An age-related exponential decline in the risk of multiple islet autoantibody seroconversion during childhood

Short running title: Islet autoimmunity risk declines exponentially

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Online-Only Supplemental Material

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HLA eligibility

The high-risk genotypes for participants screened from the general population were as follows: DRB1*04-DQA1*03-DQB1*03:02/DRB1*03-DQA1*05-DQB1*02:01 (DR3/4), DRB1*04-DQA1*03-DQB1*03:02/DRB1*04-DQA1*03-DQB1*03:02 (DR4/4), DRB1*04-DQA1*03-DQB1*03:02/DRB1*08-DQA1*04-DQB1*04:02 (DR4/8) and DRB1*03-DQA1*05-DQB1*02:01/DRB1*03-DQA1*05-DQB1*02:01 (DR3/3). Additional genotypes were included for first degree relatives (FDRs) of a subject with T1D: DRB1*04-DQA1*03-DQB1*03:02/DRB1*04- DQA1*03-DQB1*02:02 (DR4/4b), DRB1*04-DQA1*03-DQB1*03:02/DRB1*01- DQA1*01-DQB1*05:01 (DR4/1), DRB1*04-DQA1*03-DQB1*03:02/DRB1*13-DQA1*01-DQB1*06:04 (DR4/13), DRB1*04-DQA1*03-DQB1*03:02/DRB1*09- DQA1*03-DQB1*03:03 (DR4/9), and DRB1*03-DQA1*05-DQB1*02:01/DRB1*09- DQA1*03-DQB1*03:03 (DR3/9).

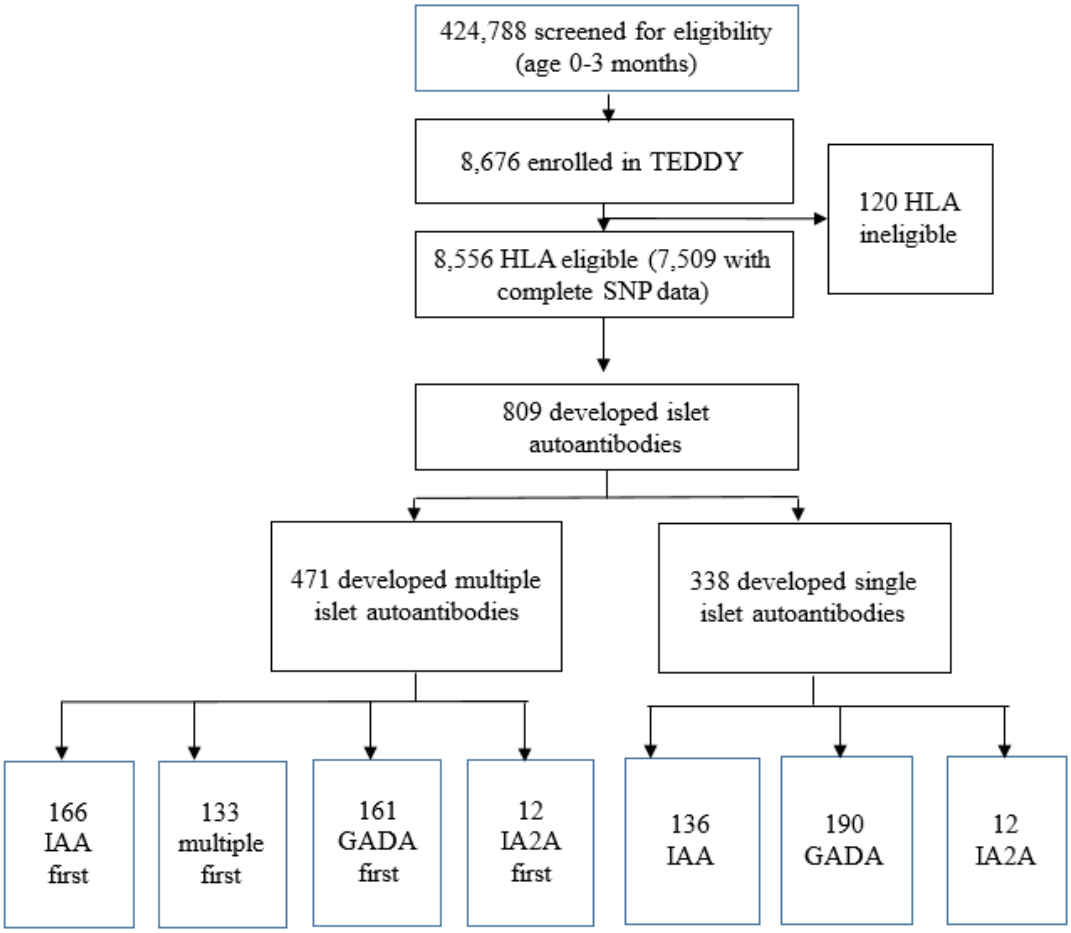
Supplemental Table 1: Characteristics of the study population (*n* = 8,556)

