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Individual and diabetes presentation characteristics associated with partial remission status in children and adults evaluated up to 12 months following diagnosis of type 1 diabetes: An ADDRESS-2 (After Diagnosis Diabetes Research Support System-2) study analysis

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ABSTRACT

Aims: People with recently-diagnosed type 1 diabetes mellitus (T1D) may undergo a transient period of glycaemic control with less exogenous insulin. Identification of predictors of this 'remission' could inform a better understanding of glycaemic control.

Methods: Participants in the ADDRESS-2 study were included who had 1 or 2 assessments of remission status (coincident insulin dose and HbA1c measurement, with remission defined by ≤ 0.4 units insulin/kg-body-weight/day with HbA1c < 53 mmol/mol). Demographic and clinical presentation characteristics were compared according to remission status and predictors of remission were explored by logistic regression analysis.

Results: 1470 first and 469 second assessments of remission status were recorded within 12 months of diagnosis of T1D. Step increases in the probability of remission were identified at age-at-diagnosis 20 years and 3 months after diagnosis (both $p < 0.001$). Among those aged < 20 years, remission was associated with male gender ($p = 0.02$), no ketoacidosis ($p = 0.02$) and fewer than 2 symptoms at presentation ($p = 0.004$). None of these characteristics predicted remission in those aged ≥ 20 years. In the subgroup with two assessments, transition to remission was independently associated with first remission assessment in months 1–2 post-diagnosis ($p = 0.01$), with age-at-diagnosis ≥ 20 years ($p = 0.01$) and, in those aged < 20 years, with an early HbA1c of < 57 mmol/mol. Adiposity, ethnicity, autoantibody status and other autoimmune disease were unrelated to remission. **Conclusions:** For those diagnosed before 20 years of age, males, ketoacidosis-free, with fewer symptoms and low early HbA1c were more likely to experience remission, but remission was most likely in anyone aged ≥ 20 at diagnosis.

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1. Introduction

Classically, people with type 1 diabetes mellitus (T1D) present with several weeks of osmotic symptoms (polyuria and polydipsia), fatigue and weight loss that, in the absence of treatment, progress rapidly towards diabetic ketoacidosis (DKA) [1]. This presentation is seen most frequently in children but symptoms and signs can be variable [2]. In adults, T1D may present even with appreciable residual insulin secreting capacity [3,4]. After diagnosis and initiation of insulin treatment, there may be a period of temporary restoration of β -cell function that can last from months to years [5,6]. Less exogenous insulin is required to maintain glycaemic control and temporary insulin independence may be possible. This period of remission has been termed 'partial remission' or the 'honeymoon phase' [7] and may be accompanied by a rise in proinsulin and C-peptide levels, peaking at 6 months after diagnosis then declining [8]. Estimates of the proportion of people undergoing remission vary by as much as 18 [9] to 72 [10] percent. Although remission is well documented, the majority of studies (although not all [8,11–13]) have involved children and adolescents and, with some exceptions [10,14,15], have been in Caucasian populations [8,9,11,12]. There are inconsistencies in reported predictors of remission [7] but these may include absence of DKA and a low HbA1c at diagnosis [5,16], less severe symptoms [10,16,17] and greater age at diagnosis [10,18]. Male gender, history of infection prior to presentation, higher body mass index (BMI), increased plasma C-peptide concentration, shorter symptom duration prior to diagnosis and lower serum bicarbonate levels at diagnosis have also been linked to remission [5,8,9,12,16,19].

The ADDRESS-2 study recruits throughout England and Wales children and adults of multiple ethnicities within 6 months of diagnosis of T1D and records individual and presentation characteristics, including islet autoantibody status based on three autoantibody assessments. ADDRESS-2 therefore provides an opportunity to evaluate, at the clinic population level in a national-level sample, independent predictors of remission in recently-diagnosed T1D in both children and adults.

2. Methods

2.1. Study design

ADDRESS-2 is an on-going, prospective, multi-centre, observational study established in 2011, currently with over 5000 children and adult participants with clinically diagnosed incident T1D recruited. The study protocol [20] and initial findings [2] have been published. Briefly, people with incident T1D are identified via the UK National Institute for Health Research Clinical Research Network and are recruited into the study if they have agreed to have their details and data placed on a database for statistical analysis and to be contacted about potential participation in other T1D-specific studies. People with incident T1D are recruited, across 134 research sites in England and Wales, all within 6 months of their T1D diagnosis. ADDRESS-2 has ethical approval from the Research Ethics Service (South Central – Berkshire NHS Research Ethics Com-

mittee: reference 10/H0505/85) and is conducted in accordance with the Helsinki agreement. Participants provide written consent to participate or, for children under the age of 16 who did not consent for themselves, consent is given by an appropriate person with parental responsibility and the child gives assent. Additionally, where acceptable, participants consent to providing blood samples. Adults who are not competent to give consent are excluded. As a foundational intention of ADDRESS-2 was to provide for recruitment to other T1D-specific studies, children under age 5 years are also excluded. Throughout the duration of the study, participant confidentiality is maintained and the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice is adhered to.

