Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix - Table of Contents

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Supplementary amplifying text

The observations reported herein cover the period of time synonymous with many reported increases in the incidence of type 1 diabetes comparing the pre- to pandemic periods. Virtually none of these included any systematic testing for the presence of the SARS-CoV-2 virus. While the virus may have mutated during this period, we continue to believe that the presence of nucleocapsid antibodies remain a valid indicator for SARS-CoV-2 infection and that spike antibodies, in the absence of nucleocapsid antibodies, are a valid indicator of vaccination. We did not intend to distinguish between different variants. In addition, the small number of infections and subsequent cases of islet autoantibody positivity in our study population would preclude an analysis of individual variants.

The study population consists of children enrolled and followed by the TEDDY study, which collects extensive data on possible diabetes-related risk factors, including past infections. Children were enrolled by 3 months of age from 2004-2009 from sites located in four countries: the U.S. (3712), Finland (1833), Germany (594), and Sweden (2528). The cumulative loss to follow-up rate is 31% (22-37% over the four countries). Data collection includes parent reporting of clinical infection and analysis of stool (viral shedding) and blood (antibodies) collected longitudinally which should detect clinical and subclinical exposures. While we cannot rule out the occurrence of antibodies that subsequently declined below detectable levels, the frequent sampling interval (3 months for those who were islet autoantibody positive and 6 months otherwise) would suggest that this is not the case.

TEDDY continues to follow this population and tests for islet autoantibodies after infection. We cannot rule out that autoantibodies might appear years after infection. But we deliberately matched the time periods reported in the literature – that is, the literature cited makes reference to the year before the pandemic and the first year of the pandemic. We show that the increase in the number of cases is not related to infection. We can speculate as to whether heightened surveillance or changes in access to care may have accounted for this observation. In our study, T1D and SARS-CoV-2 surveillance were uniform over the pre-pandemic and pandemic time periods.

Islet autoantibodies and SARS-CoV-2 antibodies were all measured centrally. Autoantibodies to insulin (IAA), glutamic acid decarboxylase (GADA), insulinoma antigen-2 (IA-2A), or zinc transporter 8 (ZnT8A) were measured in two laboratories by radio binding assays. In the U.S., all sera were assayed at the Barbara Davis Center for Childhood Diabetes at the University of Colorado Denver; in Europe, all sera were assayed at the University of Bristol, U.K. Both laboratories followed the same protocol which demonstrated high sensitivity and specificity as well as concordance. All positive islet autoantibody samples and 5% of the negative samples were re-tested in the other reference laboratory and deemed confirmed if concordant. This study only reports confirmed results.

COVID-19 antibodies were tested by Atlas Genomics, Seattle, Washington, using the Meso Scale Discovery (MSD) Assay V-PLEX SARS-CoV-2 Panel 2 (IgG) to measure IgG antibodies to the nucleocapsid (N) and spike (S) antigens. IgG antibodies to the nucleocapsid protein of the

virus were used to determine prior exposure to SARS-CoV-2 (infection) and IgG antibodies to the spike protein (not N) were used to determine prior vaccination. A sample positive for both N and S antibodies were interpreted as prior infection.

We chose to avoid issues of adjustment for multiple testing by reporting point estimates and 95% confidence intervals. The confidence intervals were calculated using exact methods.

Table S1. Supplementary Table on the Representativeness of Study Participants

Category	Example
Disease, problem, or condition under investigation	The incidence of diabetes related autoimmunity and type 1 diabetes in a prospective cohort study of individuals at elevated type 1 diabetes genetic risk.
Special considerations related to	
Sex and gender	The incidence of diabetes related autoimmunity is 30% higher among males, but the incidence of type 1 diabetes is 40% less as compared to females in a genetically at-risk population.
Age	The incidence of autoimmunity peaks under 5 years of age and the incidence of diabetes rises until 5 years of age, after which the incidence of both remains fairly constant through the second decade of life.
Race or ethnic group	Type 1 diabetes affects Hispanic and Black persons disproportionately. They are underrepresented in this study cohort.
Geography	There are country differences in the incidence of type 1 diabetes. This study cohort addressed that by enrolling those with high genetic risk.