



IA-2A positivity increases risk of progression within and across established stages of type 1 diabetes

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Abstract

Aims/hypothesis Accurate understanding of type 1 diabetes risk is critical for optimisation of counselling, monitoring and interventions, yet even within established staging classifications, individual time to clinical disease varies. Previous work has associated IA-2A positivity with increased type 1 diabetes progression but a comprehensive assessment of the impact of screening for IA-2A positivity across the natural history of autoantibody positivity has not been performed. We asked whether IA-2A would consistently be associated with higher risk of progression within and across established stages of type 1 diabetes in a large natural history study.

Methods Genetic, autoantibody and metabolic data from adult and paediatric autoantibody-negative ($n=192$) and autoantibody-positive ($n=4577$) relatives of individuals with type 1 diabetes followed longitudinally in the Type 1 Diabetes TrialNet Pathway to Prevention Study were analysed. Cox regression was used to compare cumulative incidences of clinical diabetes by autoantibody profiles and disease stages.

Results Compared with IA-2A⁻ individuals, IA-2A⁺ individuals had higher genetic risk scores and clinical progression risk within single-autoantibody-positive (5.3-fold increased 5 year risk), stage 1 (2.2-fold increased 5 year risk) and stage 2 (1.3-fold increased 5 year risk) type 1 diabetes categories. Individuals with single-autoantibody positivity for IA-2A showed increased metabolic dysfunction and diabetes progression compared with people who were autoantibody negative, those positive for another single autoantibody, and IA-2A⁻ stage 1 individuals. Individuals at highest risk within the single-IA-2A⁺ category included children (HR 14.2 [95% CI 1.9, 103.1], $p=0.009$), individuals with IA-2A titres above the median (HR 3.5 [95% CI 1.9, 6.6], $p<0.001$), individuals with high genetic risk scores (HR 1.4 [95% CI 1.2, 1.6], $p<0.001$) and individuals with *HLA DR4*-positive status (HR 3.7 [95% CI 1.6, 8.3], $p=0.002$). When considering all autoantibody-positive individuals, progression risk was similar for euglycaemic IA-2A⁺ individuals and dysglycaemic IA-2A⁻ individuals.

Conclusions/interpretation IA-2A positivity is consistently associated with increased progression risk throughout the natural history of type 1 diabetes development. Individuals with single-autoantibody positivity for IA-2A have a greater risk of disease progression than those who meet stage 1 criteria but who are IA-2A⁻. Approaches to incorporate IA-2A⁺ status into monitoring strategies for autoantibody-positive individuals should be considered.

Keywords Autoantibodies · IA-2A · Islet antigen-2 · Precision medicine · Prediction · Progression · Stratification · Type 1 diabetes

Abbreviations

DPTRS DPT-1 risk score
GRS Genetic risk score

Introduction

Type 1 diabetes is an autoimmune disease resulting in insulin deficiency due to destruction of pancreatic beta cells [1]. Often, after the establishment of persistent islet autoimmunity, the disease progresses over years before insulin treatment is required [2]. Early, pre-symptomatic stages of type 1 diabetes can be detected by measuring autoantibodies to islet antigens, including GADA, IAA, IA-2A and ZnT8A [3]. Birth

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Research in context

What is already known about this subject?

- IA-2A positivity has previously been linked to an increased risk of type 1 diabetes progression at different timepoints in the natural history of disease but the relationship between screening for IA-2A positivity and clinical progression risk has never been comprehensively addressed across type 1 diabetes stages

What is the key question?

- Does IA-2A positivity consistently identify higher risk across the natural history of autoantibody positivity?

What are the new findings?

- IA-2A positivity is linked to increased diabetes progression within traditional type 1 diabetes staging categories
- Individuals with single positivity for IA-2A exhibit increased metabolic dysfunction and clinical progression compared with IA-2A⁻ single-autoantibody-positive or stage 1 groups
- For the autoantibody-positive population as a whole, IA-2A⁺ individuals have higher genetic risk scores for type 1 diabetes, and IA-2A positivity with euglycaemia is associated with comparable progression rates compared with IA-2A negativity with dysglycaemia

How might this impact on clinical practice in the foreseeable future?

- IA-2A positivity is consistently linked to increased progression throughout the natural history of type 1 diabetes and the impact of this specific autoantibody on progression risk should be considered in addition to staging criteria

cohort studies suggest that once euglycaemic young individuals develop more than one islet autoantibody, they are at sufficiently high lifetime risk for type 1 diabetes to warrant a classification of stage 1 type 1 diabetes [2, 4]. Stage 2 type 1 diabetes marks those with more than one autoantibody who have progressed past a threshold for metabolic dysfunction, indicated by abnormal glucose levels that do not meet clinical diabetes diagnostic criteria. Stage 3 type 1 diabetes, or clinical type 1 diabetes, is marked by hyperglycaemia that has exceeded the threshold for a clinical diabetes diagnosis [4, 5].

Even within type 1 diabetes stage classifications, the individual time to stage 3 diabetes can vary [6–8]. Thus, accurate risk prediction is critical for optimal counselling of at-risk individuals for consideration of disease-modifying therapies, as well as for prevention trial design. Multiple features, including genetic profiles, immune markers such as autoantibodies, and metabolic phenotypes, can be used to predict rates of progression to stage 3 diabetes [9–11].

Given that IA-2A testing is already frequently used within type 1 diabetes screening programmes [12], our objective was to determine whether IA-2A positivity status should be considered for additional stratification of clinical diabetes progression risk that could be applied within and across the current staging paradigm. Based on reports that elevated IA-2A is linked to progression of type 1 diabetes at different timepoints [7, 13, 14], we hypothesised that IA-2A positivity would consistently be associated with higher progression risk across established stages of type 1 diabetes development.