Variable (n)	**Category**	**Number (%)**	**Risk of multiple islet autoantibodies by age 12 years [95% CI]**
Sex	Girls	4,226 (49.4)	5.2% [4.5 – 5.9]
	Boys	4,330 (50.6)	6.4% [5.6 – 7.2]
First-degree relative with type 1 diabetes	Yes	955 (11.2)	12.4% [10.2 – 14.6]
	No	7,601 (88.8)	5.0% [4.5 – 5.5]
Site	Europe	4,895 (57.2)	6.7 % [5.9 – 7.4]
	U.S.A.	3,661 (42.8)	4.7 % [3.9 – 5.5]
HLA genotype	*DR3/DR4-DQ8*	3,339 (39.0)	8.0% [7.0 – 8.9]
	DR4-DQ8/DR4-DQ8	1,674 (19.6)	6.2% [5.0 – 7.4]
	DR4-DQ8/DR8	1,474 (17.2)	4.5% [3.4 – 5.7]
	DR3/DR3	1,791 (20.9)	2.2% [1.4 – 3.0]
	Other*	278 (3.3)	7.3% [4.2 – 10.4]
Genetic risk score†	Highest quartile	1,104 (25)	12.8% [10.8 – 14.8]
(n=4,413)	2nd and 3rd quartiles	2,206 (50)	7.8% [6.6 – 8.9]
	Lowest quartile	1,103 (25)	4.1% [2.9 – 5.4]

*All of the other *HLA DR4-DQ8*-containing genotypes were in children with a first-degree relative with type 1 diabetes

†Only calculated in general population children with complete SNP data and the *HLA DR3/DR4-DQ8 or DR4-DQ8/DR4-DQ8* genotypes

Supplemental Figure 1: Flow diagram of study participants and islet autoantibody outcomes.



Supplemental Table 2: Cumulative five-year horizon risk for any and multiple islet autoantibodies from respective landmark age

Landmark age	Any islet autoantibodies	Multiple islet autoantibodies
From 7.5 months	6.3% [5.7-6.8]	4.2% [3.8-4.7]
From 1.125 years	5.4% [4.9-5.9]	4.3% [3.9-4.7]
From 1.625 years	4.8% [4.3-5.2]	3.5% [3.1-3.9]
From 2.125 years	4.1% [3.7-4.5]	2.9% [2.6-3.3]
From 2.625 years	3.7% [3.3-4.2]	2.4% [2.1-2.8]
From 3.125 years	3.4% [3.0-3.8]	2.0% [1.7-2.3]
From 3.625 years	3.3% [2.9-3.7]	1.7% [1.4-2.0]
From 4.25 years	3.2% [2.8-3.6]	1.6% [1.3-1.9]
From 5.25 years	3.1% [2.7-3.5]	1.5% [1.2-1.8]
From 6.25 years	3.2% [2.7-3.6]	1.3% [1.0-1.5]
From 7.25 years	3.3% [2.7-3.9]	1.1% [0.8-1.3]
From 8.25 years	3.3% [2.5-4.0]	1.1% [0.8-1.5]

Supplemental Table 3: Cumulative five-year horizon risk for multiple islet autoantibodies from respective landmark age by first degree family history (FDR) status

Landmark age	**Risk after 5 years of follow-up** **FDR**	**Risk after 5 years of follow-up** **No FDR**
From 7.5 months	9.9% [8.0-11.8]	3.6% [3.2-4.0]
From 1.125 years	7.7% [5.9-9.4]	3.0% [2.6-3.4]
From 1.625 years	6.2% [4.6-7.8]	2.5% [2.2-2.9]
From 2.125 years	4.9% [3.4-6.3]	2.1% [1.8-2.5]
From 2.625 years	4.0% [2.7-5.3]	1.8% [1.5-2.1]
From 3.125 years	3.2% [2.0-4.4]	1.5% [1.2-1.8]
From 3.625 years	3.3% [2.1-4.5]	1.4% [1.1-1.7]
From 4.25 years	2.9% [1.7-4.1]	1.3% [1.1-1.6]
From 5.25 years	2.0% [1.0-3.0]	1.2% [0.9-1.5]
From 6.25 years	1.9% [0.9-2.8]	1.0% [0.7-1.3]
From 7.25 years	1.8% [0.6-3.0]	1.0% [0.7-1.4]
From 8.25 years	1.5% [0.4-2.7]	0.8% [0.5-1.1]

