diabetes research and clinical practice 193 (2022) 110146

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.journals.elsevier.com/diabetes-research-and-clinical-practice

Type 1 diabetes incidence in children and adolescents during the COVID-19 pandemic in Germany

Louisa van den Boom [a,b], Karel Kostev [c,*], Oliver Kuss [d,e,f], Wolfgang Rathmann [d,e], Joachim Rosenbauer [d,e]

[a] Division of Pediatrics, DRK Hospital, Kirchen, Germany
[b] Division of Pediatric Diabetology, Endocrinology, Metabolism and Obesity, Children's Hospital, University of Bonn, Bonn, Germany
[c] Epidemiology, IQVIA, Germany
[d] Institute for Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for Diabetes Research, Heinrich Heine University Düsseldorf, Düsseldorf, Germany
[e] German Center for Diabetes Research, München-Neuherberg, Germany
[f] Centre for Health and Society, Faculty of Medicine, Heinrich Heine University Düsseldorf, Düsseldorf, Germany

ARTICLE INFO

Keywords:
Type 1 diabetes
Incidence
Children and adolescents
COVID-19
Insulin therapy

ABSTRACT

Aims/hypothesis: The aim of this study was to analyze the incidence of type 1 diabetes in children and adolescents (<20 years of age) during the COVID-19 pandemic (3/2020 to 12/2021) in Germany.

Methods: The present study was based on the IQVIA longitudinal prescription database (LRx), All persons (age ≤ 20 years) with new insulin prescriptions from 2016 to 2021 (index date) were selected and stratified by age group. Weekly (age-specific) data were used to forecast the prescription incidence for the pandemic period based on pre-pandemic data and to explore the relationship between weekly reported age-specific COVID-19 incidences and type 1 diabetes incidence and rate ratios of observed vs. predicted diabetes incidence respectively.

Results: During the pre-pandemic period, there was a stable higher insulin prescription incidence during the winter period and a lower insulin prescription incidence during summer. During the pandemic period, there was less seasonal variation in incidence related to the finding that the observed incidence during summer in 2002 and 2021 was 44 % and 65 %, higher, respectively, than the expected incidence based on pre-pandemic year. We did not find any cross-correlations between the COVID-19 incidence and the type 1 diabetes incidence for any age group. Likewise, there were no cross-correlations between the COVID-19 incidence and the incidence rate ratios of observed incidences to predicted incidences.

Conclusions/interpretation: During the COVID-19 pandemic, there was less seasonal variation in the incidence of type 1 diabetes (defined by new insulin prescriptions), with higher observed than expected incidences during summer. We found no evidence that the increase in type 1 diabetes incidence during the COVID-19 pandemic relates to direct effects of COVID-19 pandemic.

1. Introduction

Currently, there are >32,000 children and adolescents living with type 1 diabetes in Germany, with the incidence of the disease rising by 3–4 % per year [1]. Viral infections seem to play a role in the pathogenesis of type 1 diabetes; in particular, it is suspected that respiratory viral infections contracted within the first 6 months of life may initiate beta cell autoimmunity [2,3]. The data currently available on type 1 diabetes incidence rates during COVID-19 are inconclusive. One German study comparing observed rates from March to May 2020 (first COVID-19 wave) with predicted rates for that period based on data from 2011 to 2019 showed no difference in type 1 diabetes incidence in children and adolescents [4]. Another study in Germany found a significantly increased incidence of type 1 diabetes in children during the COVID-19

Abbreviations: UK, United Kingdom; HCP, healthcare professional; LRx, longitudinal prescription; LOESS, locally estimated scatterplot smoothing; MIC, minimal information criteria; AR(I)MA, autoregressive (integrated) moving average; IRR, incidence rate ratio; SAS, Statistical Analysis Software; DPV, Diabetes-Patienten-Verlaufsdokumentation; ACE-2, angiotensin-converting enzyme-2; SARS-CoV 2, severe acute respiratory syndrome coronavirus type 2; COVID-19, coronavirus disease 2019; PY, person-years; CI, confidence interval.

* Corresponding author at: Epidemiology, IQVIA, Unterschweinstiege 2–14, 60549 Frankfurt am Main, Germany.
E-mail address: karel.kostev@iqvia.com (K. Kostev).

https://doi.org/10.1016/j.diabres.2022.110146
Received 5 August 2022; Received in revised form 30 October 2022; Accepted 1 November 2022
Available online 5 November 2022

pandemic [6] from January 1, 2020 to June 30, 2021 when compared to predicted incidence derived from pre-pandemic data [5]. One multi-center study in the UK also showed an increase in type 1 diabetes diagnoses in children who had contracted SARS-CoV-2 prior to diabetes onset. To date, however, there is no clear evidence indicating that the SARS-CoV-2 virus directly induces type 1 diabetes [6,7]. Social distancing and other measures during the COVID-19 pandemic have kept children away from school, day care, and peer groups, and therefore led to a profound decrease in diagnoses of common infectious diseases (influenza, croup, bronchiolitis) [8], but it is unclear whether they have also had an impact on type 1 diabetes incidence. Furthermore, psychological stress has been linked to the pathogenesis of type 1 diabetes and its onset, but it is unclear if social distancing, school closures, and isolation, which have negatively impacted the mental health and well-being of children and adolescents, are also stressors which may play a key role in type 1 diabetes onset in these groups [9,10]. The aims of this study were (1) to analyze the incidence of type 1 diabetes in children and adolescents during the COVID-19 pandemic (3/2020 to 12/2021) in Germany and compare it to the expected incidence in the same period and (2) to explore the relationship between weekly reported age-specific COVID-19 incidences and the type 1 diabetes incidence and the rate ratios of observed to predicted incidence, respectively.

