SARS-CoV-2 and type 1 diabetes in children in Finland: an observational study

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Summary

Background Some epidemiological studies have suggested an increase in incidence of type 1 diabetes during the COVID-19 pandemic, however the mechanism(s) behind such an increase have yet to be identified. In this study we aimed to evaluate the possible role of the SARS-CoV-2 virus in the reported increase in the rate of type 1 diabetes.

Methods In this observational cohort study using data from the Finnish Pediatric Diabetes Register (FPDR), we assessed the incidence of type 1 diabetes (number of children with newly diagnosed type 1 diabetes per 100 000 person-years during the pandemic and the reference period) during the first 18 months of the COVID-19 pandemic in children in Finland younger than 15 years old compared with a reference period which included three corresponding pre-pandemic periods also obtained from the FPDR. Children with confirmed monogenic diabetes were excluded. We also compared the phenotype and HLA genotype of the disease between these two cohorts, and analysed the proportion of newly diagnosed people with type 1 diabetes testing positive for SARS-CoV-2 antibodies.

Findings 785 children and adolescents in Finland were diagnosed with type 1 diabetes from March 1, 2020, to Aug 31, 2021. In the reference period, which comprised three similar 18-month terms (from March 1, 2014, to Aug 31, 2015; March 1, 2016, to Aug 31, 2017; and March 1, 2018, to Aug 31, 2019) 2096 children and adolescents were diagnosed. The incidence of type 1 diabetes was 61·0 per 100 000 person-years (95% CI 56·8–65·4) among children younger than 15 years old during the pandemic, which was significantly higher than during the reference period (52·3 per 100 000 person-years; 50·1–54·6). The incidence rate ratio adjusted for age and sex for the COVID-19 pandemic was 1·16 (1·06–1·25; p=0·0006) when compared with the reference period. The children diagnosed during the COVID-19 pandemic had more often diabetic ketoacidosis (p<0·001), had a higher HbA_{1c} (p<0·001), and tested more frequently positive for glutamic acid debarboxylase antibodies at diagnosis (p<0·001) than those diagnosed before the pandemic. There were no significant differences in the distribution of HLA genotypes between the two periods. Only five of those diagnosed during the pandemic (0·9%) of 583 tested positive for infection-induced SARS-CoV-2 antibodies.

Interpretation Children and adolescents diagnosed with type 1 diabetes during the pandemic had a more severe disease at diagnosis. The observed increase in type 1 diabetes incidence during the first 18 months could be a consequence of lockdown and physical distancing rather than a direct effect of SARS-CoV-2 infection.

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For the Swedish translation of the abstract see **Online** for appendix 2

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Introduction

A series of epidemiological studies have reported that the number of people with newly diagnosed type 1 diabetes has increased during the COVID-19 pandemic.[1,2] According to one meta-analysis, the global incidence of type 1 diabetes among children increased by 9·5% from 2019 to 2020.[3] However, these findings have been questioned due to methodological weaknesses.[4] An increase in diabetic ketoacidosis at diagnosis has also been observed during the pandemic.[5–7] The reasons behind these findings are unknown. There is an ongoing discussion as to whether these observations are a direct effect of a SARS-CoV-2 infection or a consequence of the lockdown and social isolation due to the pandemic.

A direct effect has been implied, either through an injury to the pancreatic β cells by the SARS-CoV-2 virus or through virus-induced precipitation or acceleration of the disease process leading to type 1 diabetes.[8] An increase in diabetic ketoacidosis at diagnosis suggests a possible delayed presentation to health-care services, whereas the indirect effect on the incidence of type 1 diabetes might be mediated through an earlier unmasking of the disease process because of the substantially reduced infection load and decreased physical activity, particularly in children. A decreased infection load might affect the immune system, favouring the development of type 1 diabetes, whereas reduced physical activity increases β-cell stress.[9] In April 2020, all schools were

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See Online for appendix 3

Research in context

Evidence before this study

We set out to identify all evidence available on the possible association between SARS-CoV-2 and type 1 diabetes. We searched PubMed without any language restrictions for papers published from Jan 1, 2020, to Dec 31, 2022, with the search terms ("SARS-CoV-2 and type 1 diabetes") AND ("COVID-19 and type 1 diabetes"). Most articles, although not all, reported an increased frequency of diabetic ketoacidosis at the diagnosis of type 1 diabetes during the COVID-19 pandemic. Some of the articles suggested that the incidence of diabetes increased during the pandemic, but not all reports differentiated between type 1 and type 2 diabetes. Some papers found that the incidence of type 1 diabetes did increase during the pandemic, whereas others showed no increase in the disease rate. One meta-analysis reported that the global incidence of type 1 diabetes increased among children by 9·5% in 2020 compared with 2019. However, that meta-analysis has been criticised because of methodological weaknesses. Whether SARS-CoV-2 has an active role in increasing the rate of type 1 diabetes is controversial. A few studies have claimed that SARS-CoV-2 might be directly involved in the increase in the incidence of type 1 diabetes, whereas a larger portion of studies have concluded that currently there is no convincing evidence that SARS-CoV-2 induces type 1 diabetes.

Added value of this study

We performed an observational cohort study to analyse the relationship between type 1 diabetes and the COVID-19 pandemic in Finland. Finland has by far the highest incidence of childhood type 1 diabetes and the Finnish Pediatric Diabetes Register (FPDR) is a comprehensive database established to monitor and assess the incidence of various types of childhood diabetes. Our study shows both an increased incidence of type 1 diabetes and an increased frequency of diabetic ketoacidosis at diagnosis in children and adolescents during the first 18 months of the COVID-19 pandemic compared with the reference period before the pandemic. However the proportion of children with a confirmed SARS-CoV-2 infection preceding the diagnosis of type 1 diabetes was less than 1%.