Supplemental Table 4: Cumulative five-year horizon risk for multiple islet autoantibodies from respective landmark age by sex

Landmark age	**Risk after 5 years of follow-up** **Male**	**Risk after 5 years of follow-up** **Female**
From 7.5 months	4.8% [4.1-5.4]	3.8% [3.2-4.4]
From 1.125 years	3.7% [3.2-4.3]	3.3% [2.7-3.8]
From 1.625 years	3.2% [2.7-3.8]	2.6% [2.1-3.1]
From 2.125 years	2.9% [2.4-3-4]	2.0% [1.5-2.4]
From 2.625 years	2.4% [1.9-2.8]	1.7% [1.3-2.1]
From 3.125 years	2.0% [1.5-2.4]	1.4% [1.0-1.7]
From 3.625 years	1.9% [1.4-2.3]	1.4% [1.0-1.7]
From 4.25 years	1.7% [1.3-2.1]	1.3% [0.9-1.7]
From 5.25 years	1.6% [1.2-2.1]	1.2% [0.8-1.5]
From 6.25 years	1.2% [0.8-1.7]	1.1% [0.7-1.7]
From 7.25 years	1.1% [0.6-1.5]	1.2% [0.7-1.7]
From 8.25 years	0.8% [0.4-1.1]	1.0% [0.5-1.5]

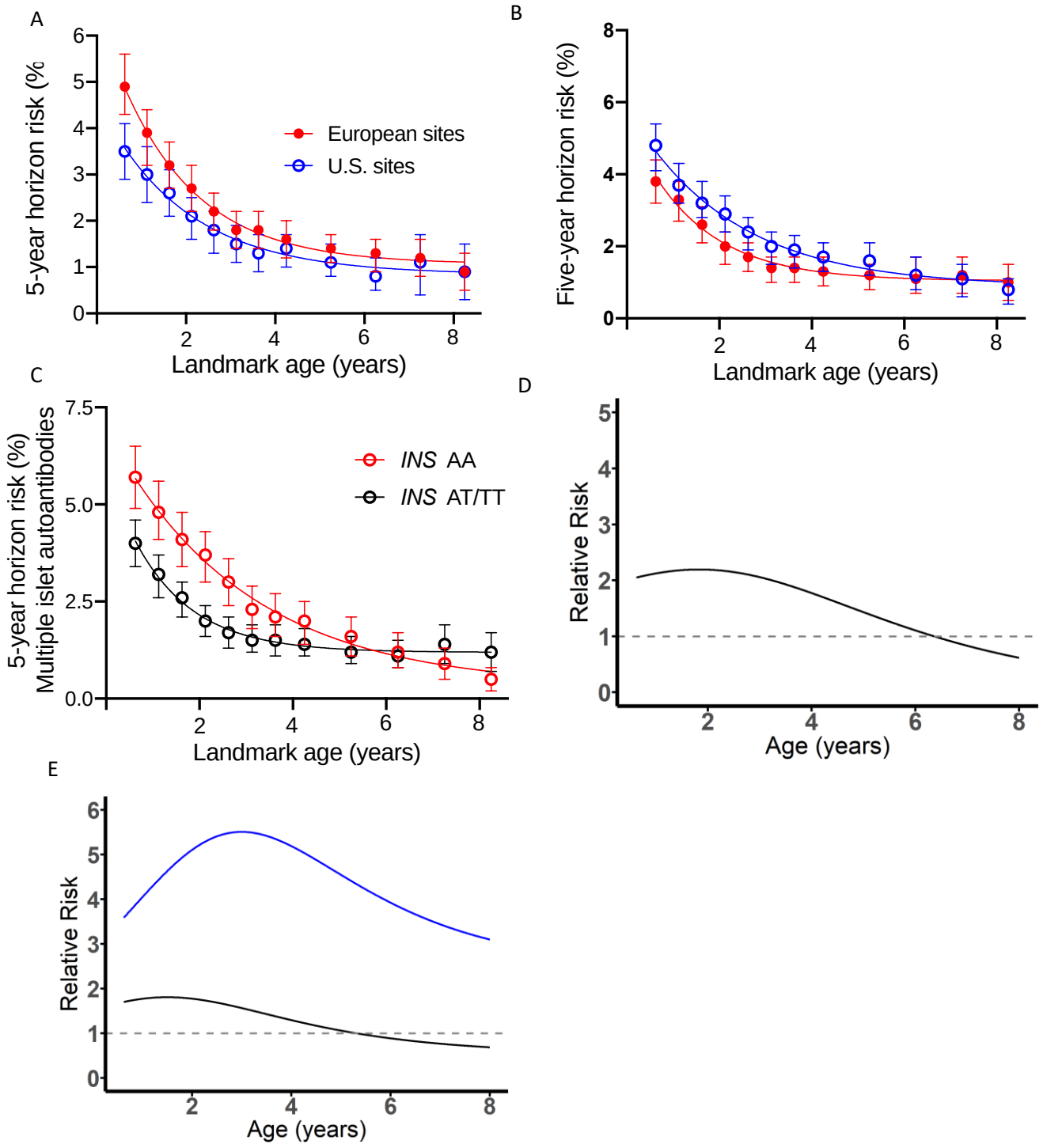
Supplemental Table 5: Cumulative five-year horizon risk for multiple islet autoantibodies from respective landmark age by *HLA* genotype