2. Methods

2.1. Database

The present analysis was based on the IQVIA longitudinal prescription database (LRx). This database comprises approximately 80 % of all prescriptions reimbursed by statutory health insurance funds in Germany. Data is available at patient level, including information on the age and sex of patients. All patient information is fully anonymized in accordance with data privacy laws. Each available prescription includes full product information (e.g., brand, substance, package size, and product form) and dates dispensed. The database does not contain diagnoses or laboratory tests. This database has been used in previous studies on insulin therapy [11,12].

All children and adolescents (age < 20 years) with new insulin prescriptions between January 1, 2016 and December 31, 2021 (index date) were included in this study. Incident insulin therapy was defined as the first insulin therapy based on the absence of insulin prescriptions for at least 365 days before the index date (starting January 1, 2015). First insulin prescription was used as a surrogate measure for new-onset type 1 diabetes. The primary outcome of the study is the weekly incidence of type 1 diabetes in children and adolescents from the 10th calendar week in 2020 (March 2 to March 8, 2020) to the last calendar week in 2021 (December 27, 2021 to January 2, 2022) (pandemic period) compared to the period from the 1st calendar week in 2016 (January 4 to January 10, 2016) to the 9th calendar week in 2020 (February 24 to March 1, 2020) (pre-pandemic time). The incidence of insulin therapy initiation was also stratified by age group (<5 years; 5–<10 years; 10–<15 years; 15–<20 years) and analyzed with respect to these groups. Age-specific weekly COVID-19 incidences were obtained from the Robert Koch Institute [13]. Population data were obtained from the Federal Statistical Office of Germany [14].

2.2. Statistical analyses

In order to estimate the weekly type 1 diabetes incidence (per 100,000 person-years [PY]), the number of new cases with first insulin prescription in the respective week was related to the respective number of person-years at risk. The incidence for the total group (<20 years) was standardized in accordance with the direct method using equal weightings for all age groups.

Descriptive plots of weekly incidences including smooth curves resulting from locally estimated scatterplot smoothing (LOESS) were generated to present the incidence trends in the pre-pandemic and pandemic periods as well as the COVID-19 incidence.

In order to investigate deviations of the observed insulin prescription incidence during the pandemic period from the predicted one, we first used time series models (autoregressive moving average (ARMA) models) to estimate predicted incidences. Second, Poisson regression models were used to compare the observed and predicted prescription incidences and to estimate respective incidence rate ratios (IRR). All time series analyses were performed for the full sample as well as separately for the four age groups.

Cross-correlation analyses were used to explore the relationship between COVID-19 incidence and type 1 diabetes incidences and incidence rate ratios at different time lags following the approach used in Wei [15].

All analyses were carried out using SAS version 9.4 (SAS Institute, Cary, USA), and we used the ARIMA procedure for all-time series analyses.

3. Results

3.1. Baseline characteristics of study patients

In total, some 23,785 children and adolescents were documented in the LRx database as having received an initial insulin therapy in 2016–2021. Of these, 3,712 were aged < 5 years, 6,493 were 5–<10 years, 8,675 were 10–<15 years, and 3,712 were 15–<20 years.

4. Time trends for type 1 diabetes and COVID-19 incidence

Fig. 1 shows time trends for type 1 diabetes incidence over the observation period. During the pre-pandemic period, there was a higher incidence during the winter period and a lower incidence during summer. This seasonality remained stable throughout the entire pre-pandemic period. During the pandemic period, there was less seasonal variation in the incidence.

4.1. Comparison of observed and predicted type 1 diabetes incidences during the pandemic period

Observed and predicted type 1 diabetes incidences were compared during the pandemic period, as shown in Fig. 2 (left column). In summer periods, observed incidences largely fell into the upper range of the 95 % prediction band. Similar patterns were observed in all age groups, indicating higher incidences than expected in the summer periods. In line with prior findings, corresponding incidence rate ratios of observed versus predicted type 1 diabetes incidences were largely higher during the summer periods, with the exception of the age group 0–4 years, also indicating that incidence rate ratios were higher than expected in the summer periods (Fig. 2, right column).

During the summer period (June to August) of 2020 and 2021, 990 and 1036 new-onset type 1 diabetes cases were observed compared to 689 and 629 predicted cases derived from the ARMA model, respectively. The observed incidences (per 100,000 person years) in summer 2020 and 2021 of 25.9 (95 % CI 24.1–27.8) and 27.1 (95 % CI 25.3–29.1) were significantly higher than the predicted incidences of 18.0 (95 % CI 16.5–19.6) and 16.5 (95 % CI 15.0–18.0). The respective IRRs for 2020 and 2021 were 1.44 (95 % CI 1.30–1.58) and 1.65 (1.49–1.82), respectively.

