**Title: Age of diagnosis does not alter the presentation or progression of robustly defined adult-onset type 1 diabetes.**

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**Running Title: Adult type 1 diabetes severity is unaffected by onset age**

**Abstract**

**Aims**

To determine whether presentation, progression and genetic susceptibility of robustly defined adult-onset type 1 diabetes (T1D) are altered by diagnosis age.

**Methods**

We compared the relationship between diagnosis age and presentation, C-peptide loss (annual change in Urine C-peptide Creatinine Ratio (UCPCR)) and genetic susceptibility (T1D genetic risk Score (T1DGRS)) in adults with confirmed T1D in the prospective StartRight study, 1,798 adults with new-onset diabetes. T1D was defined in two ways: ≥2 positive islet-autoantibodies (of GADA, IA-2A, ZNT8A) irrespective of clinical diagnosis(n=385), or 1 positive islet-autoantibody and a clinical diagnosis of T1D(n=180).

**Results**

In continuous analysis age of diagnosis was not associated with C-peptide loss for either definition of T1D [p>0.1], with mean(95% CI) annual C-peptide loss in those diagnosed before and after age 35 (median age of T1D defined by ≥2 positive autoantibodies): 39(31-46)% vs 44(38-50)% with ≥2 positive islet-autoantibodies and 43(33-51)% vs 39(31-46)% with clinician diagnosis confirmed by 1 positive islet-autoantibody [p>0.1]. Baseline C-peptide and T1DGRS were unaffected by age of diagnosis or T1D definition [p>0.1]. In T1D defined by ≥2 autoantibodies, presentation severity was similar in those diagnosed before and after age 35: unintentional weight loss 80(95% CI 74-85)% vs 82(76-87)%, ketoacidosis 23(17-29)% vs 19(14-25)% and presentation glucose 21(19-22) mmol/l vs 21(20-22) mmol/l [all p≥0.1]. Despite similar presentation, older adults were less likely to be diagnosed with T1D, insulin treated, or admitted to hospital.

**Conclusions**

When adult-onset T1D is robustly defined the presentation characteristics, progression, and T1D genetic susceptibility are not altered by age of diagnosis.

**Article Highlights**

- To avoid inadvertent inclusion of non-autoimmune diabetes adult-onset type 1 diabetes was defined by either multi autoantibody positivity (n=385) or a clinician diagnosis of type 1 diabetes and a single positive autoantibody (n=180)

- Annual loss of C-peptide was severe (≈40% annual loss) irrespective of age of diagnosis or type 1 diabetes definition.

- Genetic predisposition to type 1 diabetes was high and unaffected by onset age or definition.

- In multi autoantibody positive adults, presentation symptoms and glycaemia were severe irrespective of onset age but those presenting older were less likely to be admitted to hospital or start insulin at diagnosis.

**Background**

The impact of age on the presentation and progression of adult-onset type 1 diabetes (T1D) is unclear. It is commonly understood that T1D in older adults has a milder phenotype, with reduced rate of progression compared to those with young adult-onset disease (1-4). However, this understanding has been predominantly either: extrapolated from findings in childhood and adolescence, taken from cross sectional studies of clinically diagnosed T1D in older adults, or extrapolated from studies of those with positive islet antibodies initially diagnosed as type 2 diabetes (T2D)(Latent Autoimmune Diabetes in Adults (LADA)) (2; 5; 6). A limitation of existing studies of older adults is the possibility findings are inadvertently affected by the inclusion of individuals who do not have T1D, 'diluting' the observed phenotype. This is a major concern as diagnosing T1D in older adults is challenging (7-10). The known overlap between features of T1D and T2D and very high prevalence of T2D means the predictive value of even classical clinical features of T1D, such as ketoacidosis or low BMI, is limited in adults (11). It is unsurprising that studies using robust approaches to diabetes classification in older adults suggest that 14-20% of those with a clinician diagnosis of T1D may be misclassified (8; 10). While studies of LADA may support a changing phenotype of autoimmune diabetes with age, a combination of low prior prevalence and use of a biomarker with imperfect specificity means this phenotype may also be influenced by the inadvertent study of a mixed population of people with autoimmune and non-autoimmune aetiology diabetes (12; 13).

To study the impact of age of diagnosis on phenotype in adult-onset T1D, diagnostic tools with very high specificity are needed to avoid inadvertent inclusion of other forms of diabetes. The optimal method will depend on the research question, and disease duration. C-peptide has been recommended as a classification method that most closely relates to treatment requirements, however this measure has limited utility close to diagnosis and precludes an unbiased study of disease progression (14; 15). Multi-islet-autoantibody positivity is highly specific for T1D but will identify only ~60% of adults (10; 16) with autoimmune diabetes and it is unclear if autoantibody number directly alters phenotype (13; 17; 18). In the context of a clinical T1D diagnosis (and therefore high pre-test probability of T1D) a single positive autoantibody will usually confirm T1D (10). However clinical presentation cannot be studied as these features will have influenced classification.

