10.2337/db13-0619
8. Cherubini V, Marino M, Scaramuzza AE, et al. The silent epidemic of diabetic ketoacidosis at diagnosis of type 1 diabetes in children and adolescents in Italy during the COVID-19 pandemic in 2020. *Front Endocrinol (Lausanne)*. 2022;13(June):1-9. doi:10.3389/fendo.2022.878634
9. Birkebaek N, Kamrath C, Grimsmann J, et al. Long-term trends in the frequency of diabetic ketoacidosis at diagnosis of paediatric type 1 diabetes and impact of the COVID-19 pandemic in 2020 and 2021 – an international multicentre study using 13 national. *Lancet Diabetes Endocrinol*. 2022;8587(22):1-9. doi:10.1016/S2213-8587(22)00246-7
10. Unsworth R, Wallace S, Oliver NS, et al. New-onset type 1 diabetes in children during COVID-19: multicenter regional findings in the U.K. *Diabetes Care*. 2020;43(11):e170-e171. doi:10.2337/dc20-1551
11. Salmi H, Heinonen S, Hästbacka J, et al. New-onset type 1 diabetes in Finnish children during the COVID-19 pandemic. *Arch Dis Child*. 2022;107(2):180-185. doi:10.1136/archdischild-2020-321220
12. Tittel SR, Rosenbauer J, Kamrath C, et al. Did the COVID-19 lockdown affect the incidence of pediatric type 1 diabetes in Germany? *Diabetes Care*. 2020;43(11):e172-e173. doi:10.2337/dc20-1633
13. Kamrath C, Rosenbauer J, Eckert AJ, et al. Incidence of type 1 diabetes in children and adolescents during the COVID-19 pandemic in Germany: results from the DPV registry. *Diabetes Care*. 2022;45:1762-1771. doi:10.2337/dc21-0969
14. Carle F, Gesuita R, Bruno G, et al. Diabetes incidence in 0- to 14-year age-group in Italy: a 10-year prospective study. *Diabetes Care*. 2004;27(12):2790-2796. doi:10.2337/diacare.27.12.2790
15. Rami-Merhar B, Hofer SE, Fröhlich-Reiterer E, Waldhoer T, Fritsch M. Time trends in incidence of diabetes mellitus in Austrian children and adolescents <15 years (1989-2017). *Pediatr Diabetes*. 2020;21(5):720-726. doi:10.1111/pedi.13038

16. Rahmati M, Keshvari M, Mirnasuri S, et al. The global impact of COVID-19 pandemic on the incidence of pediatric new-onset type 1 diabetes and ketoacidosis: a systematic review and meta-analysis. *J Med Virol*. 2022;94(11):5112-5127. doi:10.1002/jmv.27996
17. Wang K, Ye F, Chen Y, et al. Association between enterovirus infection and type 1 diabetes risk: a meta-analysis of 38 case-control studies. *Front Endocrinol (Lausanne)*. 2021;12(September):1-9. doi:10.3389/fendo.2021.706964
18. 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(11):2300-2302. doi:10.2337/dc12-0205

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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