4.2. Cross-correlation between type 1 diabetes incidence or incidence rate ratios and COVID-19 incidence

The weekly time series of COVID-19 incidence clearly showed partial autocorrelation at time lags of one and two weeks for each age group. After applying the Wei approach with the optimal ARMA (2,0) model, there were no signs of autocorrelations in the residual COVID-19

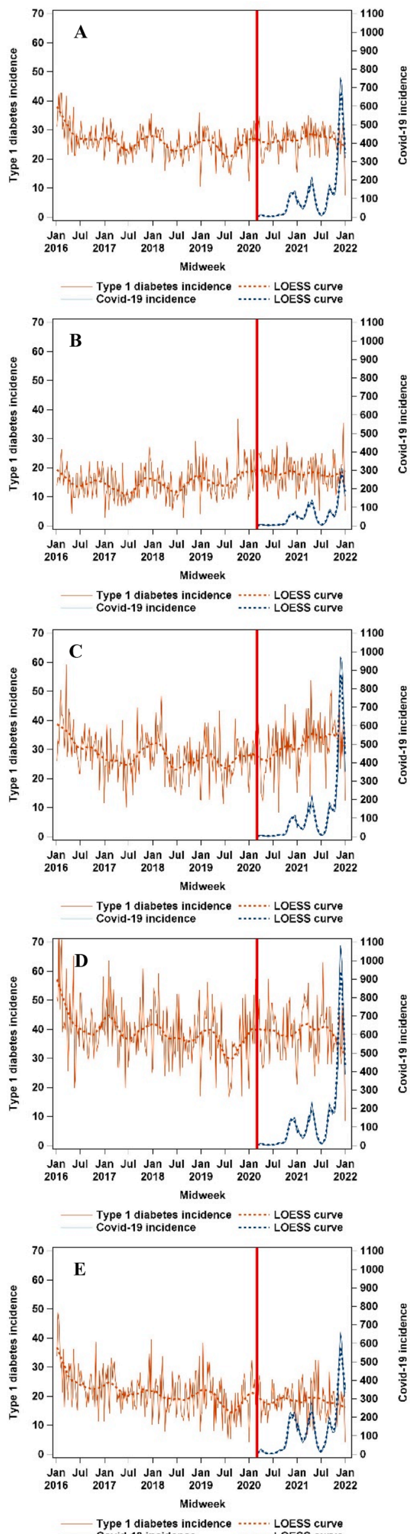

Fig. 1. Observed type 1 diabetes and COVID-19 incidences in the pre-pandemic and pandemic periods by age group. (A: 0–<20 years, B: 0–<5 years, C: 5–<10 years, D: 10–<15 years, E: 15–< 20 years, vertical line at 01/03/2020 separates the pre-pandemic (1st calendar week (January 4 to January 10) in 2016 to 9th calendar week (February 24 to March 1, 2020) and pandemic period (10th calendar week in 2020 (March 2 to March 8, 2020) to last calendar week (December 27, 2021 to January 2, 2022) in 2021, LOESS curves result from locally estimated scatterplot smoothing).

incidence series (supplementary Figure S1) or any relevant cross-correlations between COVID-19 incidence and type 1 diabetes incidence or incidence rate ratios for all time lags under investigation (Fig. 3).

5. Discussion

5.1. Main findings

This study showed an increase in observed versus predicted type 1 diabetes incidence in children and adolescents in the summer periods during the COVID-19 pandemic. The most prominent effects were seen in the age groups 5–<10 years and 10–<15 years. Time series analyses found no cross-correlation between COVID-19 and type 1 diabetes incidence or rate ratios of observed versus predicted type 1 diabetes incidence, suggesting that the increased type 1 diabetes incidence is the result of indirect rather than direct viral effects.

5.2. Comparison with other studies

Our findings are in line with those of previous studies. One study from Germany (DPV registry) showed an increase of 15 % (01.2020–06.2021), 13 % (01.2020–12.2020) and 18 % (01.2021–06.2021) in the observed versus expected incidence of type 1 diabetes in children and adolescents during the COVID-19 pandemic, respectively. The peak incidence of type 1 diabetes followed the peak SARS-CoV-2 incidence at about 3 months with the most prominent increases in new cases occurring in June and in July 2020. However, this study did not have access to information about SARS CoV-2 antibody status [7]. Another study from Finland registered 84 children with newly-diagnosed type 1 diabetes between April 1 to October 31, 2020, while an average of just 58 new cases per year was documented between 2016 and 2019, representing an increase of 45 % [16]. All children included in this study tested negative for SARS CoV-2 antibodies [16]. In a UK-based multicenter study, the number of children with new-onset type 1 diabetes observed between March 23 to June 4, 2020 was compared to the expected diabetes incidence based on data from 2015 to 2019 [17]. During the pandemic period, 30 children with newly diagnosed type 1 diabetes were registered while just 15–18 cases were predicted [17], showing an increase of 80 % in the onset of type 1 diabetes. In this study, SARS-CoV-2 infection was only detected in 5 cases. By contrast, a web-based cross-sectional survey in Italy found 160 children (<15 years of age) newly diagnosed with type 1 diabetes between February 20 and April 14, 2020, whereas 208 patients were diagnosed during the same period in 2019, resulting in a decrease of 23 % in type 1 diabetes incidence [18]. Conversely, an Australian study detected no change in type 1 diabetes incidence from March to May 2020 compared to the same period between 2015 and 2019 (11 cases versus 9 cases) [19]. Clearly then, the data currently available on type 1 diabetes incidence during the COVID-19 pandemic are inconsistent. One reason for this could be the different study methods, sample sizes (range: 11 to 256 patients), and observation times (2 months vs > 7 months) used.