We aimed to determine whether the initial presentation and progression of adult-onset T1D defined

using high specificity definitions incorporating islet-autoantibodies is altered by age of diagnosis.

**Methods**

We used longitudinal data from the prospective StartRight study, https://clinicaltrials.gov/ct2/show/NCT03737799 to evaluate the impact of age at diagnosis on the presentation characteristics and progression of adult onset T1D in a UK population cohort defined by the presence of two or more positive islet-autoantibodies (GAD, IA-2 and ZNT8). As a separate secondary comparison, progression was assessed when adult-onset T1D was defined by a single positive autoantibody in the context of a clinical diagnosis of T1D.

**Study participants**

The prospective StartRight study is a multicenter study across 55 sites in the United Kingdom that recruited 1798 adults (≥18 years of age) with diabetes onset within the previous 12 months.

Exclusion criteria for the StartRight study included: gestational and known secondary diabetes. For analysis, cases where autoantibody results were missing were also excluded (n=5). To ensure sufficient numbers of participants with late onset T1D the study was enriched for older adults receiving insulin treatment, by aiming in those diagnosed after age 50, for equal recruitment at the site level of those treated with and without insulin. A study flow diagram is shown in ESM figure 1.

**Diabetes definitions**

For the primary analysis T1D was defined as the presence of ≥2 positive autoantibodies of GAD, ZnT8 or IA-2, regardless of clinical diagnosis. A secondary analysis was performed in participants with T1D defined by a clinical diagnosis of T1D (T1D reported as clinical diagnosis and insulin within two weeks of diagnosis) and positive for a single autoantibody (one of GAD, ZnT8 and IA-2).

A comparison population of T2D cases were defined by having all of: a self-reported clinical diagnosis of T2D, absence of insulin treatment within 2 weeks of diagnosis and negative autoantibodies.

**Data Collection**

Presentation characteristics were self-reported at the baseline study visit (median duration 5 months) including: unintentional weight loss, osmotic symptoms (nocturia, polyuria, thirst), hospitalization and initial treatment. Presentation glycemia (glucose and HbA1c) and ketoacidosis were determined from reviewing participants' medical notes and laboratory records. Diabetic ketoacidosis (DKA) was defined based on the Joint British diabetes society's guidelines (19). pH <7.3 and either capillary beta-hydroxybutyrate ≥ 3.0mmol/L or ketonuria >2+ on standard urine sticks. In

the absence of an available pH measurement, cases were included as DKA if diabetic ketoacidosis was recorded in the hospital notes alongside a supportive blood or urine ketone value as above. Participants not admitted to hospital were assumed not to have had DKA.

At the baseline visit height and weight were assessed for BMI calculation and a non-fasted (within 1-5 hours of a meal) blood sample was collected for: DNA extraction, autoantibodies (GAD, IA-2 ZnT8), plasma C-peptide and paired glucose.

At each visit including baseline, participants collected a boric acid urine sample, within 1 and 5 hours of a meal, for urine creatinine C-Peptide (UCPCR) measurement (20; 21). Samples were posted by participants directly to the Exeter Clinical laboratory for analysis. Samples marked as not received within seven days of collection were excluded from analysis (1.2% of all UCPCR samples (42/3454)). UCPCR samples were aimed to be collected for year one follow up between 10-16 months of baseline visit and two year follow up between 22-28 months of baseline visit. Due to the Covid-19 pandemic 6% (63/1136) of year one and 10% (93/896) of year two results were delayed and collected outside of these ranges. UCPCR time from recruitment was therefore calculated and evaluated in 6 month bins: 12 months (within range of 9 to <15 month), 18 months (15 to <21 months), 24 months (21 to <27 months) and 30 months (27 to <33 months). For all participants median follow up time from recruitment was 25 months, interquartile range (24-28 months)

**Laboratory analysis**

Analysis of C-peptide and autoantibodies (GADA, IA-2A, ZnT8A) was performed by the Academic department of Blood Sciences Department at the Royal Devon and Exeter Hospital. GAD, IA-2 and ZnT8 autoantibodies were measured using ELISA assays (RSR Limited, Cardiff, U.K.) on a Dynex DS2 automated ELISA system (Launch Diagnostics, Longfield, U.K). Autoantibodies were considered positive if ≥97.5th centile of 1559 non-diabetic control subjects (GAD ≥11 World Health Organization (WHO) units/mL, IA-2 ≥7.5 units/mL, Znt8 ≥65 and ≥10 units/mL age <30 and ≥30 years respectively)(22). Specificity for all 3 assays was 99% in the 2020 international islet autoantibody standardization program Exeter laboratory certification, with Sensitivity 74% for both GADA and ZNT8A and 72% for IA-2A.