Landmark age	**DR3/4-DQ8**	**DR4-DQ8/DR4-DQ8**	**DR4-DQ8/DR8**	**DR3/3**
From 7.5	6.2% [5.3-7.0]	4.1% [3.2-5.1]	3.0% [2.2-3.9]	1.7% [1.1-2.3]
From 1.125	5.1% [4.3-5.9]	3.7% [2.8-4.6]	2.0% [1.3-2.8]	1.3% [0.7-1.8]
From 1.625	4.4% [3.7-5.1]	3.4% [2.5-4.3]	1.5% [0.9-2.1]	0.8% [0.4-1.2]
From 2.125	3.6% [3.0-4.3]	2.9% [2.1-3.7]	1.0% [0.5-1.6]	0.8% [0.4-1.2]
From 2.625	3.0% [2.4-3.6]	2.6% [1.9-3.4]	0.9% [0.4-1.4]	0.5% [0.2-0.9]
From 3.125	2.5% [1.9-3.1]	2.2% [1.4-2.9]	0.7% [0.3-1.2]	0.5% [0.1-0.8]
From 3.625	2.2% [1.7-2.8]	2.1% [1.4-2.8]	1.1% [0.5-1.6]	0.5% [0.2-0.9]
From 4.25 years	2.1% [1.6-2.6]	2.1% [1.4-2.8]	1.2% [0.6-1.7]	0.2% [0.0-0.5]
From 5.25 years	1.5% [1.1-2.0]	2.1% [1.3-2.8]	1.1% [0.5-1.7]	0.3% [0.0-0.6]
From 6.25 years	1.2% [0.8-1.7]	1.9% [1.1-2.6]	1.0% [0.4-1.6]	0.3% [0.0-0.9]
From 7.25 years	1.3% [0.7-1.8]	1.9% [0.9-2.9]	1.0% [0.3-1.8]	0.4% [0.0-0.9]
From 8.25 years	0.8% [0.3-1.3]	1.6% [0.7-2.6]	0.9% [0.2-1.6]	0.4% [0.0-0.8]

Supplemental Table 6: Cumulative five-year horizon risk for multiple islet autoantibodies from respective landmark age by genetic risk score in general population children with the HLA DR3/4-DQ8 or DR4-DQ8/DR4-DQ8 genotypes

Landmark age	**≤ 1st quartile of genetic risk score**	**> 1st and < 3rd quartile of genetic risk score**	**≥ 3rd quartile of genetic risk score**
From 7.5 months	2.3% [1.4-3.3]	4.5% [3.6-5.4]	9.8% [7.9-11.7]
From 1.125 years	1.9% [1.0-2.7]	3.9% [3.0-4.7]	8.9% [7.0-10.7]
From 1.625 years	1.7% [0.9-2.5]	3.2% [2.4-4.0]	7.8% [6.1-9.5]
From 2.125 years	1.2% [0.5-1.9]	2.8% [2.1-3.6]	6.8% [5.2-8.4]
From 2.625 years	0.9% [0.3-1.5]	2.4% [1.7-3.1]	5.9% [4.4-7.5]
From 3.125 years	0.8% [0.3-1.4]	2.0% [1.4-2.6]	5.0% [3.6-6.5]
From 3.625 years	1.0% [0.4-1.7]	1.8% [1.2-2.4]	4.0% [2.6-5.2]
From 4.25 years	1.3% [0.6-2.0]	1.9% [1.3-2.5]	3.3% [2.1-4.5]
From 5.25 years	1.2% [0.5-1.9]	1.9% [1.3-2.6]	2.0% [1.1-3.0]
From 6.25 years	1.4% [0.6-2.3]	1.6% [0.9-2.2]	1.1% [0.4-1.8]
From 7.25 years	1.9% [0.5-3.2]	1.7% [0.8-2.5]	0.9% [0.2-1.5]
From 8.25 years	1.6% [0.3-2.9]	1.4% [0.6-2.2]	0.1% [0.0-0.4]