Indirect and direct effects of SARS-CoV-2 may help to elucidate our findings.

5.3. Interpretation of findings

It is likely that indirect effects of COVID-19 on type 1 diabetes incidence play a key role in this regard. The preventive measures implemented in order to curb the spread of COVID-19 included social distancing and the closure of childcare facilities, schools, and sporting clubs. This led to reduced contact with peers and other children and adolescents, which may have caused increased psychological stress [20–23]. Several studies suggest that stress or psychological stress may be associated with a higher risk of developing beta cell autoimmunity

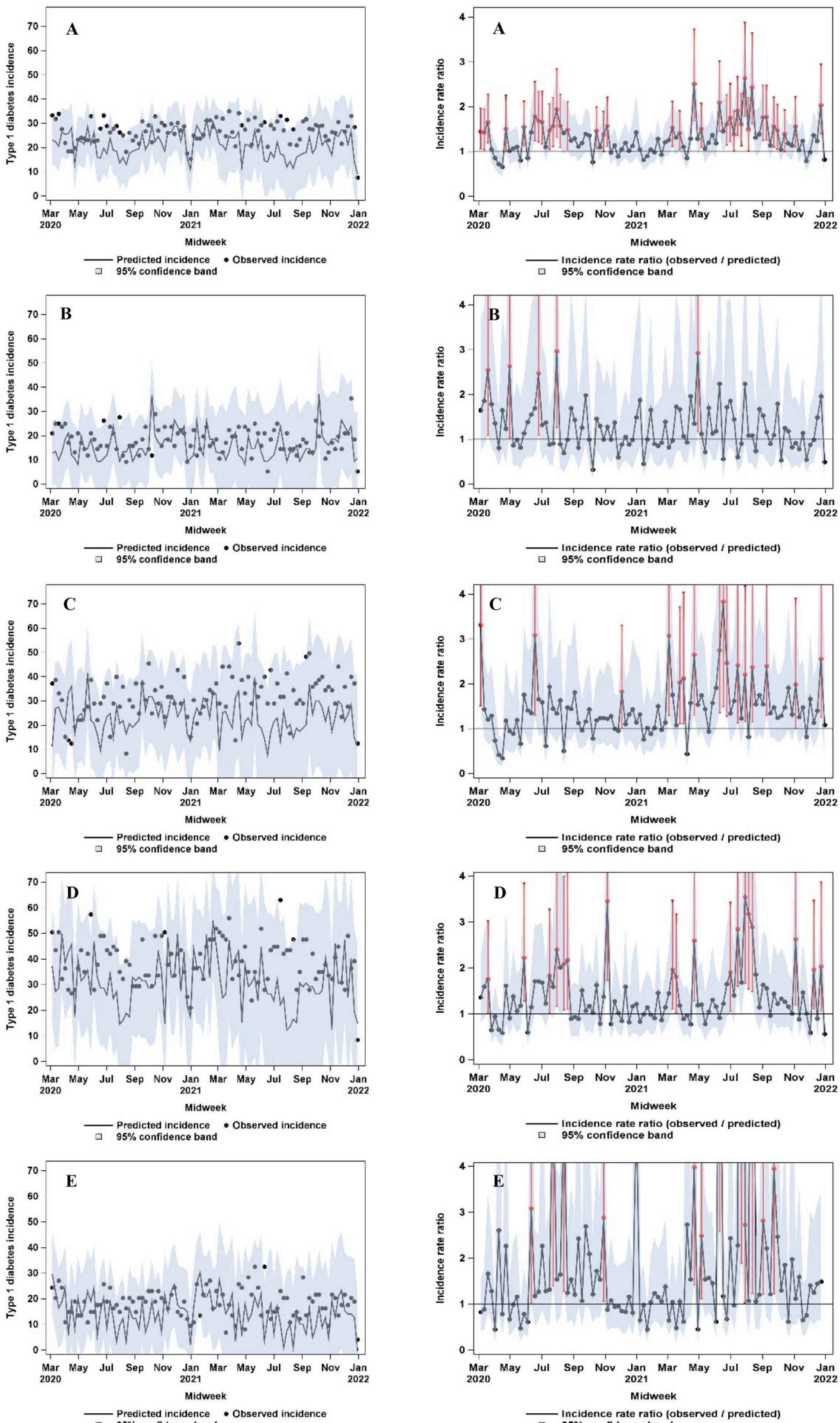

Fig. 2. Observed and predicted type 1 diabetes incidence (left column) and incidence rate ratios of observed vs. predicted incidence (right column) during the pandemic period by age group (A: 0–<20 years, B: 0–<5 years, C: 5–<10 years, D: 10–<15 years, E: 15–< 20 years, red bars indicate significant rate ratios (lower 95 % confidence limit > 1); predicted incidences were estimated from an optimal ARMA model fitted to weekly incidence data of the pre-pandemic period (1st calendar week (January 4 to January 10) in 2016 to 9th calendar week (February 24 to March 1); Optimal ARMA models were ARMA(0,0), ARMA(2,0), ARMA(3,0), ARMA(0,0), ARMA(0,0), for age groups 0–<20, 0–<5, 5–<10, 10–<15, and 15–<20 years, respectively). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and type 1 diabetes [24,25,26]. Increased stress as a result of the pandemic itself (fear of infection) and social isolation has also been reported in children and adolescents, leading to disturbed mental health, well-being, and a higher occurrence of psychiatric disorders (depression, anxiety) [27]. It is reasonable to assume that these "stressors" could increase the risk of developing type 1 diabetes, especially in those who are predisposed or in a pre-diabetic stage of autoimmunity. On the other hand, contact restrictions imposed during the lockdowns led to a decrease in common pediatric viral infections (respiratory infections, gastrointestinal infections) [28,29] which,

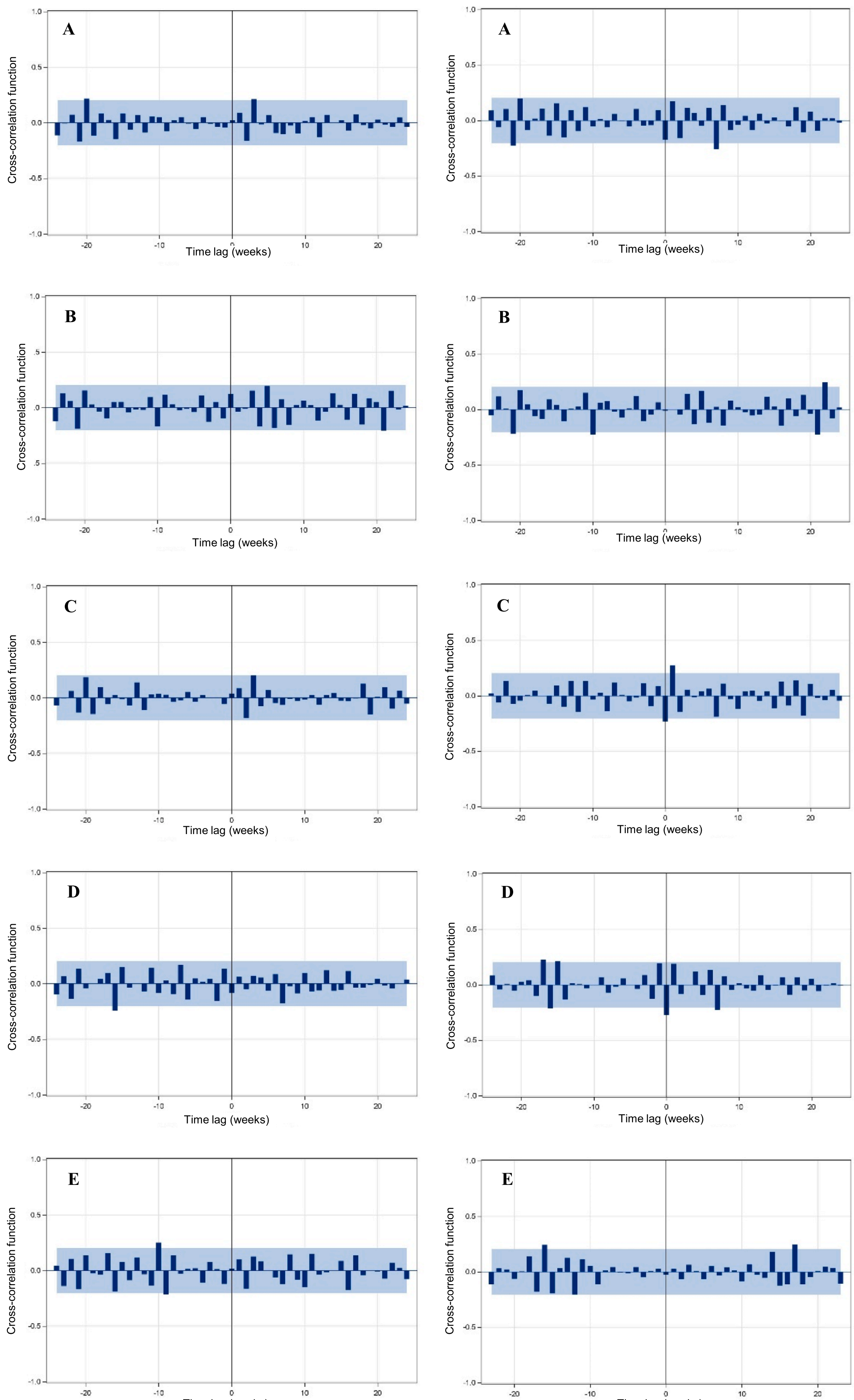

Fig. 3. Cross-correlation between type 1 diabetes incidence (left column) and incidence rate ratio for observed vs. predicted (right column) incidence with COVID-19 incidence at different time lags. (In accordance with the Wei approach, time series of Covid-19 incidence, type 1 diabetes incidence and rate ratios were pre-whitened using an optimal ARMA (2,0) model).

according to the viral hypothesis [30,31] might have reduced the risk of developing type 1 diabetes [32]. It is noteworthy that an increase in type 1 diabetes incidence during lockdown was observed in our study. This could be explained by the “microbiome hypothesis”: the “different” environmental factors during the pandemic may have influenced the balance of “good” and “bad” organisms/bacteria in the gut, which has been shown to be linked to a higher type 1 diabetes incidence, especially in young children [33,34].

