

Prevalence of early-stage type 1 diabetes in young adults: a population-based cohort study

Type 1 diabetes was once thought to be exclusively a childhood-onset disease, but recent epidemiological evidence shows that more than half of all clinical diagnoses of type 1 diabetes occur in adulthood.¹ Although substantial progress has been made in identifying presymptomatic type 1 diabetes in children,^{2,3} a 2022 systematic review involving 32 countries and regions has highlighted considerable uncertainties in prevalence data for adult-onset type 1 diabetes.⁴ Additionally, data regarding the diagnostic value of islet autoantibodies in adults are scarce. This raises the important question of whether systematic screening for early-stage type 1 diabetes should be extended beyond childhood, to offer them the opportunity to participate in clinical trials or benefit from emerging therapies aimed at delaying disease onset.

To address this issue, we aimed to determine the prevalence of islet autoantibodies in participants from the German LISA and GINIplus birth cohorts, which follow individuals from birth into adulthood (appendix p 2).⁵ Both cohorts are long-standing, population-based, with a research focus on allergic diseases. In the most recent 25-year follow-up (examinations conducted between March, 2022, and March, 2024), a total of 1377 adult participants with a median age of 25.8 years (range 24.6–28.1), comprising 792 (57.5%) female participants and 585 (42.5%) male participants, attended a physical examination and provided serum obtained from venous blood draws (appendix p 4). All samples were tested in a masked manner for islet autoantibodies, with no access to participants' medical

history. Autoantibody screening was performed using a similar approach as in the Fr1da study,² which includes initial screening via the 3-Screen ELISA (RSR, Cardiff, UK) and a LIPS insulin autoantibody (IAA) assay with positive samples tested separately for IAA and for GAD65, IA-2, and ZnT8 autoantibodies (GADA, IA-2A, ZnT8A) by radiobinding assay (appendix pp 2–3). Thresholds for positivity were those used for children.⁶ A previous diagnosis of type 1 diabetes was searched in the self-reported medical records of all participants. Thyroid peroxidase autoantibodies were measured by radiobinding assay in participants who were positive for islet autoantibodies (appendix pp 2–3).

Among the 1377 participants, 43 (3.1%; 28 [3.5%] female

participants and 15 [2.6%] male participants) screened positive in the 3-Screen ELISA (n=38) or LIPS IAA assay (n=10) and 23 (54.5%; 1.7% of total; 18 [2.3%] female participants and 5 [0.9%] male participants) were also positive for one or more islet autoantibodies by radiobinding assay (appendix p 5). Six of the 23 participants had been previously diagnosed with type 1 diabetes, yielding an islet autoantibody prevalence of 17 of 1371 (1.24%, 95% CI 0.72–1.98; figure; appendix p 5) in undiagnosed adults screened. Of these, three participants (0.22%, 0.05–0.64) had two or more islet autoantibodies consistent with early-stage type 1 diabetes (GADA with IA-2A or ZnT8A or both; figure). 14 (1.0%, 0.56–1.71) had single



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See Online for appendix



Figure: Islet autoantibody assessment

Inner and middle circles show results in samples from 25-year follow-up. Outer circle shows results in samples from 15-year follow-up. Grey indicates known type 1 diabetes. Green indicates single islet autoantibody detected. Yellow indicates multiple islet autoantibodies detected. Orange indicates newly detected multiple islet autoantibodies. Blue indicates no islet autoantibody detection at 15-year follow-up. GADA=GAD65 autoantibody. IAA=insulin autoantibody. IA-2A=IA-2 autoantibody. ZnT8A=ZnT8 autoantibody. *GADA, IA2A, ZnT8A, IAA (n=1); GADA, ZnT8A, IAA (n=1); GADA, IA2A, ZnT8A, IAA (n=1); GADA, ZnT8A, IAA (n=1); IA2A, ZnT8A, IAA (n=1); ZnT8A, IAA (n=1); GADA, IA2A, ZnT8A, IAA (n=2).

islet autoantibodies, including nine (0.65%) with GADA, four (0.3%) with IAA, and one (0.07%) with ZnT8A. No participants who tested negative for islet autoantibodies had a reported diagnosis of clinical type 1 diabetes. Two (16.7%, 2.09–48.41) of 12 undiagnosed participants with GADA also had autoantibodies against thyroid peroxidase, consistent with the known association between these two autoantibodies (appendix p 5).⁷ Similar to children,⁶ almost half of adults identified as positive in a screening assay did not have islet autoantibodies in confirmation assays, emphasising the importance of second assays to increase specificity.