Implications of all the available evidence

Our results suggest that the increase in the disease rate and in the frequency of diabetic ketoacidosis are related to the preventive measures introduced at the start of the pandemic, such as lockdown and physical distancing, rather than a direct effect of SARS-CoV-2.

closed in Finland and parents with children attending day-care centres were asked to keep their children at home, if possible. The biodiversity hypothesis assumes that reduced microbial exposure in early life increases the risk of immune-mediated diseases.[10]

Finland has by far the highest incidence of childhood type 1 diabetes, with an annual rate of approximately 60 new cases per 100 000 children younger than 15 years old.[10] In 2002, the Finnish Pediatric Diabetes Register (FPDR) was established to monitor the incidence of various types of childhood diabetes and to assess the type of diabetes in children participating in the register.[11] On the basis of the FPDR, we have previously reported that the incidence rate of type 1 diabetes has decreased among young Finnish children between 2003 and 2018.[11]

In this study, we aimed to analyse the effect of the first 18 months of the COVID-19 pandemic on the incidence of type 1 diabetes in Finnish children. We compared this period (March 1, 2020, to Aug 31, 2021) with a pre-pandemic reference period, comprised of a combination of three similar 18-month periods during the years 2014–19. We also compared the clinical characteristics, metabolic decompensation at diagnosis, signs of islet autoimmunity, and frequency of risk-associated HLA genotypes in affected children during the pandemic and reference periods. In addition, we analysed SARS-CoV-2 antibodies in all serum samples available from the children diagnosed with type 1 diabetes during the the first 18 months of the pandemic.

Methods

Study design and participants

This observational cohort study used data from the FPDR, which was established in 2002, and has continually collected data from all centres (initially 28 centres, five of which closed) taking care of children with newly diagnosed type 1 diabetes in Finland without any disruptions. Data consists of structured questionnaires and data on diabetes-associated autoantibodies and HLA genotypes from all newly diagnosed children with diabetes with parental consent to participate.[12] Children aged 10 years or older are also asked for informed consent. Type of diabetes is categorised as type 1 diabetes, type 2 diabetes, monogenic diabetes, or any other form of diabetes. The diagnosis of diabetes is based on American Diabetes Association (ADA) criteria.[13] The register has been validated to cover 92% of children with newly diagnosed diabetes.[14] Approximately 99% of the participants have type 1 diabetes, diagnosed on the basis of clinical characteristics, autoantibody status, and HLA genotype, and the same proportion are White. The current analysis includes only children diagnosed with type 1 diabetes younger than 15 years old. Children with confirmed monogenic diabetes were excluded as well as those with type 2 diabetes and other forms of diabetes.

Data sources

To determine metabolic decompensation, blood pH and concentrations of plasma β-hydroxybutyrate, glucose, and HbA_{1c} were analysed in the local laboratories when the child was admitted to hospital. The clinician in the

paediatric unit assessed the absolute weight loss, level of consciousness (normal, altered, and unconscious), and the pubertal status using the Tanner scale. The duration of classic symptoms, such as increased thirst and frequent urination, associated with type 1 diabetes before diagnosis was estimated through a questionnaire given to the child's family. Diabetic ketoacidosis was defined as a pH of less than 7·30 in combination with ketonemia. Severe ketoacidosis was defined as a pH of less than 7·10. BMI was assessed using the WHO AnthroPlus software version 3.2.2.1.[15]

Approximately 75% of the children participating in the FPDR donated blood samples, which, in this study, were taken at a median of 5 days after the diagnosis of type 1 diabetes for the isolation of serum and peripheral blood mononuclear cells. We did not include serum samples collected more than 30 days after the start of insulin treatment when islet autoantibody results were analysed, because insulin autoantibodies cannot be measured reliably in such samples. An EDTA (edetic acid) sample is used for HLA genotyping. Four islet autoantibodies including antibodies to insulin, glutamic acid debarboxylase (GAD), islet antigen 2, and zinc transporter 8 were analysed from the serum samples with specific radiobinding assays[16] as described in appendix 3 (p 4). Typing of the major HLA-DR and HLA-DQ haplotypes is done with PCR-based lanthanide-labelled hybridisation and time-resolved fluorometry detection.[17] HLA class II conferred risk for type 1 diabetes was estimated by classifying the study participants according to their HLA genotypes into six risk groups ranging from a strongly decreased risk (risk group 0) to a high risk (risk group 5).

The study protocol of the FPDR was approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa (Helsinki, Finland).

Estimates of incidence rates and ratios

We calculated overall, sex-specific, and age-specific incidence rates of type 1 diabetes per 100 000 person-years both during the pandemic and the reference period. We separated the participants into three age categories: children younger than 5 years, 5 years to younger than 10 years, and 10 years to younger than 15 years. The exact 95% CIs were assessed by assuming Poisson distributed rates. To quantify the possible change during the pandemic compared with the reference period, we assessed incidence rate ratios and their 95% CIs. We also estimated the number of excess cases with type 1 diabetes during the first 18 months of the COVID-19 pandemic based on the 16% increase observed in the incidence of type 1 diabetes during that period.