C-peptide was measured using an electrochemiluminescence immunoassay on a Roche Diagnostics E170 analyser (Roche, Mannheim, Germany, limit of detection 3.3 pmol/l, inter- and intra-assay coefficients of variation <4.5 % and <3.3 %, respectively). Blood C-peptide results were excluded if

concurrent glucose was <4 mmol/mol (n=46). Urine creatinine (for UCPCR) was analysed using the Jaffe method on the Roche P800 modular analyser.

**Assessment of T1D Genetic Risk score**

A T1D genetic risk score (T1DGRS) was calculated using 67 published variants known to be associated with T1D as described in the ESM methods and previously (23; 24)

**Statistical analysis**

The impact of age on T1DGRS and annual change in UCPCR was evaluated continuously using liner regression and mixed effects models respectively (see below). To further evaluate the impact of age on C-peptide loss, T1D genetic susceptibility, and assess impact on presentation characteristics, all participants were split by the median age of diagnosis of those with ≥2 positive autoantibodies (young adult onset ≤35 years, older adult onset >35 years). Presentation features were not evaluated where clinical diagnosis was included in the definition of diabetes type, due to the likely impact of selection bias. Chi-squared test was used to compare categorical variable between age groups and Student's t-test was used for continuous variables.

Continuous data was assessed visually for distribution and other than C-peptide were normally distributed. C-peptide and UCPCR were highly skewed and therefore log transformed in line with previous studies (3; 25; 26), with geometric mean and 95% confidence intervals presented. Mixed effect models were used to determine the percentage annual change in UCPCR with random effects at the patient level to allow each patient to contribute multiple C-peptide values at different six month time points (25). The impact of diagnosis age on the association of change in C-peptide over time was evaluated in T1D, in both continuous analysis and in subgroups using an interaction term (diagnosis age below and above 35 as above). A random-intercept, random-slope model allows for variability between individuals in terms of both C-peptide at diagnosis (the intercept) and percentage change in C-peptide over time (the slope).

As the study enriched for initial insulin treatment in the group diagnosed aged >50 years we performed a sensitivity analysis in those with ≥2 positive autoantibodies, comparing progression and T1DGRS between participants receiving and not receiving insulin within two weeks of diagnosis.

All analyses were performed using Stata 16 (StataCorp LP, College Station, TX).

**Results**

Participant characteristics of those with T1D defined by ≥2 islet-autoantibodies (n=385) are shown in Table 1. In those positive for two autoantibodies diagnosed above (n=193) or below (n=192) the median onset age of 35 years, the mean age of diagnosis was 50 years (95% CI 49-51) and 26 years (25-27) respectively. For those diagnosed above and below 35 years with T1D defined by a clinical diagnosis and 1 positive autoantibody (n=180) the mean age of onset was 50 (48-52) and 28 (27-29) years respectively. The characteristics of all 1793 participants from the StartRight study including autoantibody results are shown by age group in ESM Table 1.

**Age of onset is not associated with genetic susceptibility (T1DGRS) to adult-onset type 1 diabetes**

In adult-onset T1D defined by multi-autoantibody positivity annual increase in onset age using linear regression, had no effect on T1DGRS, β= -0.01 (-0.02, 0.003)[p=0.1]. A lack of association between age of onset and T1DGRS was also seen when T1D was defined by clinical T1D diagnosis and one positive autoantibody, β= -0.02 (-0.04, 0.008)[p=0.2]. Between participants diagnosed before and after age 35 years, mean T1DGRS was similar irrespective of the definition of T1D used: multi-autoantibody positive 13.0 (12.8, 13.3) vs 12.9 (12.7, 13.2)[p=0.5] and a clinical T1D diagnosis confirmed by a single autoantibody 13.3 (12.8, 13.8)(n=83) and 13.1 (12.6, 13.5)(n=97)[p=0.5](Figure 1a). T1DGRS was significantly higher in both age groups than a comparison group with autoantibody negative T2D 10.1 (9.9, 10.3) regardless of how T1D was defined [all p<0.0001](Figure 1a).

**Age of onset is not associated with progression of C-peptide loss in adult-onset type 1 diabetes**.

Increasing onset age (year), evaluated continuously using mixed effect models, had no effect on annual log C-peptide rate of decline in those with ≥2 positive antibodies, β= -0.002 (-0.005, 0.001)[p=0.3] or a clinical diagnosis confirmed by a single positive autoantibody β= 0.002 (-0.003, 0.007)[p=0.4]. ESM Figure 2 shows the percentage annual change in C-peptide by decile of onset age in those classified as T1D.

For both T1D definitions both age groups had comparable baseline C-peptide. For multi-autoantibody positive cases (>35 age groups shown first): geometric mean stimulated plasma C-peptide 430 pmol/l (95% CI 356, 504 pmol/l) vs 435 pmol/l (389, 480 pmol/l)) (Figure 1b) and post meal UCPCR 0.9 nmol/mmol (0.8, 1.1 nmol/mmol) vs 1.0 nmol/mmol (0.8, 1.2 nmol/mmol)[both p>0.1]. For clinician diagnosed cases confirmed by a positive autoantibody geometric mean stimulated plasma C-peptide 430 pmol/l (332, 526 pmol/l) vs 414 pmol/l (335, 493 pmol/l)) and post

meal UCPCR 1.0 nmol/mmol (0.7, 1.3 nmol/mmol) vs 0.9 nmol/mmol (0.6, 1.2 nmol/mmol)[both p>0.1].