We analysed baseline and longitudinal follow-up data from the Type 1 Diabetes TrialNet Pathway to Prevention study of relatives of individuals with type 1 diabetes [15]. Data from the following groups of individuals were considered: those who were autoantibody negative; those who were positive for a single autoantibody; those who were positive for multiple autoantibodies with euglycaemia (stage 1 type 1 diabetes) or dysglycaemia (stage 2 type 1 diabetes).

Methods

Study populations and determination of autoantibody status Demographic, OGTT, and progression data from non-diabetic islet autoantibody-positive and -negative first- and second-degree relatives of individuals with type 1 diabetes in the TrialNet Pathway to Prevention natural history study were considered [15]. Sex, race and ethnicity data were self-reported. Individuals were only considered to be positive for a single islet autoantibody if baseline testing was positive on screening and confirmation. Biochemical autoantibody testing in the Pathway to Prevention used assays included in the Islet Autoantibody Standardization Program, and initially used radiobinding assays for GADA, IA-2A and IAA performed by the Barbara Davis Center; GADA and IA-2A assays were transitioned to harmonised radiobinding assays in 2010 [16, 17]. Radiobinding assays for ZnT8A were adopted in 2012. Until 2019, screening

for all biochemical autoantibodies tested were performed for all participants and all confirmed autoantibody-positive participants were monitored with serial OGTTs. In 2019, the Pathway to Prevention protocol was changed to screen only for GADA and IAA, with initial positive screens also tested for IA-2A and ZnT8A and only individuals who were positive for multiple autoantibodies being followed with serial OGTTs. Data were also analysed from a smaller group of paediatric and adult relatives who were screened as autoantibody negative; these individuals were also followed with OGTTs over time [18]. For single-autoantibody positivity, only participants with confirmed autoantibody positivity were analysed. Analyses in multiple-autoantibody-positive groups were limited to two autoantibody-positive individuals to address confounding differences in progression related to total autoantibody number. For analysis of IA-2A, titres above the median for all positive IA-2A results in the Pathway to Prevention cohort were considered as higher positive titres. Participants in this and other type 1 diabetes research studies are overrepresented with non-Hispanic white participants from affluent socioeconomic areas [19]. Given similar distributions amongst antibody positive groups, stratification by sex was not performed as part of the current analysis. Informed consent and assent (as appropriate) were obtained from all participants and studies were approved by the responsible ethics committees, with investigations carried out in accordance with the principles of the Declaration of Helsinki.

Biochemical measurements HbA_{1c}, glucose and C-peptide testing from OGTTs were performed as described previously [20]. AUC values were calculated from 2 h OGTT data using the trapezoidal rule. Index60 was calculated as follows:

$$\text{Index60} = 0.36953 (\log_e \text{fasting C-peptide}) + 0.0165 (60 \text{ min glucose}) - 0.3644 (60 \text{ min C-peptide}) [21]$$

The DPT-1 Risk Score (DPTRS) was modelled based on age, log BMI, log fasting C-peptide, and the glucose and C-peptide sums of 30-, 60-, 90-, and 120-min values from OGTTs as described [22].

Genotyping Genotyping was performed using the T1DExomeChip array (Illumina, CA), which includes >90,000 custom SNPs selected from genetic loci previously associated with autoimmune diseases added to the Infinium CoreExome-24 v.1.1 BeadChip (Illumina, CA). Out of the 67 SNPs in a type 1 diabetes genetic risk score (GRS) 2, described by Sharp et al [23], 32 were directly genotyped. Thirty-two SNPs with a median R^2 of 0.997 (minimum 0.858, maximum 0.999) were imputed using the TOPMed Imputation Server with the multiethnic TOPMed reference panel [24, 25]. Five SNPs in the HLA region (rs72848653 [$R^2=0.999$], rs9266268 [$R^2=0.999$], rs16899379 [$R^2=0.998$], rs2524277 [$R^2=0.995$] and rs9268500 [$R^2=0.925$]) were imputed using

the Michigan Imputation Server [26]. The code for generating the HLA interaction portion of the T1D GRS2 is freely available online (<https://github.com/sethsh7/hla-prs-toolkit>).

Statistical analysis Either t tests or χ^2 tests were used to compare continuous characteristics and categorical characteristic frequencies. Since height was not routinely measured in autoantibody-negative relatives, comparisons including this group were adjusted for age but not BMI. Between-group comparisons of time to multiple-autoantibody positivity and clinical diabetes development were examined using Cox regression models with and without adjustments for potentially confounding variables, including baseline age and BMI. Analysis of factors impacting progression within the group of individuals with single-autoantibody positivity for IA-2A used Cox regression with univariable and multivariate analysis. Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). Two-sided p values < 0.05 were considered statistically significant.

Results

The presence of IA-2A is linked to greater likelihood of both metabolic abnormalities and diabetes progression within established stages of type 1 diabetes We first asked if the presence of IA-2A was associated with increased risk within groups of individuals meeting the criteria for single-autoantibody positivity ($n=3392$), stage 1 ($n=860$) or stage 2 ($n=323$) type 1 diabetes (demographic data are shown in Table 1). Metabolic data are shown in Table 2 and cumulative incidence curves showing rates of progression to stage 3 type 1 diabetes using Cox regression analyses are shown in Fig. 1, with 5 year risk provided in Table 3 and 5 year HRs provided in electronic supplementary material (ESM) Table 1. As shown in Table 2, when considered by category (adjusted for age and BMI) IA-2A⁺ individuals had a more abnormal metabolic phenotype (for single autoantibody: AUC glucose, Index60, DPTRS; for stage 1: AUC glucose, C-peptide 30–0, Index60, DPTRS; for stage 2: C-peptide 30–0, Index60, DPTRS). As shown in Fig. 1a–c, IA-2A⁺ individuals showed clear increases in rates of progression to stage 3 type 1 diabetes vs IA-2A[−] individuals within each risk category/stage: single-autoantibody-positive individuals (5.3-fold increased 5 year risk); stage 1 individuals (2.2-fold increased 5 year risk); and stage 2 individuals (1.3-fold increased 5 year risk). Within the single-autoantibody-positive group, even when stratified by glycaemic status (euglycaemia vs dysglycaemia), IA-2A positivity increased clinical progression risk (ESM Fig. 1). This association remained statistically significant with adjustment for subsequent development of multiple positive autoantibodies.

