ESM Methods: Overview of historical and harmonized islet autoantibody testing strategy for each 'parent' study.

BABYDIAB; All serum samples from BABYDIAB were tested previously for GADA, IA-2A, and IAA in Munich [1, 2]. The last available sample from these participants was tested for ZnT8A and where an individual was positive, all previous available samples were also tested [3]. Later samples were tested using the harmonized assays for GADA and IA-2A [4]. Slow progressors were mAab positive in at least two sequential samples.

DAISY; Measurement of islet autoantibodies to insulin, GAD65, IA-2 and ZnT8 was performed in the Clinical Immunology Laboratory at the Barbara Davis Center (BDC) using radio-immunoassays as described previously [5, 6]. The initial assay for GADA and IA-2A was a combined dual label radioassay [5]. Since January 2010, GADA and IA-2A have been measured using the National Institute of Diabetes and Digestive and Kidney Diseases harmonised assays [4]. All available samples from children who were ever found positive for any of the above autoantibodies or who developed type 1 diabetes were tested for ZnT8A as previously described [7]. Slow progressors were antibody positive in at least two sequential samples and all were mAab positive on at least one occasion.

ABIS; All antibody testing was carried out by the pediatric research laboratory, Linköping University , Sweden. Samples taken at age 1 and 2.5-3 years were tested on EDTA whole blood for GADA and IA-2A only [8], subsequent serum samples taken at age five years and up were tested for IAA in addition to GADA and IA-2A [9]. All slow progressors were identified through measurement of GADA, IA-2A, and IAA. After 11 years of age, ZnT8A were also tested [10]. Data were provided for 24 ABIS participants with mAabs who had not progressed to diabetes before 11 years of age. Of these, 11 were identified as Slow Progressors.

BOX; The first available serum samples from relatives in BOX and the last sample for those with a follow-up of at least 4 years were previously tested for GADA and IA-2A at the University of Bristol [11]. Insulin autoantibodies were also tested in all relatives under the age of 10 years. To identify multiple antibody positive individuals IAA and ZnT8A were tested in all IA-2A and/or GADA positive relatives [12, 13]. Multiple antibody positive samples from potential slow progressors were retested with harmonised assays for GADA and IA-2A [4], as well as for IAA and ZnT8A when serum was available, these results were used to define Slow Progressors. Where multiple samples were available, only individuals with persistent mAabs were included.

Pittsburgh family study; All serum samples from relatives in the Pittsburgh study were tested historically for IAA, GADA and ICA 512 (IA-2A) at the University of Pittsburgh from 1979 to 1984 and 2004 to 2011. In the intervening years the biochemical antibodies were tested if screening for ICA was positive or the participants developed diabetes of any type. Potential slow progressors were initially selected from those previously found positive for IAA, GADA, IA-2A, or high levels of ICA [14]. Multiple antibody positive samples from these potential slow progressors were retested with harmonised assays for IAA, GADA, IA-2A and ZnT8A [4, 6, 15] at the Clinical Immunology Laboratory at the BDC. Slow progressors were defined based on the results of harmonised assays.

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ESM Table 1

Study title	BABYDIAB	The Diabetes Autoimmunity Study in the Young (DAISY)		All Babies In Southeast Sweden (ABIS)	Bart's-Oxford Family Study (BOX)	Pittsburgh Family Study
Location	Germany	Denver, Colorado, USA		South-East Sweden	Former Oxfordshire Health Authority, UK	Pittsburgh, Pennsylvania, USA
Recruitment period	1989 to 2000	1993 to 2004		1997 to 1999	1985 to present; all Slow progressors recruited before 2002	1979 to 1984
Type	Longitudinal from birth (9 months)	Longitudinal from recruitment (< 7 years)	Longitudinal from birth (9 months)	Longitudinal from birth (1 year)	Longitudinal from recruitment	Longitudinal from recruitment
Participants	Children born to a mother or father with diabetes	Siblings or offspring (< 7 years old) of an individual with type 1 diabetes	HLA-DR/DQ genotypes identified through screening of over 31,000 newborns at St. Joseph Hospital in Denver, Colorado	All babies due to be born between October 1997 and October 1999	Siblings and parents of probands diagnosed under the age of 21 years living in the region.	First degree relatives of probands diagnosed (1950 onwards) under the age of 19 in the Children's Hospital of Pittsburgh registry. Normoglycaemia at recruitment
Genetic selection	None	None	All children with DR3/4, DQB1*0302, DR3/3, and DR4/4, DQB1*0302 and a sample of those with DR4/DRx, DQB1*0302, or DR3/DRx (where DRx≠DR3 or DR4) were invited to participate in DAISY None	None	None	None
Participants (n)	1650	2547		17055; n=7394 providing at least two samples for aab analysis	1865 families before 2002	>10,000 First degree relatives
Ethnicity	97% Caucasian	72% non-Hispanic white		>95 % Caucasian	>95% Caucasian	96 % White
Islet autoantibodies tested	IAA, GADA, IA-2A, ZnT8A	IAA, GADA, IA-2A, ZnT8A		GADA and IA-2A in all samples, IAA at 5yrs and above, ZnT8A at 11 years and above	IAA, GADA, IA-2A, ZnT8A	IAA, GADA, IA-2A (in ICA+) ZnT8A (in slow progressors)
Islet autoantibody testing schedule	9 months, and at 2, 5, 8, 11, 14, 17 and 20 years of age. Children with a positive autoantibody finding, were asked to provide a sample for confirmation of autoantibody status within 6 months and provide samples yearly.	From recruitment <7 years. Then as with HLA screened population.	9 months, 15 months, 24 months and annually thereafter; autoantibody positive children are followed and tested for islet autoantibodies, random BG and HbA1c every 3-6 months.	1, 2.5-3, 5-6 and 8 and 11 years of age, In participants with multiple antibodies and then every 6 months for 30 month. Up to 5-6 years in association with well baby clinics; After this by mail.	From recruitment; up to 6 monthly	From recruitment; up to 6 monthly
OGTT assessment	Yearly in autoantibody positive	6 monthly where participants are willing. 3 monthly HbA1C.		None	Not routine	At recruitment
Diabetes definition	Yearly: ADA criteria >2 abnormal OGTTs or following the family reporting diabetes diagnosed by a clinician	2 yearly: ADA criteria >2 abnormal OGTT or following the family reporting diabetes diagnosed by a clinician		Swedish national incidence and quality registry for childhood diabetes SWEDIABKIDS.	Yearly: Family reporting of diabetes diagnosed by a clinician	2 Yearly: Family reporting of insulin treated diabetes diagnosed by a clinician
Key references for study description	Ziegler, 1999, Diabetes	Norris, 1996, JAMA	Rewers, 1996, Diabetologia	Nygren, 2015, Diabetologia; Ludvigsson, 2001, Pediatric Diabetes	Bingley, 1989, BMJ	Pietropaolo, 2005, Pediatric Diabetes; Morran, 2010, Endocrinology.

ESM Table 1: Summary of the protocols for SNAIL study cohorts.