Analysis of SARS-CoV-2 antibodies

Serum samples from the participants diagnosed during the pandemic taken soon after the diagnosis of type 1 diabetes were analysed for SARS-CoV-2 antibodies. Samples were first screened with an ELISA for IgG and IgA antibodies against SARS-CoV-2 Spike protein using a 384-well-based high-throughput ELISA.[18] Subsequently, positive samples were studied for IgG antibodies against the nucleoprotein (which are not induced by the Spike-based vaccines used in Finland), as well as for neutralising antibodies to contemporary variants using a pseudovirus neutralisation assay.[19] Because of similar neutralisation titres between wild-type and alpha (B.1.1.7) variant, only the alpha variant was used.[20] We compared the characteristics of the children with infection-induced SARS-CoV-2 antibodies and all other children (appendix 3 pp 6–7).

Statistical analysis

Most analyses were done using IBM SPSS Statistics for Windows version 27. In addition, R Software for Statistical Computing for Windows, versions 3.4.0 and 3.5.0 were used. A two-tailed p value of 0·05 or less was considered significant.

For assessing differences between the pandemic and the reference cohorts, several analyses were performed. We used cross-tabulation for the categorical data and compared frequencies with Pearson's χ^2 test with continuity correction when appropriate or Fisher exact test. A Bonferroni correction for multiple comparisons was not applied because of its overly conservative nature.[21] Differences in continuous variables were analysed using Student's *t* test or one-way ANOVA for parametric variables and Mann-Whitney U test or Wilcoxon's rank-sum test or Kruskal-Wallis test for skewed variables. 95% CIs for frequencies were calculated using the interval proportion tool in R.[22] Age at diagnosis and sex were assumed to be confounding factors and adjustment for them was performed with logistic regression for dichotomous variables or multinomial regression for categorical variables; linear regression was used for parametric variables and quantile regression in R (package quantreg) was used for skewed variables.

The incidence rate ratios and their 95% CIs were assessed by fitting multiplicative Poisson regression models to the numbers of children diagnosed with type 1 diabetes, when using the natural logarithm of person-years as an offset term. As a sensitivity analysis, we compared the incidence during the pandemic to the most recent preceding 18-month period (March 1, 2018, to Aug 31, 2019) and assessed the incidence rate ratio when comparing these two periods.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

785 children diagnosed with type 1 diabetes were enrolled during the pandemic period, comprising of 18 months from March 1, 2020, to Aug 31, 2021 (appendix 3 p 5).

The reference periods comprised three similar 18-month terms (from March 1, 2014, to Aug 31, 2015; March 1, 2016, to Aug 31, 2017; and March 1, 2018, to Aug 31, 2019). Altogether, 2096 children diagnosed with type 1 diabetes during the combined 54-month reference period joined the FPDR. The baseline characteristics of the participants in the pandemic and reference cohorts are shown in table 1.

During the pandemic, the incidence of type 1 diabetes was 61·0 per 100 000 person-years (95% CI 56·8–65·4) among all children younger than 15 years old. This disease rate was significantly higher than during the reference period (52·3 per 100 000 person-years; 50·1–54·6). The rate was significantly higher in boys during the pandemic compared with the reference period, whereas the incidence difference between the pandemic and reference periods was non-significant in girls (table 2). When comparing the two periods, the crude incidence rate ratio for the pandemic was 1·17 (95% CI 1·07–1·27; p<0·0003), whereas the age-adjusted