Table 1 Demographics at screening

Characteristic	Ab ⁻ (n=192)	Single Ab ⁺		Stage 1 ^a		Stage 2 ^a	
		IA-2A ⁻ (n=3229)	IA-2A ⁺ (n=163)	IA-2A ⁻ (n=541)	IA-2A ⁺ (n=319)	IA-2A ⁻ (n=165)	IA-2A ⁺ (n=158)
Age at draw, years	16.3 (10.44)	21.4 (14.1)*	18.3 (13.5)	12.2 (9.6)	15.0 (10.3)*	15.6 (12.2)	13.4 (9.1)*
% (n) Female sex	52.6 (101)	57.4 (1853)*	47.9 (78)	45.8 (248)	45.1 (144)	46.1 (76)	49.4 (78)
% (n) Black or African American	1.6 (3)	3.1 (101)	1.8 (3)	5.7 (31)	2.8 (9)	6.1 (10)	1.9 (3)
% (n) White	90.6 (174)	83.7 (2704)	91.4 (149)	82.8 (448)	88.1 (281)	84.8 (140)	86.7 (137)
% (n) Hispanic or Latino	6.8 (13)	11.3 (366)	6.7 (11)	9.1 (49)	6.0 (19)	6.1 (10)	10.1 (16)
BMI, kg/m ² , ^b	21.5 (5.1)	22.7 (6.8)*	21.1 (5.3)	19.1 (5.1)	20.9 (5.7)* [†]	21.1 (6.8)	19.9 (5.6)*
% (n) GADA only	n/a	77.1 (2490)	n/a	n/a	n/a	n/a	n/a
% (n) IAA only	n/a	22.8 (736)	n/a	n/a	n/a	n/a	n/a
% (n) IA-2A only	n/a	n/a	100 (163)	n/a	n/a	n/a	n/a
% (n) ZnT8A only	n/a	0.1 (3)	n/a	n/a	n/a	n/a	n/a
% (n) GADA + IAA	n/a	n/a	n/a	67.8 (367)	0 (0)*	67.3 (111)	0 (0)*
% (n) GADA + IA-2A	n/a	n/a	n/a	0 (0)	76.5 (244)*	0 (0)	72.2 (114)*
% (n) GADA + ZnT8A	n/a	n/a	n/a	29.8 (161)	0 (0)*	29.7 (49)	0 (0)*
% (n) IAA + IA-2A	n/a	n/a	n/a	0 (0)	12.2 (39)*	0 (0)	13.3 (21)*
% (n) IAA + ZnT8A	n/a	n/a	n/a	2.4 (13)	0 (0)*	3.0 (5)	0 (0)*
% (n) IA-2A + ZnT8A	n/a	n/a	n/a	0 (0)	11.3 (36)*	0 (0)	14.6 (23)*

Data shown as mean (SD) unless indicated

^aStage 1 and stage 2 groups were limited to positivity for two autoantibodies to address confounding due to total autoantibody number

^bBMI data were available for the following numbers of individuals: 22 Ab⁻; 2986 single Ab⁺ IA-2A⁻; 148 single IA-2A⁺; 504 stage 1 IA-2A⁻; 295 stage 1 IA-2A⁺; 157 stage 2 IA-2A⁻; and 144 stage 2 IA-2A⁺

* $p \leq 0.05$ unadjusted and [†] $p \leq 0.05$ with adjustment for age compared with the corresponding IA-2A⁺ group (except for the Ab⁻ group, where comparisons are with single IA-2A⁺)

Ab, autoantibody; n/a, not applicable

In individuals positive for a single autoantibody, despite the approximate fivefold increase in progression to stage 3 type 1 diabetes, the 5 year risk of multiple autoantibody development was lower (but not statistically different) in the IA-2A⁺ group than in the IA-2A⁻ group (19.8% [95% CI 11.0, 33.9] vs 27.1% [95% CI 24.7, 29.6]; age- and BMI-adjusted $p=0.287$) (Table 3).

Individuals positive for a single autoantibody who are IA-2A⁺ exhibit an increased risk of progression compared with individuals positive for other single autoantibodies or IA-2A⁻ individuals meeting stage 1 type 1 diabetes criteria Given the increased risk profiles associated with IA-2A positivity within established type 1 diabetes stages, we next examined whether

IA-2A positivity was linked to differences in metabolic phenotypes and progression risk across staging categories. We first considered the group of individuals who were positive for a single autoantibody, who were not classified as early-stage type 1 diabetes, and overall were considered to be at low risk for disease progression [4]. Importantly, the single-autoantibody-positive IA-2A⁺ population exhibited substantial metabolic compromise (manifested by higher AUC glucose, lower C-peptide 30–0, and higher Index60 values) when compared with demographically similar autoantibody-negative relatives, suggesting a relatively advanced disease process despite only manifesting a single measured autoantibody (Table 2).