The percentage annual decline in UCPCR in those aged below and above age 35 at diagnosis was similar regardless of T1D definition. In those with multi-autoantibody positivity diagnosed >35 years UCPCR declined by 44% (38, 50%) annually, compared to a 39% (31, 46%) annual decline in those diagnosed ≤35 years [p=0.2](Figure 2a). This corresponds to a half-life for C-peptide loss of 1.2 years (1.0, 1.4 years) and 1.4 years (1.1, 1.9 years) respectively. In single autoantibody positive cases with a clinician diagnosis of T1D the percentage annual decline in UCPCR in those diagnosed >35 years was 39% (31, 46%)), and those diagnosed ≤35 years 43% (33, 51%))[p= 0.6](Figure 2b). In the T2D comparison group the annual C-peptide decline was 6% (1, 11%) corresponding to a half-life of 11.1 years (5.9, 98.3 years).

**Presentation of adult-onset type 1 diabetes defined by multi-autoantibody positivity is similar above and below 35 years of age**

In those positive for ≥2 autoantibodies management at presentation was strikingly different between age groups. Those diagnosed over 35 years (n=193) were far less likely than those diagnosed 35 and under (n=192) to report being: admitted at diagnosis 40% (95% CI 33, 47%) vs 60% (53, 67%), treated with insulin at diagnosis 73% (67, 79%) vs 93% (90, 97%) or report a diagnosis of T1D at recruitment 87% (82, 91%) vs 96% (94, 99%)[all p<0.001](Table 1). These differences in clinical management and diagnosis did not reflect differences in phenotype or clinical presentation which were similar between age groups. At presentation (>35 years shown first): HbA1c was 103 mmol/mol (95% CI 100, 107 mmol/mol) vs 103 mmol/mol (99, 107 mmol/mol), glucose 21 mmol/l (20, 22 mmol/l) vs 21 mmol/l (19-22 mmol/l) and recruitment BMI 26 kg/m$^2$ (25, 26 kg/m$^2$) vs 25 kg/m$^2$ (24, 26 kg/m$^2$))[all p>0.05]. Symptoms at presentation of those with ≥2 positive antibodies were also similar between those diagnosed above and below 35 years: reported unintentional weight loss 82% (76, 87%) versus 80% (74, 85%), DKA 19% (14, 25%) versus 23% (17, 29%) and osmotic symptoms 92% (88, 96%) vs 96% (93, 99%)[all p>0.05]. Characteristics of those with T1D (by either definition, n=565), in comparison to antibody negative T2D are shown in ESM table 2. At 2 years follow up, 88% (57/65) of multi autoantibody positive cases not insulin treated at diagnosis had started insulin treatment versus 3% (24/715) of those with T2D.

**In multi-autoantibody positive participants genetic susceptibility and progression were not**

**associated with initial insulin treatment**

In those with T1D defined by ≥2 positive autoantibodies who received insulin treatment within two weeks of diagnosis (n=320) and those initially treated without insulin (n=65) decline in UCPCR was near identical: in those insulin treated at diagnosis UCPCR declined by 44% (37, 50%) yearly in comparison to 41% (26, 53%)[p=0.7] in those not receiving insulin at diagnosis (ESM figure 3). This was despite recruitment C-peptide being significantly lower in those initially insulin treated compared to those not: stimulated plasma C-peptide 407 pmol/l (366, 447 pmol/l)) vs 581 pmol/l (390, 772 pmol/l) and post meal UCPCR 0.9 nmol/mmol (0.8, 1.0 nmol/mmol) vs 1.4 nmol/mmol (0.9, 1.8 nmol/mmol)[both p<0.05]. T1DGRS was similar between the two treatment groups: insulin treated at diagnosis 13.0 (12.8, 13.2) vs no insulin at diagnosis 12.9 (12.5-13.3)[p=0.7](ESM figure 4).

**The number of positive autoantibodies does not alter the progression or genetic characteristics of robustly defined adult-onset type 1 diabetes**

In all participants with a clinical diagnosis of T1D we evaluated C-peptide progression and T1D genetic risk score by antibody number. Neither differed between those positive for one autoantibody (n=180), compared to those with ≥2 positive autoantibodies (n=307): T1DGRS was 13.2 (12.9, 13.5) vs 13.0 (12.8, 13.2)[p=0.3] and annual loss of C-peptide 41% (32, 48%) vs 44% (37, 50%)[p=0.5](ESM figure 5).