Direct effects of SARS CoV-2 on beta cells could be another pathomechanism that explains the higher incidence of type 1 diabetes identified during the pandemic period in our study [35–42]. To date, however, there is no conclusive evidence of a causal relationship between viral infections and autoimmune diabetes [28]. There is also no evidence that the COVID-19 pandemic led to a significantly increased number of new autoantibody negative type 1 diabetes cases in children, adolescents, and young adults [43]. Our study does not contain any data about previous SARS-CoV-2 infection or SARS-CoV-2 antibodies in the study population, nor do we have any data about type 1 diabetes autoantibodies. We therefore cannot explore any association between SARS-CoV-2 infection and type 1 diabetes incidence and autoimmunity versus non-autoimmune effects. However, in time series analyses, no correlations between national data on COVID-19 incidence and type 1 diabetes incidence were found, suggesting that indirect rather than direct effects of SARS-CoV-2 were at work.

5.4. Strengths and limitations

The main strengths of our study are the longer observation period during the COVID-19 pandemic until December 2021 and the nationally representative data on insulin prescriptions as well as the extensive coverage (80 %) of the database used. Nevertheless, the present study is also subject to several limitations, which should be mentioned here. First, the LRx prescription database does not contain information about diagnoses and lab values. As a result, type 1 diabetes was defined based on insulin prescriptions and age (<20 years). This approach may have introduced some selection bias into our analyses. However, a possible selection bias is likely to be comparable (non-differential) over time, thus the results of the time series analysis can be assumed to be valid. Second, we cannot entirely exclude that some new prescriptions may reflect patients moving to Germany during the pandemic, but number of such cases is likely to be low and will not seriously affect the results. Third, some new prescriptions may relate to patients with type 2 diabetes. During the pandemic, a COVID-19 infection and a more sedentary and unhealthy lifestyle as a result of containment measures may have increased insulin resistance in some young people with type 2 diabetes [44–47] who subsequently may have progressed to needing insulin therapy. However, due to the low prevalence type 2 diabetes in adolescent [48] new insulin prescriptions in adolescent type 2 diabetes patients most likely occurred only in a few number of cases and are very unlikely to have affected the findings seriously.

6. Conclusions

In conclusion, during the COVID-19 pandemic, there was less seasonal variation in the incidence of type 1 diabetes (defined by new insulin prescriptions), with higher observed than expected incidences during summer. No cross-correlations between COVID-19 and type 1 diabetes incidence were found in any of the age groups observed. Our results suggest that indirect (pandemic measures associated with isolation, school closures, fear of infection, induced stress) rather than direct effects are causative with respect to the increase in type 1 diabetes diagnoses.

Funding

None.

Author contributions

Karel Kostev, Wolfgang Rathmann, Joachim Rosenbauer, and Oliver Kuss contributed to the study design. Joachim Rosenbauer and Oliver Kuss planned and performed the statistical analysis. Louisa van den Boom and Joachim Rosenbauer were responsible for drafting the article. All authors were responsible for critical review of the article for important intellectual content. All authors approved the version to be published.

Declaration of Competing Interest

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

Data availability

The Disease Analyzer data are not publicly available due to confidentiality requirements. Investigators should contact IQVIA, Frankfurt, Germany, to inquire about data availability.

Acknowledgments

None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2022.110146.

References

[1] Bendas A, Rothe U, Kiess W, et al. Trends in Incidence Rates during 1999–2008 and Prevalence in 2008 of Childhood Type 1 Diabetes Mellitus in Germany–Model-Based National Estimates. PLoS ONE 2015;10(7):e0132716.

[2] Lönnrot M, Lynch KF, Elding Larsson H et al. TEDDY Study Group. Respiratory infections are temporally associated with initiation of type 1 diabetes autoimmunity: the TEDDY study. Diabetologia 2017. 60(10):1931-1940. doi: 10.1007/s00125-017-4365-5. Epub 2017 Aug 2. Erratum in: Diabetologia. 2018 Jan;61(1):254. PMID: 28770319; PMCID: PMC5697762.

[3] Beyerlein A, Wehweck F, Ziegler AG, Pflueger M. Respiratory infections in early life and the development of islet autoimmunity in children at increased type 1 diabetes risk: evidence from the BABYDIET study [published correction appears in JAMA Pediatr 2017;171:94]. JAMA Pediatr 2013;167:800–7.