We next asked whether the presence of single-autoantibody positivity for IA-2A identifies greater metabolic abnormality

Table 2 Metabolic variables for IA-2A⁻ and IA-2A⁺ relatives of individuals with type 1 diabetes

Variable	Ab ⁻ (n=192)	Single Ab ⁺		Stage 1 ^a		Stage 2a	
		IA-2A ⁻ (n=3229)	IA-2A ⁺ (n=163)	IA-2A ⁻ (n=541)	IA-2A ⁺ (n=319)	IA-2A ⁻ (n=165)	IA-2A ⁺ (n=158)
AUC C-peptide, nmol/l	2.2 (0.8)	2.2 (1.0)	2.1 (1.0)*	1.8 (0.8)	1.8 (0.7)	2.0 (1.0)	1.8 (0.9)*
AUC glucose, nmol/l	6.9 (1.2) [†]	7.1 (1.3)	7.3 (1.3)* [‡]	6.8 (1.0)	7.0 (1.0)* [‡]	8.9 (1.2)	9.0 (1.2)
C-peptide 30–0, nmol/l	1.6 (0.8) [†]	1.5 (0.9)	1.4 (0.9)*	1.3 (0.8)	1.2 (0.6)* [‡]	1.2 (0.9)	1.0 (0.6)* [#]
Index60	-0.4 (0.9) [†]	-0.4 (1.2)	-0.06 (1.2)* [‡]	-0.06 (1.0)	0.04 (0.9) [‡]	0.7 (1.2)	1.1 (1.0)* [‡]
DPTRS ^b	n/a	5.6 (1.3)	6.1 (1.4) * [‡]	6.1 (1.0)	6.2 (1.0) [‡]	7.1 (1.2)	7.5 (1.1)* [‡]

Data are shown as mean (SD)

^aStage 1 and stage 2 groups were limited to positivity for two autoantibodies to address confounding due to total autoantibody number

^bDPTRS available for only 3013 single Ab⁺ IA-2A⁻ and 146 single-IA-2A⁺ individuals

* $p \leq 0.05$ unadjusted and [‡] $p \leq 0.05$ with adjustment for age and BMI compared with corresponding IA-2A⁺ group

[†] $p \leq 0.05$ both unadjusted and adjusted for age and BMI compared with single-IA-2A⁺ group

[‡] $p \leq 0.05$ with adjustment for age and BMI compared with corresponding IA-2A⁺ group

Ab, autoantibody; AUC C-peptide 30–0, OGTT 30–0 min C-peptide

and/or risk of disease compared with established type 1 diabetes stages (Table 2). Compared with IA-2A⁻ individuals meeting stage 1 criteria, after adjustment for age and BMI, single-autoantibody (IA-2A)-positive individuals exhibited higher AUC glucose (unadjusted/age and BMI-adjusted $p < 0.001$), Index60 ($p = 0.79/0.026$) and DPTRS ($p = 0.98/p < 0.001$). The differences in p values after adjustment were likely attributable to the older age in the group positive for a single autoantibody (IA-2A⁺) (21.4 ± 14.1 vs 12.2 ± 9.6 years, Table 1), given that older age is typically associated with lower progression risk. Absolute mean AUC C-peptide values were higher in the single-IA-2A⁺ compared with the stage 1 group but the difference was not statistically significant after adjustment for older age and BMI (unadjusted/adjusted $p < 0.001/p = 0.19$). Cumulative incidence curves and Cox regression analyses are shown in Fig. 2a. Compared with IA-2A⁻ individuals meeting stage 1 criteria, single-autoantibody-positive IA-2A⁺ individuals had a 2.5-fold increased 5 year risk of stage 3 type 1 diabetes (42.1% [95% CI 32.7, 53.1] vs 16.8% [95% CI 12.7, 22.0]; unadjusted/age- and BMI-adjusted both $p < 0.001$).

As might be predicted based on established staging criteria, IA-2A⁻ individuals meeting criteria for stage 2 disease showed substantial metabolic abnormalities, with lower 30–0 C-peptide (unadjusted/age and BMI-adjusted $p = 0.029/0.044$) and higher AUC glucose, Index60 and DPTRS (unadjusted/age and BMI-adjusted both $p < 0.001$) compared with single-autoantibody-positive IA-2A⁺ individuals (Table 2). As shown in Table 3, Cox regression showed increased association with progression to stage 3 type 1 diabetes for stage 2 individuals who were IA-2A⁻ vs those who were singly positive for IA-2A⁺, although the difference was not as pronounced as might be expected

(1.3-fold increased progression; Fig. 2b) and was not statistically significantly different after adjustment for age and BMI (54.2% [95% CI 43.4, 65.7] vs 42.1% [95% CI 32.7, 53.1], unadjusted/age- and BMI-adjusted $p = 0.015/p = 0.082$). Comparison between IA-2A⁺ stage 1 and IA-2A⁻ stage 2 individuals (Fig. 2c) also showed statistically significant higher progression rates in stage 2 (unadjusted/age and BMI-adjusted both $p < 0.001$).

IA-2A positivity is associated with increased genetic risk for type 1 diabetes To test the hypothesis that IA-2A⁺ individuals are distinct from those testing positive for other autoantibodies, we applied GRS2 scores to compare genetic predisposition to type 1 diabetes among individuals who were screened and confirmed as IA-2A⁺ vs those who were autoantibody positive but IA-2A⁻ (Fig. 3a). In the single-autoantibody-positive groups, those positive for IA-2A exhibited higher GRS2 scores than those negative for IA-2A. Similarly, among individuals positive for multiple autoantibodies, the IA-2A⁺ individuals had higher GRS2 values than the IA-2A⁻ individuals. Intriguingly, consistent with the aforementioned metabolic and progression data, no statistically significant differences in GRS2 values were present between IA-2A⁺ single-autoantibody-positive individuals and IA-2A⁻ multiple-autoantibody-positive individuals. In aggregate, these data suggest that the presence of IA-2A is linked to increased genetic risk of type 1 diabetes, and that single-IA-2A⁺ individuals are at similar genetic risk to those who are IA-2A⁻ but meet the criteria for stage 1 disease.

