Supplemental Online Content

Rewers M, Bonifacio E, Ewald D, et al; ASK Study Group; Fr1da Study Group. SARS-CoV-2 infections and presymptomatic type 1 diabetes autoimmunity in children and adolescents from Colorado, USA, and Bavaria, Germany. *JAMA*. doi:10.1001/jama.2022.14092

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

SARS-CoV-2 antibody detection

Colorado: In ASK participants, total SARS-CoV-2 antibodies, including IgM, IgG, IgA, and IgD to receptor binding domain of the spike protein (RBD) and, separately, to nucleocapsid protein (NP) were measured by electrochemiluminescent (ECL) assay[1]. An RBD antibody index >5 defined past SARS-CoV2 infection in an unvaccinated child. In children who have received a SARS-CoV-2 vaccine, NP antibody index >5 defined past SARS-CoV2 infection. In addition, parents of 359 ASK participants reported that their child had received a positive SARS-CoV-2 diagnostic test prior to the screening. Of those, 37 children were negative for the RBD antibody, but were included in the analyses as previously SARS-CoV-2 infected.

Bavaria: In Fr1da participants, SARS-CoV-2 antibodies to RBD and NP were measured using a luciferase immunoprecipitation system (LIPS) as previously described[2]. An RBD antibody level > 1 arbitrary unit (AU) and NP antibody level > 13 AU defined past SARS-CoV2 infection. The requirement for NP positivity was important in 2020 when the prevalence of infection was ~0.1%; while NP antibodies do not appear to add to the screening accuracy in 2021, the criteria for positivity were not changed. SARS-CoV-2 vaccines were not available to German children younger than 11 y during the study period.

Measurement of islet autoantibodies

Colorado: In ASK participants, autoantibodies to insulin, GAD, IA-2, and ZnT8 were measured in the Immunogenetics Laboratory at the Barbara Davis Center using previously described radiobinding assays (RBA) and high-affinity ECL assays[3-5]. In the 2020 Islet Autoantibody Standardization Program (IASP) Workshop, sensitivities and specificities, respectively, for the RBA among patients newly diagnosed with type 1 diabetes were 62% and 99% for insulin, 78% and 99% for GAD, 72% and 100% for IA-2, and 74%

and 100% for ZnT8 autoantibodies. For ECL they were 66% and 99% for insulin, 78% and 100% for GAD, 72% and 100% for IA-2, and 74% and 100% for ZnT8 autoantibodies. A single autoantibody in ASK is associated with a 30% risk of progression to clinical diabetes in the next 5-years[5].

Bavaria: In Fr1da participants, autoantibodies to insulin, GAD, IA2, and ZnT8 were measured at the Helmholtz Institute using previously described methods[6]. First-line screening was performed with a sensitive enzyme-linked immunosorbent assay (3 Screen; RSR Ltd) to detect autoantibodies to GAD, IA-2, and ZnT8[7], and with a luciferase immunoprecipitation system (LIPS) assay to detect insulin autoantibodies in serum prepared from capillary blood[8]. Screening samples positive for islet autoantibodies and confirmation venous blood samples were tested for autoantibodies to insulin, GAD, IA-2, and ZnT8 using reference radiobinding assays. In the 2020 IASP Workshop, sensitivities and specificities were 94% and 100% for the 3 Screen ELISA, 46% and 98% for the LIPS insulin autoantibodies. For the radiobinding assays, they were 48% and 98% for insulin, 74% and 100% for GAD, 74% and 100% for IA-2, and 76% and 100% for ZnT8 autoantibodies. Single autoantibody positivity in Fr1da is defined by higher cutoffs, high-affinity, and positivity in two different assay formats (LIPS and RBA or RBA and ELISA) and predicts a 40% risk of progression to clinical diabetes in 10 years in genetically susceptible children[9].

eReferences

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