[4] Tittel SR, Rosenbauer J, Kamrath C, et al.. DPV Initiative. 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. Epub 2020 Aug 21. PMID: 32826282; PMCID: PMC7576433.

[5] 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;dc210969 . doi. Epub ahead of print. PMID: 35043145.

[6] Boddu SK, Aurangabadkar G, Kuchay MS..New onset diabetes, type 1 diabetes and COVID-19. Diabetes Metab Syndr. 2020 ;14(6):2211-2217. doi: 10.1016/j.dsx.2020.11.012. Epub 2020 Nov 17. PMID: 33395782; PMCID: PMC7669477.

[7] Barrett CE, Koyama AK, Alvarez P, et al. Risk for Newly Diagnosed Diabetes >30 Days After SARS-CoV-2 Infection Among Persons Aged <18 Years - United States, March 1, 2020-June 28, 2021. MMWR Morb Mortal Wkly Rep 2022 Jan 14;71(2): 59–65. https://doi.org/10.15585/mmwr.mm7102e2. PMID: 35025851; PMCID: PMC8757617.

[8] Hatoun J, Correa ET, Donahue SMA, Vernacchio L..Social Distancing for COVID-19 and Diagnoses of Other Infectious Diseases in Children. Pediatrics. 2020Oct;146 (4):e2020006460. doi: 10.1542/peds.2020-006460. Epub 2020 Sep 2. PMID: 32879032.

[9] Nygren M, Carstensen J, Koch F, Ludvigsson J, Frostell A. Experience of a serious life event increases the risk for childhood type 1diabetes: the ABIS population-based prospective cohort study. Diabetologia 2015;58:1188–97.

[10] Meherali S, Punjani N, Louie-Poon S, et al. Mental Health of Children and Adolescents Amidst COVID-19 and Past Pandemics: A Rapid Systematic Review. Int J Environ Res Public Health 2021;18(7):3432. https://doi.org/10.3390/ijerph18073432. PMID: 33810225; PMCID: PMC8038056.

[11] Jacob L, Yakkali B, Parekh M, Kostev K. No effects of the COVID-19 pandemic on the prescription of insulin in Germany. Prim Care Diabetes 2022;S1751–9918(22): 00083–93. https://doi.org/10.1016/j.pcd.2022.04.007.

[12] van den Boom L, Kostev K. Patterns of insulin therapy and insulin daily doses in children and adolescents with type 1 diabetes in Germany. Diabetes Obes Metab 2022;24(2):296–301. https://doi.org/10.1111/dom.14581.

[13] https://www.rki.de/.

[14] https://www-genesis.destatis.de/genesis/online?operation=table&code=12411-0006&bypass=true&levelindex=1&levelid=1644998637276#abreadcrumb.

[15] Wei WWS. Time series analysis: Univariate and Multivariate Methods (2nd Edition). Boston: Pearson Addison Wesley; 2006.

[16] 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. Epub 2021 May 27. PMID: 34045208; PMCID: PMC8172262.

[17] 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. https://doi.org/10.2337/dc20-1551. Epub 2020 Aug 17. PMID: 32816997.

[18] Rabbone I, Schiaffini R, Cherubini V, Maffeis C, Scaramuzza A. Diabetes Study Group of the Italian Society for Pediatric Endocrinology and Diabetes. Has COVID-19 Delayed the Diagnosis and Worsened the Presentation of Type 1 Diabetes in Children? Diabetes Care 2020;43(11):2870–2872. https://doi.org/10.2337/dc20-1321. Epub 2020 Aug 10. PMID: 32778554.

[19] Atlas G, Rodrigues F, Moshage Y, Welch J, White M, O'Connell MA. PRESENTATION OF PAEDIATRIC TYPE 1 DIABETES IN MELBOURNE, AUSTRALIA DURING THE INITIAL STAGES OF THE COVID-19 PANDEMIC. J Paediatr Child Health 2020;56(10):1654-1655. doi: 10.1111/jpc.15081. Epub 2020 Sep 22. PMID: 32959935; PMCID: PMC7537060.

[20] Ghosh R, Dubey MJ, Chatterjee S, Dubey S. Impact of COVID -19 on children: special focus on the psychosocial aspect. Minerva Pediatr 2020;72:226–35.

[21] Loades ME, Chatburn E, Higson-Sweeney N. Rapid Systematic Review: The Impact of Social Isolation and Loneliness on the Mental Health of Children and Adolescents in the Context of COVID-19. J Am Acad Child Adolesc Psychiatry 2020;59: 1218–39.

[22] Lee J. Mental health effects of school closures during COVID-19. Lancet Child Adolesc Health 2020;4:421.

[23] Brooks SK, Webster K, Smith LE, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. Lancet 2020;395:912–20.

[24] Sharif K, Watad A, Coplan L, et al. Psychological stress and type 1 diabetes mellitus: what is the link? Expert Rev Clin Immunol 2018;14:1081–8.

[25] Stojanovich L. Stress and autoimmunity. Autoimmun Rev 2010;9:A271–6.

[26] Thernlund GM, Dahlquist G, Hansson K, et al. Psychological stress and the onset of IDDM in children. Diabetes Care 1995;18:1323–9.