Supplemental Figure 2: Exponential risk decay curves for multiple islet autoantibodies stratified by (A) children in European and U.S. sites, (B) sex, and (C) *INS* genotype. The relative 5-year risks for multiple islet autoantibodies is also shown for (D) children with the *INS* AA genotype as compared to other *INS* genotypes, and (E) for children with the *HLA DR3/DR4-DQ8* genotype compared to children with the *HLA DR4-DQ8/DR4-DQ8* or *DR4-DQ8/DR8* genotypes (black line) and compared to children with the *DR3/3* genotypes (blue line).



Supplemental Table 7: Relative cumulative five-year horizon risks for multiple islet autoantibodies and respective 95% confidence intervals at different timepoints

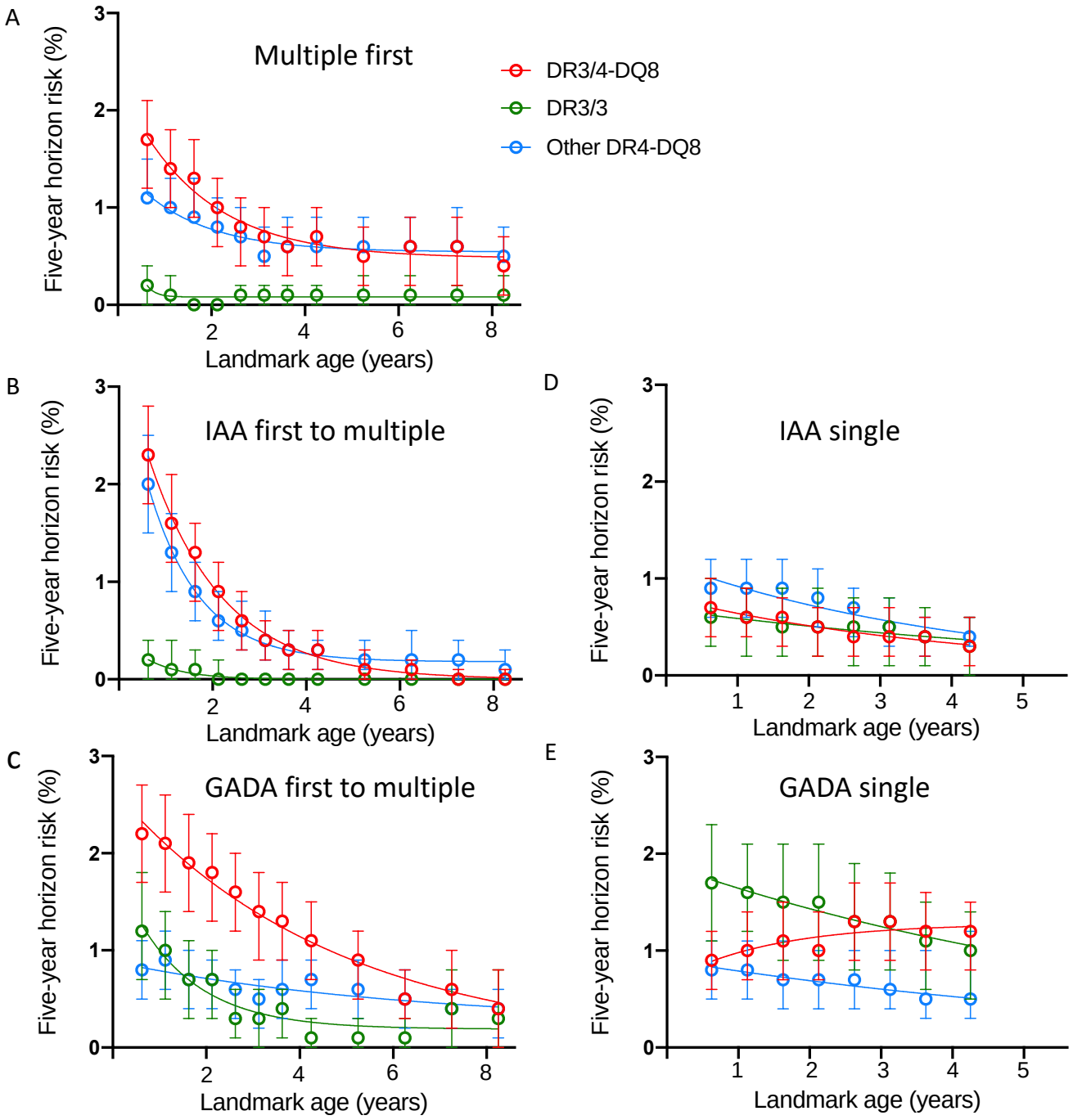
Age	**GRS highest quartile vs. lowest quartile**	**GRS highest quartile vs. middle quartiles**	**DR3/4-DQ8 vs. DR3/3**	**DR3/4-DQ8 vs. DR4-DQ8/DR4-DQ8 or DR4-DQ8/DR8**
0.625 years	4.2 [2.7-6.5]	2.2 [1.6-2.9]	3.6 [2.5-5.3]	1.7 [1.4-2.1]
2.125 years	5.7 [3.1-10.5]	2.4 [1.7-3.5]	4.5 [2.6-7.8]	1.8 [1.3-2.5]
5.25 years	1.8 [0.8-3.8]	1.1 [0.6-2.0]**	5.0 [2.0-12.5]	1.0 [0.6-1.5]***
6.25 years	1.0 [0.4-2.3]*	0.8 [0.4-1.8]***	3.5 [1.4-9.0]	0.8 [0.5-1.4]***