**In multi autoantibody positive cases BMI was not associated with progression or genetic characteristics.**

In T1D defined by multiple positive islet-autoantibodies BMI (assessed continuously) was not associated with presentation DKA, osmotic symptoms, diagnosis HbA1C, T1DGRS or annual loss of C-peptide (all p>0.1)(ESM table 4). However higher BMI was associated with higher C-peptide at diagnosis [p<0.0001].

**Discussion**

This study demonstrates that when adult-onset T1D is classified using a high specificity definition, presentation, progression and genetic predisposition for T1D are similar across all onset ages. Participants defined as T1D with multiple positive autoantibodies, irrespective of reported clinical diagnosis, showed near identical clinical characteristics and marked levels of dysglycaemia when diagnosed above and below 35 years of age. However, despite similar presentation there was substantial variation in initial clinical management: older patients less likely to be diagnosed with T1D, initially treated with insulin, or admitted to hospital. Regardless of T1D being defined by multi autoantibody positivity or a single positive autoantibody confirming a clinical T1D diagnosis, progression of C-peptide loss in adults was marked (≈40% annual C-peptide loss) and unaffected by diagnosis age.

A key strength of this study is that we used high specificity biomarker based definitions to evaluate adult onset T1D clinical characteristics at presentation in a large mixed cohort, and prospectively followed participants to evaluate early change in endogenous insulin secretion. Use of high specificity definitions of T1D is important as performing this analysis in those selected solely by clinical diagnosis could suffer from inadvertently including non-T1D. This would bias results towards falsely low progression and T1D genetic susceptibility in older adults, where misclassification is more common (8; 9; 13). The high specificity of T1D definitions in our study is supported by near identical high genetic predisposition to T1D and progression irrespective of participants being defined by multi-autoantibody positivity or a clinical diagnosis with a confirmatory single autoantibody. This is despite these definitions capturing entirely separate participants, and 13% of older adults with multi-autoantibody positivity not reporting a diagnosis of T1D at recruitment and 27% not receiving insulin within two weeks of diagnosis. The high specificity of our T1D definitions has also been previously demonstrated, with very low prevalence of multiple positive islet antibodies in populations without diabetes (27), and a single positive antibody in the context of a clinical diagnosis shown mathematically and using genetic approaches to confirm autoimmune diabetes in older adults (10; 13; 17)

A limitation of our study is that our study cohort is enriched for early insulin treatment in older participants. 15% of participants diagnosed over 35 years of age were multi-autoantibody positive, far higher than the reported ~5% of this age group with diabetes having T1D (28). Enriching for insulin treatment could have selected a more rapidly progressive older T1D cohort. Reassuringly our

sensitivity analysis within T1D cases defined by multi-autoantibody positivity showed identical progression with and without initial insulin treatment. This enrichment also means that the 27% of older adults with ≥2 positive autoantibodies not initially insulin treated will be an underestimate, consistent with higher proportions reported in other studies (9; 29). We only assessed early progression of C-peptide loss, and further studies will be needed to determine whether long term residual endogenous insulin secretion is altered by diagnosis age in robustly defined adult-onset T1D. Our specific definitions of T1D might pick out a more severe T1D phenotype in adults, however reassuringly progression and T1DGRS were identical irrespective of the number of autoantibodies included in the definition of T1D.

Our results are different from previous studies of adults using different approaches to defining autoimmune etiology diabetes. When autoimmune diabetes is defined by a clinical diagnosis of T2D, lack of initial insulin, and one or more positive autoantibodies (LADA), genetic characteristics and progression are, on average, intermediate between classical T1D and T2D (12; 30). In adults with T1D defined by clinical diagnosis alone there appears to be a modest reduction in both C-peptide (assessed cross-sectionally)(2-4) and T1D genetic susceptibility with increasing diagnosis age (2). This difference in phenotype, and progression of beta cell loss, observed by ourselves compared to previous studies can be explained by the specificity of T1D definition used (13). T2D is extremely common in older adults, this low prior prevalence means in adults a single positive antibody test, or clinical diagnosis alone may not confirm autoimmune aetiology diabetes, resulting in the study of a mixed population of autoimmune and non-autoimmune diabetes, with a higher proportion of non-autoimmune diabetes as age increases (10; 13; 31). This is supported by previous research showing adults with autoantibody negative clinician diagnosed T1D have T1D genetic susceptibility and C-peptide loss intermediate to T1D and T2D and by research showing the relationship between characteristics (genotype and phenotype) and antibody titre and number (which impact test specificity) seen in LADA appear absent or modest in the setting of a high prior likelihood of T1D (10; 18; 32)