[27] Golberstein E, Wen H, Miller BF. Coronavirus disease 2019 (COVID-19) and mental health for children and adolescents. JAMA Pediatr 2020;174:819–20.

[28] Kuitunen I, Artama M, Mäkelä L, et al. Effect of Social Distancing Due to the COVID-19 Pandemic on the Incidence of Viral Respiratory Tract Infections in Children in Finland During Early 2020. Pediatr Infect Dis J 2021;39:e423–7.

[29] Kruizinga MD, Peeters D, van Veen M, et al. The impact of lockdown on pediatric ED visits and hospital admissions during the COVID19 pandemic: a multicenter analysis and review of the literature. Eur J Pediatr 2021;180:2271–9.

[30] Knip M, Simmel O. Environmental Triggers of Type 1 Diabetes. Cold Spring Harb Perspect Med 2012;2:a007690.

[31] Rodriguez-Calvo T, Sabouri S, Anquetil F, von Herrath MG. The viral paradigm in type 1 diabetes: Who are the main suspects? Autoimmun Rev 2016;15:964–9.

[32] Bach JF. Revisiting the hygiene hypothesis in the context of autoimmunity. Front Immunol 2021;11:615192.

[33] Finlay BB, Amato KR, Azad M et al. The hygiene hypothesis, the COVID pandemic, and consequences for the human microbiome. Proc Natl Acad Sci U S A 2021. ;118 (6):e2010217118. doi: 10.1073/pnas.2010217118. Erratum in: Proc Natl Acad Sci U S A. 2021 Mar 16;118(11): PMID: 33472859; PMCID: PMC8017729.

[34] Traversi D, Rabbone I, Scaioli G, et al. Risk factors for type 1 diabetes, including environmental, behavioural and gut microbial factors: a casecontrol study. Sci Re 2020;10:17566.

[35] Hollstein T, Schulte DM, Schulz J, et al. Autoantibody-negative insulin-dependent diabetes mellitus after SARS-CoV-2 infection: a case report. Nat Metab 2020;2: 1021–4.

[36] Benton DJ, Wrobel AG, Xu P, et al. Receptor binding and priming of the spike protein of SARS-CoV-2 for membrane fusion. Nature 2020;588:327–30.

[37] Müller JA, Groß R, Conzelmann C, et al. SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. Nat Metab 2021;3:149–65.

[38] Bornstein SR, Rubino F, Khunti K, et al. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol 2020;8:546–50.

[39] DiMeglio LA. COVID-19 and Type 1 Diabetes: Addressing Concerns and Maintaining Control. Diabetes Care 2021;44:1–5.

[40] Lönnrot M, Lynch KF, Elding Larsson H, et al. TEDDY Study Group. Respiratory infections are temporally associated with initiation of type 1 diabetes autoimmunity: the TEDDY study [published correction appears in Diabetologia 2018;61:254]. Diabetologia 2017;60:1931–40.

[41] Beyerlein A,Wehweck F, Ziegler AG, Pflueger M.. Respiratory infections in early life and the development of islet autoimmunity in children at increased type 1 diabetes risk: evidence from the BABYDIET study [published correction appears in JAMA Pediatr 2017;171:94]. JAMA Pediatr 2013, 167:800–807.

[42] Ruiz PLD, Tapia G, Bakken IJ, et al. Pandemic influenza and subsequent risk of type 1 diabetes: a nationwide cohort study. Diabetologia 2018;61:1996–2004.

[43] Kamrath C, Rosenbauer J, Tittel SR, et al. Frequency of Autoantibody-Negative Type 1 Diabetes in Children, Adolescents, and Young Adults During the First Wave of the COVID-19 Pandemic in Germany. Diabetes Care 2021;44:1540–6.

[44] Govender N, Khaliq OP, Moodley J, Naicker T. Insulin resistance in COVID-19 and diabetes. Prim Care Diabetes 2021 Aug;15(4):629–34.

[45] Dunton GF, Do B, Wang SD. Early effects of the COVID-19 pandemic on physical activity and sedentary behavior in children living in the U.S. BMC Public Health 2020 Sep 4;20(1):1351.

[46] Maltoni G, Zioutas M, Deiana G, Biserni GB, Pession A, Zucchini S. Gender differences in weight gain during lockdown due to COVID-19 pandemic in adolescents with obesity. Nutr Metab Cardiovasc Dis 2021 Jun 30;31(7):2181–5.

[47] La Fauci G, Montalti M, Di Valerio Z, Gori D, Salomoni MG, Salussolia A, et al. Obesity and COVID-19 in Children and Adolescents: Reciprocal Detrimental Influence-Systematic Literature Review and Meta-Analysis. Int J Environ Res Public Health 2022 Jun 21;19(13):7603.

[48] Baechle C, Stahl-Pehe A, Prinz N, Meissner T, Kamrath C, Holl RW, Rosenbauer J; in cooperation with the German Paediatric Surveillance Unit (ESPED), the DPV initiative and the German Center for Diabetes Research (DZD). Prevalence trends of type 1 and type 2 diabetes in children and adolescents in North Rhine-Westphalia, the most populous federal state in Germany, 2002-2020. Diabetes Res Clin Pract. 2022 Aug;190:109995.