	N respondents	Pandemic cohort, n=785 (27·2%)	Control cohort, n=2096 (72·8%)	p value	p value adjusted for age at diagnosis and sex
Demographics and clinical data					
Age at diagnosis, years	2881	8·41 (3·75)	8·20 (3·86)	0·208	..
Boys	2881	458 (58·3%; 54·9 to 64·7%)	1185 (56·5%; 54·4 to 58·6%)	0·406	..
Girls	2881	327 (41·7%; 38·3 to 45·1%)	911 (43·5%; 41·4 to 45·6%)	..	..
Pubertal	1894	77/492 (15·7%; 12·7 to 19·1%)	211/1402 (15·0%; 13·3 to 17·0%)	0·806	0·158
BMI z-score	2493	−0·19 (−10·45 to 4·23)	−0·24 (−6·43 to 9·44)	0·830	0·794
First-degree relative with type 1 diabetes	2881	89 (11·3%; 9·3 to 13·7%)	291 (13·9%; 12·5 to 15·4%)	0·083	0·090
Father with type 1 diabetes	2881	45 (5·7%; 4·3 to 7·6%)	123 (5·9%; 4·9 to 7·0%)	0·961	0·979
Mother with type 1 diabetes	2881	19 (2·4%; 1·6 to 3·7%)	64 (3·1%; 2·4 to 3·9%)	0·436	0·446
Sibling with type 1 diabetes	2881	36 (4·6%; 3·3 to 6·3%)	115 (5·5%; 4·6 to 6·5%)	0·383	0·316
0	..	696 (88·7%; 86·3 to 90·7%)	1805 (86·1%; 84·6 to 87·5%)	..	..
1	..	76 (9·7%; 7·8 to 12·0%)	271 (12·9%; 11·6 to 14·4%)	..	..
2	..	12 (1·5%; 0·9 to 2·7%)	18 (0·9%; 0·5 to 1·4%)	..	..
3	..	0 (0%; 0·0 to 0·5%)	2 (0·1%; 0·0 to 0·3%)	..	..
4	..	1 (0·1%; 0·0 to 0·7%)	0 (0%; 0·0 to 0·2%)	..	..
Number of family members affected by type 1 diabetes	2881	..	..	0·015	0·024
Season of diagnosis	2881	..	..	0·108	0·101
Spring	..	242 (30·8%; 27·7 to 34·1%)	634 (30·2%; 28·3 to 32·2%)	..	..
Summer	..	282 (35·9%; 32·6 to 39·4%)	670 (32·0%; 30·0 to 34·0%)	..	..
Fall	..	139 (17·7%; 15·2 to 20·5%)	413 (19·7%; 18·1 to 21·5%)	..	..
Winter	..	122 (15·5%; 13·2 to 18·2%)	379 (18·1%; 16·5 to 19·8%)	..	..
Season of birth	2880	..	..	0·005	0·004
Spring	..	167 (21·3%; 18·6 to 24·3%)	565 (27·0%; 25·1 to 28·9%)	..	..
Summer	..	232 (29·6%; 26·5 to 32·9%)	524 (25·0%; 23·2 to 26·9%)	..	..
Fall	..	210 (26·8%; 23·8 to 30·0%)	519 (24·8%; 23·0 to 26·7%)	..	..
Winter	..	175 (22·3%; 19·5 to 25·4%)	488 (23·3%; 21·5 to 25·1%)	..	..
Metabolic decompensation at diagnosis					
Duration of symptoms	2706	..	..	0·195	0·241
No symptoms	..	37/732 (5·1%; 3·4 to 6·9%)	65/1974 (3·3%; 2·6 to 4·2%)	..	..
<1 week	..	123/732 (16·8%; 14·3 to 19·7%)	344/1974 (17·4%; 15·8 to 19·2%)	..	..
1–4 weeks	..	425/732 (58·1%; 54·5 to 61·6%)	1173/1974 (59·4%; 57·2 to 61·6%)	..	..
>4 weeks	..	147/732 (20·1%; 17·3 to 23·1%)	392/1974 (19·9%; 18·2 to 21·7%)	..	..
Impaired consciousness	2741	56/744 (7·5%; 5·8 to 9·6%)	131/1997 (6·6%; 5·6 to 7·7%)	0·419	0·408
Ketoacidosis	2723	228/741 (30·8%; 27·6 to 34·2%)	448/1982 (22·6%; 20·8 to 24·5%)	<0·001	<0·001
Severe ketoacidosis	2723	65/741 (8·8%; 6·9 to 11·0%)	116/1982 (5·9%; 4·9 to 7·0%)	0·008	0·009
Weight loss, % of bodyweight	1792	6·5 (0·0 to 34·0)	5·5 (0·0 to 28·3)	0·036	0·220
pH	2723	7·36 (6·82 to 7·55)	7·37 (6·8 to 7·55)	<0·001	<0·001
β-hydroxybutyrate, mmol/L	2663	2·6 (0·0 to 15·0)	2·0 (0·0 to 13·8)	<0·001	0·024

(Table 1 continues on next page)

	N respondents	Pandemic cohort, n=785 (27·2%)	Control cohort, n=2096 (72·8%)	p value	p value adjusted for age at diagnosis and sex
(Continued from previous page)					
Plasma glucose, mmol/L	2748	22·8 (4·2 to 71·0)	23·9 (3·2 to 88·0)	0·023	0·009
HbA_{1c}, mmol/mol	2504	97·7 (28·0)	94·2 (27·1)	0·004	0·004
HbA_{1c}, %	2504	11·1 (2·6)	10·8 (2·5)	0·004	0·004
Autoantibodies					
Insulin autoantibodies	2176	339/581 (58·3%; 54·3 to 62·3%)	920/1595 (57·7%; 55·2 to 60·1%)	0·818	0·341
Insulin autoantibodies, RU	1259	6·3 (1·7 to 289·6)	6·4 (1·6 to 829·8)	0·757	0·845
Islet antigen 2 antibodies	2176	432/581 (74·4%; 70·7 to 77·7%)	1166/1595 (73·1%; 70·9 to 75·2%)	0·596	0·579
Islet antigen 2 antibodies, RU	1598	106·9 (0·8 to 679·2)	100·1 (0·8 to 266·5)	0·160	0·132
Glutamic acid decarboxylase antibodies	2176	424/581 (73·0%; 69·2 to 76·4%)	1036/1595 (65·0%; 62·6 to 67·3%)	<0·001	<0·001
Glutamic acid decarboxylase antibodies, RU	1460	38·5 (5·5 to 323·4)	33·5 (5·4 to 473·9)	0·151	0·196
Zinc transporter 8 antibodies	2176	420/581 (72·3%; 68·5 to 75·8%)	1104/1595 (69·2%; 66·9 to 71·4%)	0·183	0·218
Zinc transporter 8 antibodies, RU	1524	15·0 (0·5 to 289·5)	11·0 (0·5 to 263·2)	0·003	0·076
Number of positive antibodies	2176	3 (2·78)	3 (2·65)	0·012	0·043
Autoantibody negative	2176	19/581 (3·3%; 2·1 to 5·1%)	61/1595 (3·8%; 3·0 to 4·9%)	0·632	0·445
Positivity for multiple (≥2) autoantibodies	2176	506/581 (87·1%; 84·1 to 89·6%)	1342/1595 (84·1%; 82·3 to 85·8%)	0·102	0·062

Data shown as n (%; 95% CI), mean (SD), or median (range). RU=relative unit.