To date studies of progression of C-peptide loss in T1D have predominantly focused on those with childhood onset. These have shown that within children rates of C-peptide decline are fairly consistent across different onset ages, although C-peptide levels close to diagnosis are lower in younger children (3; 5; 25; 26). In our adult study C-peptide level close to diagnosis was unaffected by onset age, fitting with studies showing minimal differences in C-peptide close to diagnosis between older children (>10 years) and adults (5). In studies of progression including robustly

defined adult onset T1D cases progression is slower relative to childhood onset cases, but the low number of adults included, mainly ≤45 years at onset, means evaluating the impact of age on progression within adult onset T1D has not been possible (5; 6; 26). Larger adults studies have assessed clinician diagnosed T1D which may include non-autoimmune cases not associated with marked C-peptide loss (3). Childhood onset cases were not recruited In the StartRight study but the estimated ≈50% annual C-peptide loss seen in previous Childhood onset studies is only modestly higher than the ≈40% annual loss seen in our study (3; 5; 6; 25; 26). However progression may be faster in very young children with histopathological studies suggesting a more rapid loss of beta cells in those who developed T1D before seven years of age (33; 34) consistent with age related immune differences at the level of the beta cell (35). Interestingly in studies evaluating the development of T1D in multi-antibody positive children and young adults, in those developing T1D age of diagnosis does not appear to affect pre-diagnosis progression rates (36; 37).

Our results have implications for the clinical management and study of adult-onset T1D. We demonstrate that late onset T1D remains rapidly progressive, even if insulin is not needed at diagnosis, highlighting that absence of initial insulin requirement does not exclude T1D. Our findings further emphasize the high prevalence of misdiagnosis of adult onset T1D and support recent ADA and EASD guidance advising a single positive antibody confirms T1D where this is clinically suspected (15). Older adults have largely been excluded from studies of interventions to preserve beta cell function. Our findings of ≈40% annual loss in C-peptide in adults irrespective of onset age support the potential inclusion of all adults in intervention studies where T1D is robustly defined. Importantly some people with true autoimmune diabetes may not meet the definitions of T1D used in this study. In those with uncertain diabetes type further research, for example the use of advanced antibody assays, or combining clinical, antibody and genetic information, is required to help improve classification close to diagnosis (38; 39).

In summary, our findings suggest that when adult-onset T1D is robustly defined the presentation characteristics, progression, and T1D genetic susceptibility of adult-onset T1D are not altered by age of onset.

**Contributors**

AGJ, and NJT designed the study. AGJ and AVH researched the data. NJT, and AGJ analyzed the data with assistance from BMS. NJT wrote the first draft of the report. All authors provided helpful discussion and reviewed and edited the manuscript. AGJ is the guarantor of this work.

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**Data Availability**

Data is available by contacting Dr Jones (angus.jones@exeter.ac.uk).

**Ethics statement**

StartRight study was approved by the South West- Cornwall & Plymouth NHS Research Ethics Committee on the 06/06/2016, ref: 16/SW/0130.

**Conflict of interest statement**

RA is a co-Investigator on a Randox R&D research grant. The study has received translational industry-academic funding from Randox R&D relating to autoimmune genetic risk scores for prediction and classification of disease. There are no established patents, loyalties or licensing agreements relating to this grant. It is a 3 year grant (Feb 2022-2025). The approximate value is a

£2.2m program grant on genetic risk scores across autoimmune disease.

All other authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

**Table 1: Clinical characteristics of those defined as having type 1 diabetes based on the presence of ≥2 positive islet-autoantibodies split by median age of diagnosis.** Results shown are percentage for binary outcomes and mean for continuous data (95% CI). * Severe insulin deficiency defined as C-peptide <200pmol/l.

| | **Diabetes diagnosed ≤35 n=192** | **Diabetes diagnosed >35 n=193** | **p** |
|---|---|---|---|
| **Baseline characteristics** | | | |
| Age at diagnosis | 25.9 (25.1-26.6) | 49.9 (48.5-51.4) | <0.0001 |
| Duration at recruitment (months) | 4.2 (3.7-4.8) | 4.9 (4.4-5.5) | 0.06 |
| BMI kg/$m^2$ | 24.8 (24.2-25.5) | 25.6 (25.0-26.3) | 0.08 |
| Gender (male) | 53% (46-60) | 52% (45-59) | 0.9 |
| White European etnicity | 92% (88-96) | 91% (87-95) | 0.7 |
| **Symptoms at presentation** | | | |
| Unintentional weight loss | 80% (74-85) | 82% (76-87) | 0.6 |
| Diabetic Ketoacidosis | 23% (17-29) | 19% (14-25) | 0.3 |
| Osmotic symptoms | 96% (93-99) | 92% (88-96) | 0.09 |
| **Biochemistry at presentation** | | | |
| Hba1c at diagnosis mmol/mol | 103.0 (99.0-107.0) | 103.2 (99.5-106.9) | 0.96 |
| Hba1c at diagnosis % | 11.6 (11.2-11.9) | 11.6 (11.2-11.9) | 0.96 |
| Glucose at diagnosis mmol/l | 20.6 (19.1-22.1) | 20.9 (19.5-22.4) | 0.8 |
| **Management at presentation** | | | |
| Hospitalised at admission | 60% (53-67) | 40% (33-47) | <0.0001 |
| Initial insulin | 93% (90-97) | 73% (67-79) | <0.0001 |
| Initial tablets (+/- insulin) (%) | 9% (5-13) | 31% (25-38) | <0.0001 |
| **Baseline visit characteristics** | | | |
| Stimulated geometric C-peptide pmol/l | 434.5 (388.7-480.3) | 430.1 (356.4-503.7) | 0.9 |
| Non fasted UCPCR (nmol/mmol) | 1.0 (0.8-1.2) | 0.9 (0.8-1.1) | 0.6 |
| Severe Insulin deficiency * | 9% (5-13) | 11% (6-15) | 0.5 |
| Reported type 1 | 96% (94-99) | 87% (82-91) | 0.001 |
| Reported type 2 | 2% (0-3) | 7% (3-10) | 0.01 |
| Insulin treatment | 97% (95-100) | 90% (86-94) | <0.01 |
| T1D genetic risk score | 13.0 (12.8-13.3) | 12.9 (12.7-13.2) | 0.5 |
| GADA | 95% (92-98) | 97% (94-99) | 0.3 |
| IA-2A | 76% (69-82) | 75% (69-81) | 0.9 |
| ZNT8 | 82% (77-88) | 85% (80-90) | 0.4 |