* P=0.003 vs 0.625 years; ** P=0.001 vs 0.625 years; *** p<0.0001 vs 0.625 years

Supplemental Table 8: Cumulative five-year horizon risk for islet autoantibody phenotypes from respective landmark age

Landmark age	IAA first to multiple	Multiple first	GADA first to multiple	Single IAA	Single GADA
From 7.5 months	1.7% [1.5-2.0]	1.2% [0.9-1.4]	1.4% [1.2-1.7]	0.8% [0.6-1.0]	1.0% [0.8-1.2]
From 13.5 months	1.2% [0.9-1.4]	1.0% [0.7-1.2]	1.4% [1.1-1.6]	0.7% [0.5-0.9]	1.0% [0.8-1.3]
From 19.5 months	0.8% [0.6-1.0]	0.9% [0.7-1.1]	1.2% [0.9-1.4]	0.7% [0.5-0.9]	1.0% [0.8-1.3]
From 25.5 months	0.6% [0.4-0.8]	0.7% [0.5-0.9]	1.1% [0.9-1.3]	0.6% [0.4-0.8]	1.0% [0.8-1.2]
From 31.5 months	0.4% [0.3-0.6]	0.6% [0.4-0.7]	0.9% [0.7-1.1]	0.5% [0.4-0.7]	1.0% [0.8-1.3]
From 37.5 months	0.3% [0.2-0.5]	0.5% [0.3-0.6]	0.8% [0.6-1.0]	0.5% [0.3-0.6]	1.0% [0.8-1.3]
From 43.5 months	0.2% [0.1-0.3]	0.5% [0.3-0.6]	0.8% [0.6-1.0]	0.4% [0.3-0.5]	0.9% [0.7-1.1]
From 51 months	0.2% [0.1-0.3]	0.5% [0.3-0.7]	0.7% [0.5-0.9]	0.4% [0.3-0.5]	0.9% [0.7-1.1]
From 63 months	0.2% [0.1-0.2]	0.5% [0.3-0.6]	0.6% [0.4-0.8]		
From 75 months	0.1% [0.0-0.2]	0.5% [0.3-0.7]	0.4% [0.3-0.6]		
From 87 months	0.1% [0.0-0.2]	0.5% [0.3-0.7]	0.5% [0.3-0.7]		
From 99 months	0.1% [0.0-0.1]	0.4% [0.2-0.6]	0.4% [0.2-0.6]		

Supplemental Figure 3: Exponential risk decay curves for islet autoantibody phenotypes stratified by HLA genotype.