Table 1: **Demographic, clinical, metabolic, and autoimmune characteristics of children with type 1 diabetes diagnosed during the COVID-19 pandemic and those diagnosed during the reference period**

and sex-adjusted incidence rate ratio was 1·16 (1·06–1·25; p<0·0006). All comparisons resulted in incidence rate ratios higher than 1 (figure; appendix 3 p 9). The highest absolute incidence rate ratio was observed for boys younger than 5 years old (1·34; 1·06–1·67). In the sensitivity analysis, the incidence of type 1 diabetes was 51·2 per 100 000 person-years (47·4–55·2) in 2018–19, which was significantly lower than during the pandemic period, which was 61·0 per 100 000 person-years (56·8–65·4). The crude incidence rate ratio for the pandemic was 1·19 (1·07–1·32; p=0·0009).

There were no significant differences in the sex distribution or age at diagnoses between the patients diagnosed during the pandemic and those diagnosed during the reference period. Significantly more children had diabetic ketoacidosis at diagnosis during the pandemic (30·8% *vs* 22·6%; p<0·001) There was also a significantly increased frequency of severe ketoacidosis at disease presentation (8·8% *vs* 5·6%; p=0·009; table 1).

The pH was lower and the plasma β-hydroxybutyrate higher in the pandemic period than the reference period. Plasma glucose was lower at diagnosis, but HbA_{1c} was higher during the pandemic. Patients diagnosed with type 1 diabetes during the pandemic tested positive for GAD antibodies more frequently than those presenting with type 1 diabetes before the pandemic, and they had a higher number of detectable autoantibodies (median 3, mean 2·78 *vs* median 3, mean 2·65; p=0·043). The proportion of children with a family member affected by type 1 diabetes was lower among those diagnosed during the pandemic; these children were more often born in summer and fall (table 1). The proportion of children without HLA risk genotypes was higher among those diagnosed during the pandemic, but the difference was not significant (table 3).

SARS-CoV-2 antibodies were analysed in 583 children with type 1 diabetes diagnosed during the pandemic. No

	COVID-19 period (n=785)	Reference period (n=2096)
All	61·0 (56·8–65·4)	52·3 (50·1–54·6)
Girls	52·0 (46·5–58·0)	46·5 (43·5–49·6)
Boys	69·6 (63·4–76·3)	57·8 (54·6–61·2)
Age <5 years	47·0 (40·2–54·5)	39·6 (36·2–43·2)
Age <5 years, girls	40·0 (31·3–50·3)	38·7 (34·0–44·0)
Age <5 years, boys	53·6 (43·7–65·2)	40·4 (35·6–45·6)
Age 5 to <10 years	70·0 (62·4–78·2)	59·3 (55·3–63·5)
Age 5 to <10 years, girls	62·2 (52·2–73·6)	52·8 (47·5–58·5)
Age 5 to <10 years, boys	77·4 (66·4–89·6)	65·6 (59·7–71·8)
Age 10 to <15 years	63·5 (56·5–71·1)	57·0 (53·1–61·2)
Age 10 to <15 years, girls	51·7 (42·8–61·9)	47·3 (42·2–52·9)
Age 10 to <15 years, boys	74·8 (64·2–86·5)	66·3 (60·3–72·6)

Data shown as rate (95% CI).

Table 2: **Incidence rates of type 1 diabetes in Finnish children younger than 15 years old per 100 000 person-years during the COVID-19 pandemic and during the reference period**

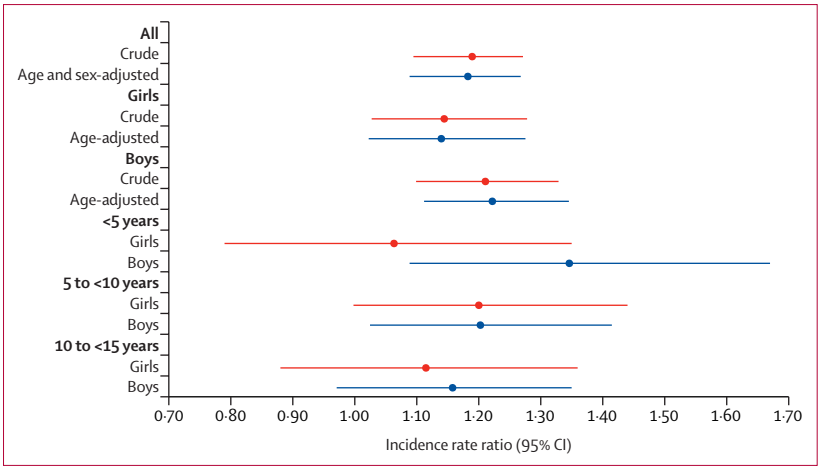

Figure: **Incidence rate ratios of type 1 diabetes in Finnish children younger than 15 years in the COVID-19 pandemic compared with the reference period**