Identification of features linked to high stage 3 progression risk in single-autoantibody-positive IA-2A⁺ individuals Practically, features identifying individuals who are

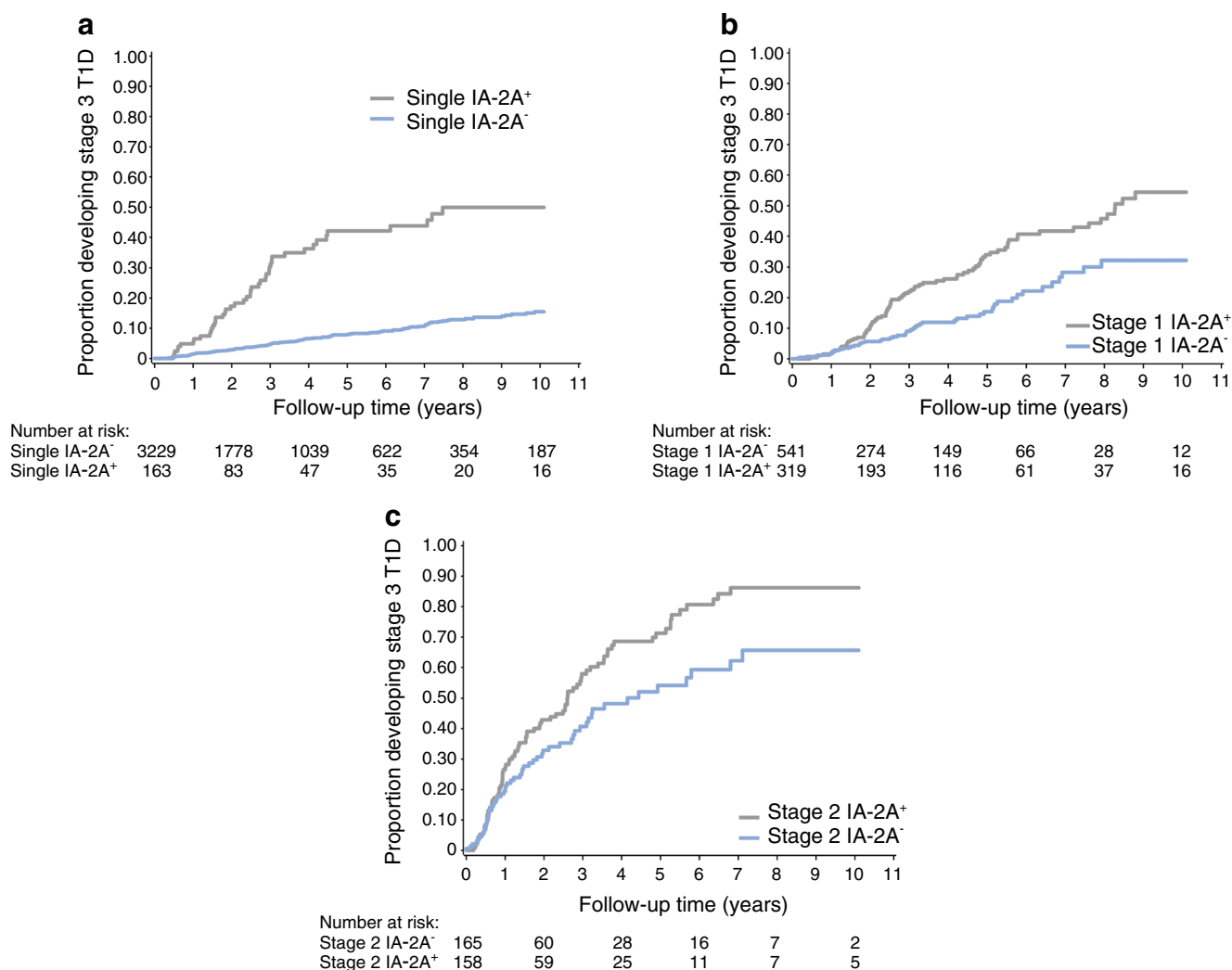


Fig. 1 IA-2A positivity is associated with increased progression to stage 3 (clinical) type 1 diabetes within established current stages of type 1 diabetes. Cumulative incidence curves comparing progression to stage 3 type 1 diabetes between IA-2A⁻ and IA-2A⁺ individu-

als with single-autoantibody positivity (a), stage 1 type 1 diabetes (b) and stage 2 type 1 diabetes (c). Created in BioRender. Sims, E. (2025) <https://BioRender.com/p41p030>

singly positive for IA-2A at the highest risk would be helpful for determining monitoring approaches and consideration for disease modification trials in this group. Therefore, we asked whether baseline participant features previously linked to increased progression risk (IA-2A titre, paediatric age, higher GRS2), and linked to IA-2A positivity (presence of *HLA-DR4* genotype), could help inform subsequent risk of stage 3 clinical progression in individuals positive for a single autoantibody (IA-2A⁺) [13, 27–29]. For titres, values were considered high if they were above the median for the entire IA-2A⁺ study population. Univariate Cox regression (shown in Table 4) identified each of these features, particularly belonging to the paediatric age group, as being statistically significantly associated with increased stage 3 progression. Multivariate Cox regression showed similar relationships, but

HLA-DR4 was no longer statistically significant, likely due to overlap with the GRS2 score. Additionally, we tested whether subsequent conversion to multiple-autoantibody positivity (thus meeting criteria for stage 1 or 2 type 1 diabetes) was associated with increased risk of progression to stage 3. Here, among the single-IA-2A⁺ population, those who converted to multiple-autoantibody positivity during follow-up were at markedly increased risk of clinical disease progression: HR 31.9 (95% CI 4.4, 231.8), $p < 0.001$.