To further investigate the age of seroconversion and persistence of islet autoantibodies, all four antibodies were additionally assessed in samples taken approximately 10 years earlier (between April, 2011, and May, 2014) at the 15-year follow-up (appendix pp 2, 5). Samples at age 15 years were available for five of the six participants with clinical type 1 diabetes, all three with early-stage type 1 diabetes (ie, two or more islet autoantibodies and no clinical type 1 diabetes), and eight of 14 with single islet autoantibodies. At age 15 years, two or more islet autoantibodies were detected in all five participants with clinical type 1 diabetes, two of whom developed type 1 diabetes between age 15 and 25 years (highlighted in yellow in the outer circle of the figure), and in two of the three participants with early-stage type 1 diabetes (highlighted in orange in the outer circle of the figure), leaving one new case presenting with early-stage type 1 diabetes after age 15 years (highlighted in blue in the outer circle and orange in the middle circle of the figure). These findings correspond to an incidence rate of early-stage type 1 diabetes between age 15 years and age 25 years of 7.3 per 100 000 person-years (95% CI 0.7–40.1). In total, six (54.5%; four female participants and two male participants) of the

11 participants with undiagnosed type 1 diabetes who were tested at age 15 years were already islet autoantibody positive at the earlier timepoint and five (45.4%; three female and two male) newly developed autoantibodies between the two timepoints, yielding an overall incidence rate of islet autoantibody seroconversion between age 15 years and age 25 years of 36.6 per 100 000 person-years (95% CI 11.9–85.4). Of the eight participants with single islet autoantibodies at 25 years and with samples available from age 15 years, four had the same single antibody (three GADA, one IAA) at age 15 years, whereas the remaining four developed the autoantibodies between the ages of 15 years and 25 years (two GADA, one IAA, and one ZnT8A).

This analysis shows that adults in the general population have frequencies of islet autoantibodies (1.2%) and of early-stage type 1 diabetes (0.2%; figure) that are similar to those in young children. Around half of those with islet autoantibodies developed these autoantibodies between the ages of 15 and 25 years, the majority of these presenting with single islet autoantibodies, extending previous findings in the TEDDY study, which showed a steady low rate of seroconversion after age 4 years.⁸ Compared with screening in preschool children where an incidence of early-stage type 1 diabetes of around 100 per 100 000 person-years was observed,² the incidence in our study was considerably lower after age 15 years in this analysis.

The findings of this analysis need to be interpreted after considering limitations. First, the sample size is relatively small for a screening study and confidence intervals for prevalences and incidence rates are correspondingly wide. Second, infants whose mothers had diabetes were excluded from the study, which might have led to a slight underestimation of the incidence. Third, it is possible that the selected thresholds for positivity

from screening in children might require adjustment for adults. Fourth, larger sample sizes and longitudinal follow-up of those with early-stage type 1 diabetes are required to assess the prognostic value of early-stage type 1 diabetes in adults. Nevertheless, this analysis offers the first estimates of the prevalence of early-stage type 1 diabetes in a population-based sample of young German adults, along with novel insights into the age of seroconversion and the persistence of islet autoantibodies.

In summary, our findings suggest that screening for islet autoantibodies and early-stage type 1 diabetes could be of value in young adults and, in particular, for those who have not been previously tested in adolescence.

For data protection reasons, the datasets generated and analysed during the current study cannot be made publicly available. The datasets are available to interested researchers from the corresponding author upon reasonable request (eg, reproducibility), provided the release is consistent with the consent given by the GINIplus and LISA study participants. Ethical approval might be obtained for the release and a data transfer agreement from the legal department of the Helmholtz Zentrum München must be accepted. The authors thank all the families for their participation in the GINIplus and LISA studies. Furthermore, we thank all members of the GINIplus Study Group and the LISA Study Group for their excellent work. The GINIplus study was mainly supported for the first 3 years by the Federal Ministry for Education, Science, Research and Technology (interventional arm) and Helmholtz Zentrum München (former GSF; observational arm). The 4-year, 6-year, 10-year, 15-year, and 20-year follow-up examinations of the GINIplus study were covered from the respective budgets of the 5 study centres (Helmholtz Zentrum München (former GSF), Research Institute at Marien-Hospital Wesel/ Department of Pediatrics, EVK Düsseldorf, LMU Munich, TU Munich and from 6 years onwards also from IUF-Leibniz Research Institute for Environmental Medicine Düsseldorf) and a grant from the Federal Ministry for Environment (IUF Düsseldorf, FKZ 20462296). Furthermore, the 15-year follow-up examination of the GINIplus study was supported by the Commission of the European Communities, the 7th Framework Program: MeDALL project. The 15-year and 20-year follow-up examinations were additionally supported by Mead Johnson and Nestlé. The follow-up questionnaire during the COVID pandemic was covered by the respective budgets of the participating study centres (Helmholtz Zentrum München, Department of Pediatrics, EVK Düsseldorf, and IUF-Leibniz Research Institute for Environmental Medicine Düsseldorf). The 25-year follow-up examination was funded by the

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