	Pandemic cohort, n=657	Reference cohort, n=1722	p value	p value adjusted for age at diagnosis and sex
DR3–DQ2 and DR4–DQ8	128 (19·5%; 16·6–22·7%)	347 (20·2%; 18·3–22·1%)	0·759	0·799
DR3–DQ2 and x*	89 (13·5%; 11·1–16·4%)	234 (13·6%; 12·1–15·3%)	1·000	0·982
DR4–DQ8 and y†	255 (38·8%; 35·2–42·6%)	701 (40·7%; 38·4–43·0%)	0·426	0·394
z‡	109 (16·6%; 13·5–19·1%)	230 (13·4%; 11·8–15·0%)	0·051	0·056
DR3–DQ2 homozygote	16 (2·4%; 1·5–3·9%)	40 (2·3%; 1·7–3·1%)	0·992	0·864
DR4–DQ8 homozygote	55 (8·4%; 6·5–10·7%)	151 (8·8%; 7·5–10·2%)	0·821	0·754
DR3–DQ2 positive	238 (36·2%; 32·6–40·0%)	637 (37·0%; 34·7–39·3%)	0·765	0·801
DR4–DQ8 positive	438 (66·7%; 63·0–70·2%)	1202 (69·8%; 67·6–71·9%)	0·153	0·161
Risk group	..	..	0·495	0·537
0	6 (0·9%; 0·4–2·0%)	11 (0·6%; 0·4–1·1%)	..	..
1	17 (2·6%; 1·6–4·1%)	44 (2·6%; 1·9–3·4%)	..	..
2	117 (17·8%; 15·1–20·9%)	260 (15·1%; 13·5–16·9%)	..	..
3	142 (21·6%; 18·6–24·9%)	420 (24·4%; 22·4–26·5%)	..	..
4	247 (37·6%; 34·0–41·3%)	640 (37·2%; 34·9–39·5%)	..	..
5	128 (19·5%; 16·6–22·7%)	347 (20·2%; 18·3–22·1%)	..	..

Data shown as % (95% CI). *x≠DR4–DQ8. †y≠DR3–DQ2. ‡z≠DR3–DQ2 and DR4–DQ8.

Table 3: **HLA class II genotypes in children with type 1 diabetes diagnosed during the COVID-19 pandemic and in those diagnosed during the reference period**

samples were available from 202 participants (25·7%) of the 785 included children. Nine children (1·5%) of 583 tested positive for SARS-CoV-2 Spike IgG antibodies using a high-throughput ELISA,[18] and those samples were further analysed for SARS-CoV-2 N protein antibodies and neutralising antibodies to contemporary variants by a lentivirus-based neutralisation test (table 4).[19] The parents of the children who were antibody-positive were interviewed for their child's history of any SARS-CoV-2 infection or vaccinations before the diagnosis of type 1 diabetes. Based on the accumulated data, only five children (1%) of 583 were considered to have had an acute COVID-19 infection before their type 1 diabetes diagnosis. In four children this was confirmed because they had neutralising SARS-CoV-2 titres of 80 or more and the presence of N antibodies, leaving uncertain only the diagnosis of one child who had high neutralising SARS-CoV-2 titres but no N antibodies. Five children who were diagnosed with type 1 diabetes in August 2021 (after the voluntary COVID-19 vaccinations of children had started in Finland) had S antibodies compatible with vaccination before sampling. However, one of these five vaccinated children also had a positive anti-N response, suggesting a history of infection. We compared the five children with a COVID-19 infection preceding the diagnosis of type 1 diabetes with the other 578 children (appendix 3 pp 6–7). The children with a history of a preceding COVID-19 infection had significantly lower plasma β-hydroxybutyrate concentrations than the other children (0·5 mmol/L *vs* 2·3 mmol/L; p<0·001). The children with a history of COVID-19 infection were older at diagnosis of type 1 diabetes, had more conspicuous weight loss, higher plasma glucose levels, and all five tested positive for GAD autoantibodies; but these differences were not significant.

We compared the 202 children with no biological samples to the other 583 patients (appendix 3 p 10). Those without biological samples were 0·7 years younger than all the other children (p=0·026), had a lower proportion of fathers affected by type 1 diabetes (p=0·043), a slightly higher HbA_{1c} value (p=0·025), and a higher β-hydroxybutyrate concentration, the difference of which was not significant after adjustment for age and sex.

We would have expected to see 93 excess cases among the 583 children tested for SARS-CoV-2 antibodies in line with a 16% increase in the rate of type 1 diabetes, but among these only five cases could be attributed to SARS-CoV-2 infections based on the current data.

Discussion

This study shows that a small proportion of Finnish children with type 1 diabetes diagnosed during the first 18 months of the COVID-19 pandemic had a documented SARS-CoV-2 infection before the diagnosis of type 1 diabetes. We also observed a statistically significant increase in the incidence of type 1 diabetes in the country with the highest rate of type 1 diabetes in the world.[10] This result suggests that the increase in type 1 diabetes incidence is unlikely to be a direct effect of SARS-CoV-2 (because of the discrepancy between the proportion of infected children [0·9%] and the increase in the incidence of type 1 diabetes [16%]). This finding is in line with an early report from Colorado, USA, showing that the prevalence of SARS-CoV-2 antibodies was similar during the first 10 months of 2020 in children and adults with type 1 diabetes to that in those without type 1 diabetes,[23] and with study findings in children and adolescents from Colorado, USA, and Bavaria, Germany, which showed no association between SARS-CoV-2 infections and islet autoimmunity that is predictive of clinical type 1 diabetes.[24] In addition, an experimental study showed