Across autoantibody-positive groups, progression rates are similar in dysglycaemic IA-2A⁻ individuals and euglycaemic IA-2A⁺ individuals Finally, we asked how, as a distinct risk factor, the link between IA-2A positivity and progression to clinical/stage 3 disease compared with dysglycaemia, a

Table 3 Risk comparisons for IA-2A⁺ and IA-2A⁻ individuals by type 1 diabetes stage

Parameter	Confirmed single-autoantibody positive		Stage 1 ^a		Stage 2 ^a	
	IA-2A ⁻ (n=3229)	IA-2A ^{**} (n=163)	IA-2A ⁻ (n=541)	IA-2A ^{**‡} (n=319)	IA-2A ⁻ (n=165)	IA-2A ^{**‡} (n=158)
5 year MAB ⁺ % risk	27.1 (24.7, 29.6)	19.8 (11.0, 33.9)	n/a	n/a	n/a	n/a
5 year T1D % risk	7.9 (6.7, 9.4)	42.1 (32.7, 53.1)	15.4 (11.2, 20.9) [†]	33.9 (27.5, 41.4)	54.2 (43.4, 65.7) [‡]	71.3 (61.9, 80.1)

Data are shown as % risk from baseline OGTT (95% CI)

^aStage 1 and stage 2 groups were limited to positivity for two autoantibodies

* $p \leq 0.05$, with and without adjustment for age and BMI, for comparison of IA-2A⁻ vs IA-2A⁺ groups within stages; for individuals with confirmed single-autoantibody positivity for IA-2A⁺, the comparison remained statistically significant after adjustment for subsequent development of multiple-autoantibody positivity

[†] $p \leq 0.05$ compared with single-IA-2A⁺ status, with and without adjustment for age and BMI; comparisons were performed across stages to compare IA-2A⁻ vs IA-2A⁺ groups

[‡] $p \leq 0.05$ compared with stage 1 IA-2A⁺, with and without adjustment for age and BMI; comparisons were performed across stages to compare IA-2A⁻ vs IA-2A⁺ groups

MAB, multiple autoantibody, n/a, not applicable; T1D, type 1 diabetes

well-established risk factor that is part of the definition of stage 2 type 1 diabetes. Figure 3b shows cumulative incidence of stage 3 disease in the entire autoantibody-positive population stratified by the presence or absence of either IA-2A positivity or dysglycaemia. Here, dysglycaemic IA-2A⁻ individuals had a similar rate of progression when compared with euglycaemic IA-2A⁺ individuals.

Discussion

Accurate understanding of type 1 diabetes risk is critical to optimisation of counselling, monitoring and interventions for at-risk individuals. The current approach to staging early type 1 diabetes is based on natural history data showing increased rates of progression to clinical disease based on islet autoantibody numbers coupled with the presence or absence of dysglycaemia [2, 4]. However, additional individual features could more precisely define the varying rates of progression within staging categories. This is especially critical in single-autoantibody-positive individuals who exhibit early signs of islet autoimmunity but who, as a group, are traditionally categorised as low risk and so are not even included in current asymptomatic type 1 diabetes ‘staging’ paradigms. Such increased precision could ultimately improve management and prevention strategies as well as inform efforts to understand mechanisms underlying different immunomodulatory therapies. In the current work, we identify IA-2A positivity as a feature consistently associated with increased genetic risk and rates of clinical diabetes progression before, within and across early stages of type 1 diabetes. In fact, the presence of a positive IA-2A titre without dysglycaemia was associated with only slightly lower risk of clinical disease

progression than IA-2A⁻ individuals with dysglycaemia, a feature used to define relatively advanced, stage 2 disease.

Comparison with autoantibody-negative relatives showed substantial metabolic abnormalities in individuals positive for IA-2A only, who would be classified as lower risk based on autoantibody number in the current staging system. Interestingly, birth cohorts have shown that IA-2A is rarely the first positive islet autoantibody at the time of seroconversion [30–32]. Combined with epitope analyses, these data could be consistent with the idea that development of IA-2A positivity reflects epitope spreading/progressing islet autoimmunity due to beta cell destruction [33, 34]. We speculate that it is possible that individuals positive for only IA-2A, identified via cross-sectional screening, have a prior history of multiple-autoantibody positivity, with subsequent reversion of seropositivity for other autoantibodies. Although impossible to test in this cross-sectional screening cohort, such prior history could explain our observed increases in rates of progression of individuals with single-autoantibody positivity for IA-2A to stage 3 disease. This would also be consistent with similar observed genetic risk for type 1 diabetes among individuals with single-autoantibody positivity for IA-2A and those who are multiple-autoantibody-positive. Alternatively, individuals only positive for IA-2A may exhibit more rapid progression across each stage of disease, without intervening detection of early type 1 diabetes stages. Regardless, an understanding of the implications of single-IA-2A positivity at the time of screening is critical for clinical implementation, given that most individuals identified moving forward as part of clinical care will not be participating in a birth cohort study. This study takes an important step in this direction by identifying single-IA-2A⁺ groups at the highest risk: children; and individuals