**Figure 1. Comparison of type 1 diabetes genetic susceptibility (T1DGRS) (a) and recruitment blood C-peptide (b) in participants with type 1 diabetes defined by both study definitions aged below and above age 35 at diabetes diagnosis.** Horizontal lines represent the mean, error bars represent 95% confidence intervals. Comparisons by age group are shown for each definition and across all definitions and age groups.

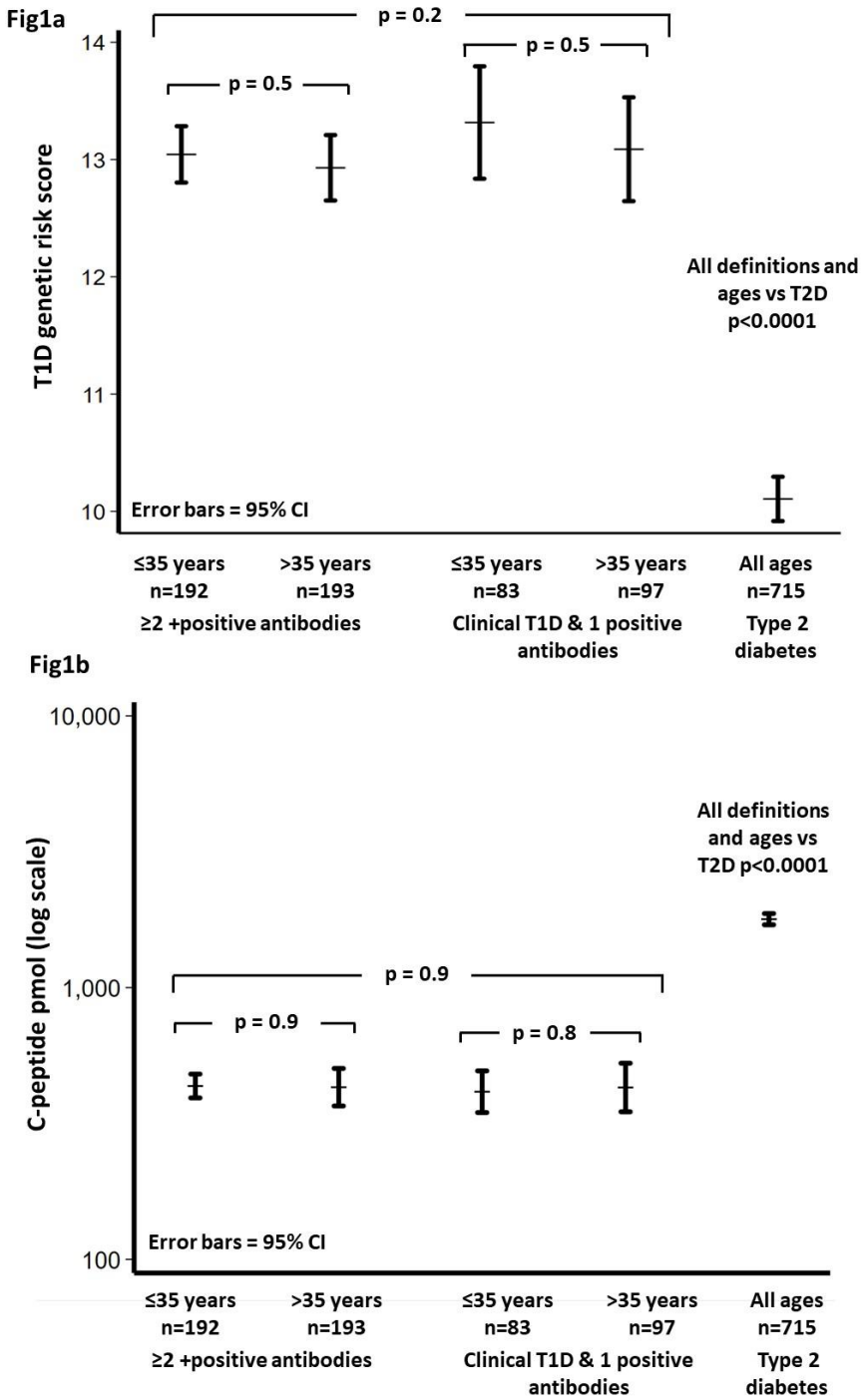
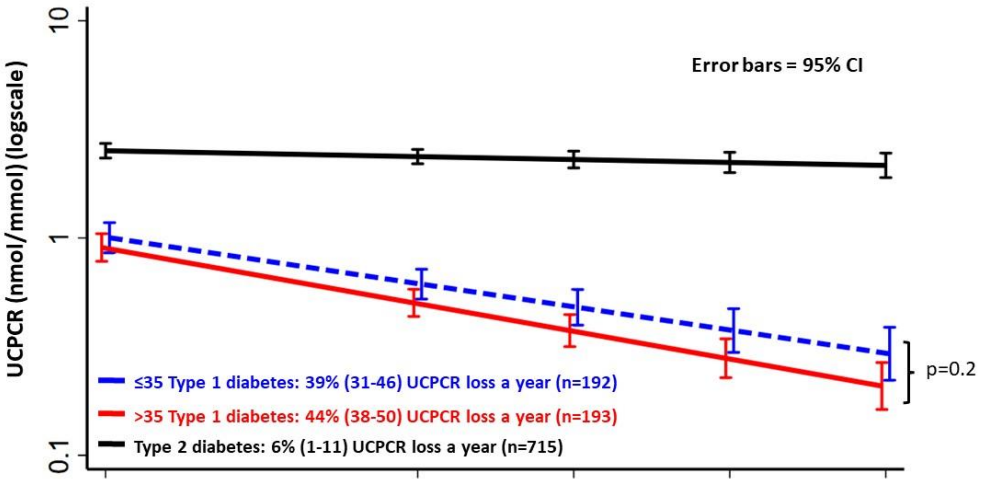