	Month and year of diagnosis of type 1 diabetes	Interval from type 1 diabetes diagnosis to sampling, days	Month and year of COVID-19 infection before type 1 diabetes	History of COVID-19 vaccination before type 1 diabetes	Test for SARS-CoV-2 antibodies: ELISA IgG antibodies		Tests for SARS-CoV-2 antibodies: neutralising antibody titres			Interpretation of history and serological findings
					Spike	N protein	Alpha	Delta	Omicron	
1, girl, 6·9 years	May, 2020	4	April, 2020	No	Positive	Positive	160	40	<20	Antibodies induced by infection
2, boy, 10·5 years	October, 2020	6	September, 2020	No	Positive	Negative	<20	<20	<20	Only Spike antibodies; diagnosis less certain
3, boy, 13·1 years	February, 2021	40	November, 2020	No	Positive	Positive	160	80*	<20	Antibodies induced by infection
4, girl, 13·0 years	August, 2021	4	July, 2021	No	Positive	Positive	<20	320	<20	Antibodies induced by infection
5, boy, 12·7 years	August, 2021	46	No	Yes	Positive	Positive	80	<20	<20	Antibodies induced probably by both infection and vaccination
6, boy, 12·4 years	August, 2021	4	No	Yes	Positive	Negative	80	40	<20	Antibodies induced by vaccination
7, girl, 12·0 years	August, 2021	13	No	Yes	Positive	Negative	80	20	<20	Antibodies induced by vaccination
8, boy, 13·7 years	August, 2021	18	No	Yes	Positive	Negative	160	40	<20	Antibodies induced by vaccination
9, boy, 18 years	August, 2021	113	No	Yes	Positive	Equivocal	>2560	2560	320	Antibodies induced by vaccination†

*The pseudoneutralisation titer was also 80 against the beta variant; this was the only case that occurred during the time beta variant was co-circulating in Finland in spring, 2021. †Serum taken in February, 2022; the date of diagnosis was Aug 1, 2021; the patient was vaccinated twice but an infection could not be ruled out.

Table 4: **History of acute COVID-19 infection and vaccination and results of antibody tests in the nine children with newly type 1 diabetes who tested positive for SARS-CoV-2 Spike antibodies by ELISA in the sample obtained close to the diagnosis of type 1 diabetes**

that the infection of human pancreatic islets with the SARS-CoV-2 virus resulted in modest cellular perturbations and inflammatory responses.[25] Preliminary data indicate that the rate of type 1 diabetes has decreased in Finnish children after the mitigation of the lockdown measures in the summer 2021, because the number of new cases registered in the period from September 2021, to February 2022, was 211 children, versus 301 new cases in the period from March 1 to August 31, 2021.[26]

An increased incidence rate of type 1 diabetes during the pandemic was observed both among boys and girls, although the increase was statistically non-significant in girls. The reason behind this sex difference is unclear. However, the high proportion of boys among the number of children with newly diagnosed diabetes both before and especially during the pandemic provides more statistical power to the comparison of disease rates among boys.

Some earlier studies have reported a temporal association between SARS-CoV-2 infection and incidental diabetes diagnosis. In the USA, a survey based on two medical claims databases indicated that in one of the databases, the risk of newly diagnosed diabetes more than 30 days after a SARS-CoV-2 infection increased in children younger than 18 years old,[27] whereas no significant increase was seen in after other acute respiratory infections. The analysis of the first database could distinguish between type 1 and type 2 diabetes, whereas the other database analysis was unable to do so. Additionally, a significant increase in the incidence of diabetes after SARS-CoV-2 infections in older people was observed in an extensive cohort study done in the USA, but the increase was almost exclusively in type 2 diabetes.[28] A Scottish study reported an increased risk for new onset type 1 diabetes within 30 days after a SARS-CoV-2 infection, but that was not the case later than 30 days from infection.[29] The authors suggested that more active testing probably contributed to the increased detection of SARS-CoV-2 infections within 30 days from the diagnosis of type 1 diabetes, because tests were done more frequently in that period.

Indirect effects of the pandemic have to be considered as potential causes of the increase in the incidence rate of type 1 diabetes. The lockdown of society implemented in most countries when the pandemic started, and the resulting social isolation, have had numerous consequences that are reflected in the everyday life of the citizens.[8] In children, the pandemic resulted in decreased physical activity and a substantially reduced rate of both viral and bacterial infections. A British population-based study found that the hospital admission rate for both common and severe childhood infections decreased substantially (by 50–93%) in England during the COVID-19 pandemic.[30] Rocafort and colleagues[31] reported that the stringent COVID-19 lockdown in Spain significantly affected the composition of the nasopharyngeal microbiota in children, reflected in a reduced abundance of common respiratory pathobionts. The role of infections in the development of type 1 diabetes is ambiguous.

On one hand, we have the old hygiene hypothesis,[32] which has evolved into the modern biodiversity hypothesis, claiming that a reduced microbial exposure in early childhood is associated with an enhanced risk of immune-mediated diseases, including type 1 diabetes.[33] On the other hand, a series of studies have reported that early viral infections increase the risk of progression to type 1 diabetes.[34–36] In both scenarios, the effect is assumed to be mediated through the immune system. The lockdown in Finland during the first 18 months of the COVID-19 pandemic is likely to have substantially reduced the microbial exposure in children; for example, the circulation of influenza A and B and respiratory syncytial virus was almost completely interrupted.[37] The observed temporal association between the marked reduction in infection load and the reported increase in the incidence of type 1 diabetes in children corroborates the biodiversity hypothesis.

In the present study, children who presented with type 1 diabetes during the COVID-19 pandemic had more severe metabolic decompensation reflected by an increased frequency of diabetic ketoacidosis, more severe ketonemia, and higher HbA_{1c} concentrations. Similar observations have been reported in earlier studies from various countries.[5–7] Positivity for GAD antibodies was more common among those diagnosed during the COVID-19 pandemic. GAD antibodies have been reported to be associated with a slow progression to type 1 diabetes.[38] The increased frequency of GAD antibodies among those diagnosed with type 1 diabetes during the COVID-19 pandemic might indicate that the proportion of those with slowly progressing disease is increased in the pandemic cohort.