Supplemental Table 9: Cumulative 5-year risk for islet autoantibody phenotypes from respective landmark age by *HLA* genotype

Landmark age	***Risk after 5 years of follow-up***	***Risk after 5 years of follow-up***	***Risk after 5 years of follow-up***
	DR3/DR4-DQ8	***DR3/DR3***	***Other HLA genotype***
IAA first to multiple			
From 0.625 years	2.3% [1.8-2.8]	0.2% [0.0-0.4]	2.0% [1.5-2.5]
From 1.125 years	1.6% [1.2-2.1]	0.1% [0.0-0.3]	1.3% [0.9-1.7]
From 1.625 years	1.2% [0.8-1.6]	0.1% [0.0-0.2]	0.9% [0.6-1.2]
From 2.125 years	0.9% [0.5-1.2]	0% [0-0]	0.6% [0.4-0.9]
From 2.625 years	0.6% [0.3-0.9]	0% [0-0]	0.5% [0.3-0.8]
From 3.125 years	0.4% [0.2-0.6]	0% [0-0]	0.4% [0.2-0.7]
From 3.625 years	0.3% [0.1-0.5]	0% [0-0]	0.3% [0.1-0.5]
From 4.25 years	0.3% [0.1-0.5]	0% [0-0]	0.3% [0.1-0.4]
From 5.25 years	0.1% [0.0-0.3]	0% [0-0]	0.2% [0.1-0.4]
From 6.25 years	0.1% [0.0-0.2]	0% [0-0]	0.2% [0.0-0.5]
From 7.25 years	0.0% [0.0-0.1]	0% [0-0]	0.2% [0.0-0.4]
From 8.25 years	0.0% [0.0-0.1]	0% [0-0]	0.1% [0.0-0.3]
Multiple first			
From 0.625 years	1.7% [1.2-2.1]	0.2% [0.0-0.4]	1.1% [0.8-1.5]
From 1.125 years	1.4% [1.0-1.8]	0.1% [0.0-0.3]	1.0% [0.6-1.3]
From 1.625 years	1.3% [0.9-1.7]	0% [0-0]	0.9% [0.6-1.3]
From 2.125 years	1.0% [0.6-1.3]	0% [0-0]	0.8% [0.5-1.1]
From 2.625 years	0.8% [0.4-1.1]	0.1% [0.0-0.2]	0.7% [0.4-1.0]
From 3.125 years	0.7% [0.4-1.0]	0.1% [0.0-0.2]	0.5% [0.3-0.8]
From 3.625 years	0.6% [0.3-0.8]	0.1% [0.0-0.2]	0.6% [0.3-0.9]
From 4.25 years	0.7% [0.4-1.0]	0.1% [0.0-0.2]	0.6% [0.3-0.9]
From 5.25 years	0.5% [0.2-0.8]	0.1% [0.0-0.3]	0.6% [0.3-0.9]
From 6.25 years	0.6% [0.2-0.9]	0.1% [0.0-0.3]	0.6% [0.3-0.9]
From 7.25 years	0.6% [0.2-0.9]	0.1% [0.0-0.2]	0.6% [0.2-1.0]
From 8.25 years	0.4% [0.1-0.7]	0.1% [0.0-0.2]	0.5% [0.2-0.8]
GADA first to multiple			
From 0.625 years	2.2% [1.7-2.7]	1.2% [0.7-1.8]	0.8% [0.5-1.1]
From 1.125 years	2.1% [1.6-2.6]	1.0.% [0.5-1.4]	0.9% [0.6-1.2]
From 1.625 years	1.9% [1.4-2.4]	0.7% [0.3-1.1]	0.7% [0.4-1.0]
From 2.125 years	1.8% [1.3-2.2]	0.7% [0.3-1.1]	0.6% [0.4-0.9]
From 2.625 years	1.6% [1.2-2.0]	0.3% [0.1-0.6]	0.6% [0.3-0.8]
From 3.125 years	1.4% [0.9-1.8]	0.3% [0.0-0.6]	0.5% [0.2-0.7]
From 3.625 years	1.3% [0.9-1.7]	0.4% [0.1-0.6]	0.6% [0.3-0.9]
From 4.25 years	1.1% [0.7-1.5]	0.1% [0.0-0.3]	0.7% [0.4-0.9]
From 5.25 years	0.9% [0.5-1.2]	0.1% [0.0-0.3]	0.6% [0.3-0.9]