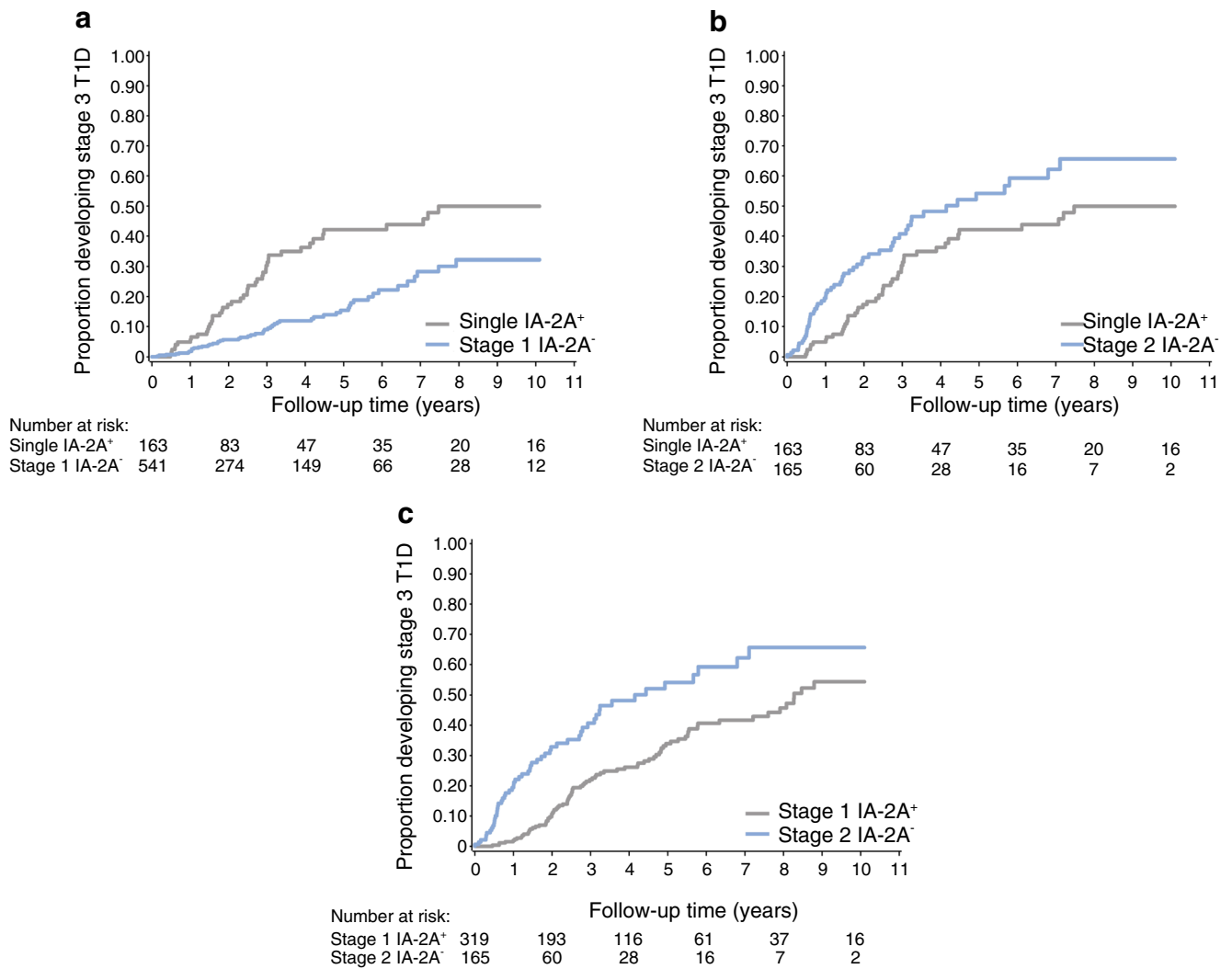


Fig. 2 Single-autoantibody-positive IA-2A⁺ individuals exhibit substantial risk of stage 3 (clinical) type 1 diabetes progression. Cumulative incidence curves comparing progression to stage 3 type 1 diabetes for single-IA-2A⁺ individuals vs IA-2A⁻ individuals with

stage 1 disease (**a**), single-IA-2A⁺ individuals vs IA-2A⁻ individuals with stage 2 disease (**b**) and individuals with stage 1 disease who are IA-2A⁺ vs individuals with stage 2 disease who are IA-2A⁻ (**c**). Created in BioRender. Sims, E. (2025) <https://BioRender.com/u93u720>

with markedly elevated IA-2A titres and higher genetic risk or DR4 positivity.

Other smaller studies have identified IA-2A positivity as a feature linked to more rapid progression at different time points relative to clinical disease. For example, 37 children participating in birth cohorts with a single-IA-2A autoantibody had faster rates of progression than those with single-autoantibody positivity for GADA or IAA [2]. The presence of IA-2A was also associated with increased progression in multiple-autoantibody-positive children identified via cross-sectional autoantibody screening, with IA-2A positivity and titre identified as a statistically significant contributor to a progression score predicting likelihood of more rapid progression to stage 3 [7, 13]. Positive IA-2A titres increase in the years preceding diagnosis among individuals who

progress to disease [27]. Here, we chose to focus mostly on IA-2A⁺ or IA-2A⁻ status, rather than quantification of titre elevation, as a pragmatic read-out that could be easily applied across screening and testing platforms. However, as noted in our single-autoantibody analysis, titres could be applied to optimise performance of this marker. Overall, our work complements and expands these combined analyses by demonstrating that, in a large group of individuals screened for IA-2A, the presence of IA-2A is associated with increased stage 3 type 1 diabetes risk at all stages of islet autoimmunity and is linked to more rapid progression in individuals positive for IA-2A alone than in those at stage 1 who are IA-2A⁻.

A limitation of this analysis is that, like all modern longitudinal type 1 diabetes natural history studies, the TrialNet