There is a pool of children in the general population who are asymptomatic for diabetes but autoantibody-positive. A population-based cross-sectional study in unselected Finnish children showed that 0·6% of them tested positive for multiple (≥2) islet autoantibodies.[39] It has previously been shown in an international multicentre study that children with multiple autoantibodies have an approximately 70% risk of progressing to clinical type 1 diabetes over the subsequent 10 years.[40] The duration of the period from seroconversion to autoantibody positivity up to overt type 1 diabetes is highly individual.[41] Accumulated data suggest that the mean duration of this period is 2·5–3·0 years.[42] Accordingly, the increased number of children with type 1 diabetes during the early phase of the COVID-19 pandemic might be derived from the population pool of children testing positive for multiple autoantibodies.

During the 18-month pandemic period studied, 128 595 people were diagnosed with SARS-CoV-2 infections in Finland according to the national statistics.[43] Of these, 31 383 were children or young people 20 years old or younger, representing 2·6% of the overall Finnish population 20 years old or younger. From that point of view, the 0·9% of children with infection-induced SARS-CoV-2 antibodies among children presenting with type 1 diabetes during the pandemic is relatively low. In our study, the total prevalence of SARS-CoV-2 antibodies was 1·5% among those tested, which is quite similar to that reported from other countries in the same region (0·6–1·9%).[44–46] The comparison of children with SARS-CoV-2 antibodies due to a preceding infection to the group with no signs of such an infection is limited by the low number of infected children. Accordingly, the results should be interpreted cautiously. The only significant differences were lower plasma β-hydroxybutyrate concentrations and a higher frequency of homozygosity for the HLA DR3-DQ2 haplotype in the children with a preceding infection, which might be chance findings. The voluntary SARS-CoV-2 vaccination of children was initiated in Finland in July 2021. As expected, there were a few children (n=4) with SARS-CoV-2 antibodies induced solely by the vaccination.

One strength of this study is that the participants do represent people with type 1 diabetes based on clinical features, autoantibody status, and HLA genotype. Another strength is that SARS-CoV-2 antibodies have been analysed with two different methods in all samples available from the participants.

A limitation of this study is that serum samples were not available from all participants. To test whether this limitation might question our observation that COVID-19 infections are unlikely to explain the increased incidence of type 1 diabetes, we did an additional analysis. We did not find any definite indication that those who were not tested for SARS-CoV-2 antibodies would have had a more aggressive form of type 1 diabetes or a higher frequency of SARS-CoV-2 infections, or both. The younger age of those without serum samples suggests that they were at a lower risk of testing positive for SARS-CoV-2 antibodies, because the few children testing positive for such antibodies in the present study were on an average 4 years older than those testing negative for SARS-CoV-2 antibodies. In addition, the proportion of children younger than 9 years old among all those diagnosed with COVID-19 in Finland younger than 30 years old during the first 20 months of the COVID-19 pandemic was 20·5%, whereas the proportion of the 10–19 year age group was 32·8%, and the oldest age group made up 46·8% according to the national statistics.[43]

The short follow-up period (18 months) represents another limitation. A full understanding of the effect of COVID-19 on islet autoimmunity and clinical type 1 diabetes will require a considerably longer observation period. A further consideration is that not all COVID-19 infections induce seroconversion to positivity for SARS-CoV-2 antibodies.[7,47] Toh and colleagues[48] reported that only approximately 37% of children with a mild COVID-19 infection developed SARS-CoV-2 antibodies. Applied to the present study, that data indicates that if we have five participants who test positive for such antibodies, there might be eight additionally affected

children who have not developed antibodies in our population (n=583). Accordingly, the total number of participants affected by the SARS-CoV-2 virus would be 13 (1·7%). However, that proportion is still more than nine times lower than the observed 16% increase in the incidence of type 1 diabetes among Finnish children during the pandemic.

Taken together, our observations suggest that the increase in type 1 diabetes incidence is unlikely due to a previous SARS-COV-2 infection. Possible explanations for the increase include the effects from lockdown and social isolation implemented in Finland to reduce the spreading of SARS-CoV-2 infections. Therefore, the extent and nature of restrictions applied for reducing the spreading of any future pandemic virus and the associated trade-offs should be carefully considered.

Contributors

MK, AP, MT, and AB analysed the data and conceptualised the analyses. MK wrote the first version of the manuscript. JH and OV helped with conceptualising the analyses and with interpreting the SARS-CoV-2 antibody results. TH was responsible for the analyses of islet autoantibodies. JL and JI were responsible for the HLA typing. TS, RI-E, HU, and KS were involved in the analysis of SARS-CoV-2 antibodies. MK is the principal investigator for the Finnish Pediatric Diabetes Register. MK, MT, and OV have accessed and verified the data, and MK and OV were responsible for the decision to submit the manuscript.

Declaration of interests

AP has received a grant from the Pediatric Research Center and Helsinki University Hospital. JL has received grants from the Diabetes Research Foundation and the Pediatric Research Foundation in Finland. OV has received grants from the Academy of Finland; and declares support from Pfizer for attending a meeting on tick-borne encephalitis virus vaccine. The other authors declare no competing interests.

Data sharing

The de-identified individual participant data that underlie the results reported in this Article can be obtained from the corresponding author (mikael.knip@helsinki.fi) upon reasonable request.

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