From 6.25 years	0.5% [0.3-0.8]	0.1% [0.0-0.3]	0.5% [0.2-0.8]
From 7.25 years	0.6% [0.2-1.0]	0.4% [0.0-0.8]	0.4% [0.2-0.6]
From 8.25 years	0.4% [0.0-0.8]	0.3% [0.0-0.8]	0.4% [0.1-0.6]
Single IAA			
From 0.625 years	0.7% [0.4-1.1]	0.6% [0.3-1.0]	0.9% [0.6-1.2]
From 1.125 years	0.6% [0.4-0.9]	0.6% [0.2-0.9]	0.9% [0.6-1.2]
From 1.625 years	0.6% [0.3-0.8]	0.5% [0.2-0.9]	0.9% [0.6-1.2]
From 2.125 years	0.5% [0.2-0.7]	0.5% [0.2-0.9]	0.8% [0.5-1.1]
From 2.625 years	0.4% [0.2-0.7]	0.5% [0.1-0.8]	0.7% [0.4-0.9]
From 3.125 years	0.4% [0.2-0.7]	0.5% [0.1-0.8]	0.5% [0.3-0.8]
From 3.625 years	0.4% [0.2-0.6]	0.4% [0.1-0.7]	0.4% [0.2-0.6]
From 4.25 years	0.3% [0.1-0.6]	0.3% [0.1-0.7]	0.4% [0.2-0.6]
Single GADA			
From 0.625 years	0.9% [0.6-1.2]	1.7% [1.1-2.3]	0.8% [0.5-1.1]
From 1.125 years	1.0% [0.7-1.4]	1.6% [1.0-2.1]	0.8% [0.5-1.1]
From 1.625 years	1.1% [0.7-1.5]	1.5% [0.9-2.1]	0.8% [0.5-1.1]
From 2.125 years	1.0% [0.7-1.4]	1.5% [0.9-2.1]	0.7% [0.4-1.0]
From 2.625 years	1.3% [0.9-1.7]	1.3% [0.8-1.8]	0.7% [0.4-0.9]
From 3.125 years	1.3% [1.0-1.8]	1.3% [0.8-1.8]	0.7% [0.4-0.9]
From 3.625 years	1.2% [0.8-1.6]	1.1% [0.6-1.5]	0.6% [0.4-0.9]
From 4.25 years	1.2% [0.8-1.5]	1.0% [0.5-1.4]	0.5% [0.3-0.8]

Supplemental Table 10: Sensitivity and positive predictive value of screening for islet autoantibodies

Screening Age	Positive predictive value* [95 % CI]	Sensitivity † [95% CI]
Multiple autoantibodies as positive		
1 year	84.0% [60.7-93.5]	6.6% [4.3-10.0]
2 years	68.1% [57.6-76.0]	24.2% [19.7-29.2]
3 years	55.5% [47.0-62.6]	33.5% [29.5-38.9]
4 years	51.6% [44.1-58.1]	37.2% [32.0-42.6]
5 years	49.6% [42.1-56.1]	34.1% [29.1-39.6]
6 years	47.7% [40.0-54.4]	30.8% [25.9-36.1]
7 years	47.7% [39.4-55.0]	26.9% [22.3-32.1]
8 years	49.4% [39.3-57.7]	20.8% [16.7-25.7]
Any autoantibodies as positive		
1 year	49.5% [39.1-58.2]	19.3% [15.3-24.1]
2 years	41.8% [35.0-47.9]	37.2% [32.0-42.6]
3 years	33.9% [28.4-39.0]	45.3% [39.9-50.9]
4 years	32.8% [27.9-37.4]	46.2% [40.8-51.8]
5 years	29.1% [24.4-33.6]	41.1% [35.8-46.6]
6 years	27.9% [23.1-32.4]	35.3% [30.2-40.8]
7 years	28.5% [23.3-33.4]	30.8% [25.9-36.1]
8 years	29.7% [23.4-35.5]	23.9% [19.5-28.9]
Single autoantibodies as positive		
1 year	24.5% [20.5-28.2]	12.4% [9.1-16.5]
2 years	14.9% [11.3-18.3]	13.0% [17.2-26.3]
3 years	12.2% [8.7-15.6]	11.8% [8.6-15.9]
4 years	11.5% [7.9-14.9]	9.1% [6.3-12.8]
5 years	9.2% [5.8-12.5]	6.9% [4.6- 10.4]
6 years	10.3% [6.4-14.1]	4.5% [2.7-7.5]
7 years	11.6% [6.8-16.1]	3.9% [2.2-6.8]
8 years	11.8% [5.8-17.4]	3.0% [1.5-5.7]

* Positive predictive value refers to the five-year horizon risk to develop type 1 diabetes from the screening age.

† Sensitivity was calculated as the proportion of the total number of children in the TEDDY study who developed type 1 diabetes by age 12 years.

Supplemental Figure 4: Models of multiple islet autoantibody pathogenesis based on the landmark analysis of the TEDDY study.