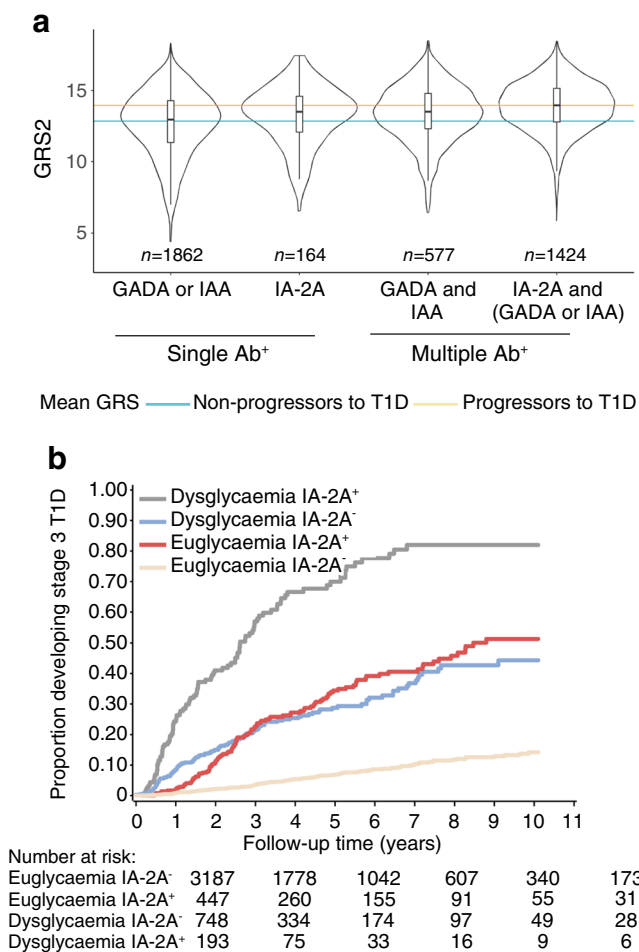


Fig. 3 IA-2A positivity is linked to increased genetic risk and stage 3 (clinical) type 1 diabetes progression across traditional risk stratifications used for staging. **(a)** Individuals who are positive for a single autoantibody (Ab⁺) and multiple-autoantibody-positive individuals who are positive for IA-2A are at higher genetic risk for type 1 diabetes compared with single-autoantibody-positive or multiple-autoantibody-positive individuals who are IA-2A⁻ ($p < 0.001$ for both comparisons). Violin plots show GRS (GRS2) density for each group based on autoantibody number and IA-2A status. The lower and upper hinges of the boxplot correspond to the first and third quartiles (the 25th and 75th percentiles). The whiskers extend to the values 1.5 × the interquartile range from the hinges. The yellow line represents mean GRS2 values for individuals who progressed to type 1 diabetes during follow-up (progressors); the blue line represents mean GRS2 values for individuals who did not develop diabetes during follow-up (non-progressors). **(b)** Progression to stage 3 type 1 diabetes for all autoantibody-positive participants stratified by glycaemia or by IA-2A status. T1D, type 1 diabetes. Created in BioRender. Sims, E. (2025) <https://BioRender.com/n69h182>

protocol for autoantibody screening has changed over time, with the addition of ZnT8A starting in 2012 and screening for IA-2A and ZnT8A restricted to those with IAA⁺ or GADA⁺ status after 2019, impacting our numbers of individuals with single-autoantibody positivity for IA-2A and ZnT8A. It is possible that earlier inclusion of ZnT8A

Table 4 Risk factors for stage 3 progression in individuals who screen and confirm single-autoantibody positivity (IA-2A)

Variable	HR (95% CI)	<i>p</i> value
Univariate analysis		
IA-2A titre above median	3.5 (1.9, 6.6)	<0.001
Age <18 years	14.2 (1.9, 103.1)	0.009
DR4 positivity	3.7 (1.6, 8.3)	0.002
GRS2	1.4 (1.2, 1.6)	<0.001
Multivariate analysis		
IA-2A titre above median	1.9 (1.0, 3.8)	0.047
Age <18 years	14.0 (1.9, 102.6)	0.009
DR4 positivity	1.6 (0.6, 4.2)	0.321
GRS2	1.2 (1.0, 1.5)	0.025

n=110 for multivariate analysis

testing would have classified larger numbers of individuals with single-autoantibody positivity for IA-2A as being double-autoantibody positive. However, like IA-2A, ZnT8A is also infrequently an initial positive autoantibody at seroconversion and appears to be more associated with epitope spreading [33], suggesting IA-2A⁺/ZnT8A⁺ as an uncommon initial autoantibody combination at seroconversion. Furthermore, even with changes to initial testing, the current study represents a large cohort of individuals with single-autoantibody positivity for IA-2A. Other studies have shown that assays distinguishing low- vs high-affinity islet autoantibodies can improve predictive value of diabetes progression in single-autoantibody-positive individuals [35]. Although our testing did not include these types of assays, inclusion could potentially allow for further stratification of single-autoantibody-positive individuals. IA-2A has been shown to most optimally identify individuals at high risk for progression as part of a model or score that incorporates multiple risk factors [11, 13]. Analyses integrating this measure into current models in a practical and clinically meaningful manner that offers improved prediction over and above current risk stratification (such as in the small but important subset of single-IA-2A⁺ individuals) could help to identify optimal approaches to application. We did not study the impact of sex on associations of IA-2A with disease progression, but this could be considered as part of future analyses.

In conclusion, our analyses suggest that, particularly for individuals identified as autoantibody positive via cross-sectional screening, the presence of IA-2A positivity at baseline is linked to increased risk of clinical diabetes progression. Cross-sectional screening for the presence of abnormal IA-2A provides important perspective on the natural history of type 1 diabetes and potentially could be applied to further hone and stratify disease staging. IA-2A positivity is particularly appealing for stratification of staging given that it is

typically obtained as part of the staging process and thus would be a relatively simple, straightforward marker to interpret. Application could be relevant to diabetes prediction as well as enrolment into prevention studies. Especially given the substantial risk of progression for individuals with single-autoantibody positivity for IA-2A, IA-2A testing should be included as part of initial islet autoantibody screening. Furthermore, predictive implications of IA-2A positivity status should be tested and applied to risk estimations for individuals with autoantibody positivity to guide monitoring approaches and consideration for disease modification aimed at prevention and delay.

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Data availability Data are publicly available upon request at www.trialnet.org/researchers.

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Contribution statement EKS and JMS conceived the project, analysed data and wrote and edited the manuscript. DC, LF and RO designed and performed analyses and edited the manuscript. EB, CEM, LJ, BN, HI, LAD and MR interpreted results and edited and revised the manuscript. All authors approved the final version of the manuscript. EKS is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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