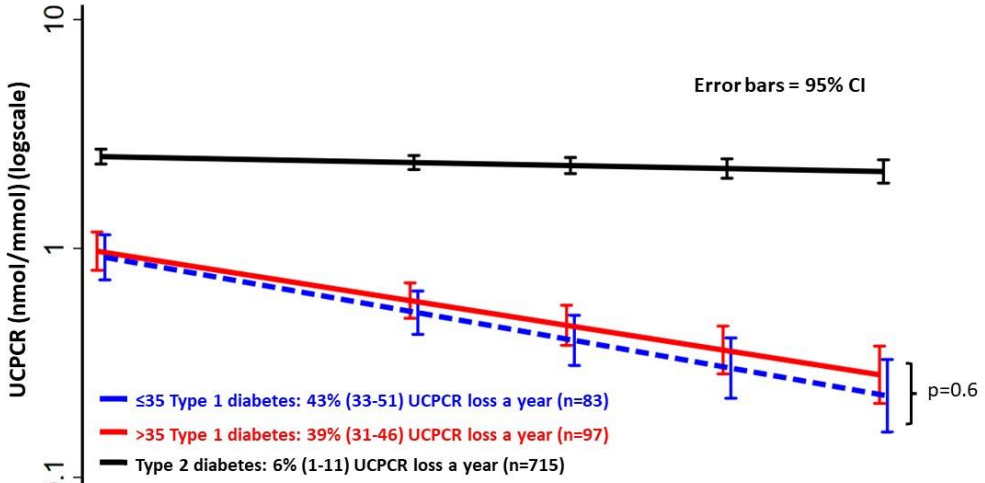
**Figure 2. Progression of change in log UCPCR from mixed effect models with age as an interaction term for a) type 1 diabetes defined by multi-antibody (≥2) positivity and b) a single positive antibody in the context of a clinical diagnosis of type 1 diabetes.** Error bars represent 95% confidence intervals. Comparison type 2 diabetes group shown for reference.

**A) Type 1 diabetes defined by ≥2 positive islet autoantibodies**




| | Baseline visit | 12 Months | 18 Months | 24 Months | 30 Months |
|---|---|---|---|---|---|
| ≤35 T1D | n=137 | n=77 | n=23 | n=52 | n=22 |
| >35 T1D | n=165 | n=96 | n=32 | n=66 | n=29 |
| T2D | n=584 | n=371 | n=84 | n=267 | n=102 |

**B) Type 1 diabetes defined by a clinician diagnosis and single positive islet autoantibody**




| | Baseline visit | 12 Months | 18 Months | 24 Months | 30 Months |
|---|---|---|---|---|---|
| ≤35 T1D | n=63 | n=31 | n=5 | n=22 | n=16 |
| >35 T1D | n=86 | n=65 | n=16 | n=42 | n=18 |
| T2D | n=584 | n=371 | n=84 | n=267 | n=102 |

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