Information is recorded according to standardised case report forms by a research nurse at or shortly after recruitment into the study ('baseline') and, for those providing follow-up information, at 4–8 months following baseline. Additional diabetes-related information, including biochemical data and confirmation of treatment details, is collected by interview and from secondary care records. Data collected include age, gender, ethnicity, body weight, height, parental or sibling family history of diabetes, HbA1c concentration, and diabetes treatment information (insulin type, dose, regimen). Presentation characteristics recorded at diagnosis include ketoacidosis (blood glucose level >11.1 mmol/L, a moderate degree of ketonaemia, serum bicarbonate <15 mEq/l, arterial pH <7.3 , and an increased anion gap), osmotic symptoms (polyuria and/or polydipsia), weight loss, fatigue, and duration of symptoms prior to diagnosis (median (IQR), weeks). Positive autoantibody status is assigned on the basis of positivity for any one of GAD, IA2 or ZnT8 autoantibodies. Validation checks are carried out on all ADDRESS-2 data. Data queries are raised on any incomplete, missing, inconsistent or inappropriately outlying data entries for all variables on the database.

The present analysis includes people with clinically diagnosed incident T1D recruited to ADDRESS-2 from 1st September 2011 to 30th April 2016. Participant visits were included in the analysis if participants had information recorded for total daily insulin dose, with body weight and HbA1c concentration recorded within a week of the insulin dose record. First and second records with this information were included, if recorded within 12 months of diagnosis. Time from diagnosis for each remission record was calculated as the difference between the date of diagnosis and the date of the insulin dose record. Only those treated by multiple dose injection (MDI) therapy (97% of participants) were included in the analysis since validated recording of daily insulin dosing by continuous subcutaneous insulin infusion (CSII) was less consistent than for MDI therapy in the ADDRESS-2 data record.

2.2. Definition of partial remission

Many different definitions of partial remission have been used in previous studies. The majority have sought to combine cut-offs for daily insulin dose and HbA1c that identify those with both a relatively low insulin requirement and relative normoglycaemia. Daily insulin dose cut-offs of <0.3 [8],

<0.4 [11] and <0.5 [10] U/kg/day in association with HbA1c cut offs of <6.0 [10], <7.0 [11] and <8.0 [17] percent have been used. More recently, an insulin dose-adjusted HbA1c index has been introduced with a cut off corresponding to a stimulated C-peptide of >300 pmol/L [6] and variants of this, based on glycaemic variability, have been proposed [21]. However the relationship between insulin dose, HbA1c and residual beta cell function as measured by stimulated C-peptide appears to vary with age [22] and age-specific cut-offs have yet to be established for general use. Moreover, more rigorous evaluations are needed of the relationship between C-peptide levels and beta cell function in T1D, with consideration given to cut-offs that reflect the degree of loss of beta cell function. For the present analysis, we have used, as a working index of partial remission, the mid-points in the ranges used in previous studies; i.e an insulin dose of ≤ 0.4 units/kg body weight/day and HbA1c < 53 mmol/mol (i.e. <7.0%).

2.3. Data analysis

For the present analysis, those aged 5–16 years were categorised as ‘children’ and ≥ 17 years old as ‘adults’. Ninety percent of participants were White, 4 percent Asian, 2 percent Black, 3 percent mixed and 1 percent other. Accordingly, ethnicity was defined as White European or non-White European. Body mass index (BMI) was calculated as body weight (kg) per height in meters squared (kg/m^2). WHO-specified BMI z-scores were used as a measure of adiposity in children [23]. Children were classified as ‘overweight or obese’ if they had a BMI z-score of 1 or more [24], and adults if they had a BMI of $25 \text{ kg}/\text{m}^2$ or more. Statistical analysis was carried out using Stata SE 13 (Stata, College Station, TX). A two-sided significance level of $p < 0.05$ was used throughout as a guide to interpretation. The following series of analyses was undertaken, with first and second records variously included or excluded as appropriate:

Age at diagnosis and probability of remission: the probabilities of participants in successive age categories experiencing remission were compared by proportions test. Because preliminary analyses had established that participants with two remission assessments were more likely to be detected as experiencing remission and more likely to be younger second remission assessments were excluded from this analysis to avoid bias.

Time from diagnosis and probability of remission: the probabilities of participants in successive months following diagnosis experiencing remission were compared by proportions test. For those with two records of remission status, both records of remission status were included in this analysis, if the two records were not made in the same month-from-diagnosis category. If they were, only the first record was included.

Individual and presentation characteristics associated with remission: For this comparison, only first remission assessments were included. categorical data were summarized as percentages with categories compared by chi-square test. Median and interquartile ranges were used to summarize continuous variables with groups compared by Mann-Whitney U test.

Independent discriminators of remission status: Independent discriminators of those in and not in remission were explored

using mixed effects logistic regression analyses with inclusion of both first and second remission assessments and with participant identification number serving as grouping variable.

Discriminators of transition to remission: in the subgroup of those with two assessments of remission status, those transitioning from not in remission to in remission were compared by chi-square test or Mann Whitney test with those remaining not in remission. Multiple logistic regression analysis was used to identify independent predictors of transition to remission.

3. Results

At the time of data closure for this analysis, the ADDRESS-2 study had recruited, within 6 months of diagnosis, 3312 people with type 1 diabetes. Of these, 1470 had at least one assessment of remission status (1121 children, 349 adults) and 469 had a second assessment (435 children, 34 adults), both assessments having been made within 12 months of diagnosis.

3.1. Age at diagnosis and probability of remission

To investigate variation with age at diagnosis in the probability of experiencing remission during the 12 months following diagnosis, 15 percentile age categories were distinguished, the almost equal numbers of participants in each category ($n = 97-99$) ensuring equal weighting for between-category comparisons (Fig. 1). Up to 19.8 years of age, the probability of experiencing remission remained relatively constant at between 9 and 18 percent. However, between ages 19.9 and 27.2 remission prevalence was 27 percent and, between 27.3 and 34.4 years, 29 percent, falling to 20 percent thereafter. The only significant difference in remission prevalence between adjacent age categories was between the 16.1–19.8 and 19.9–26.9 years of age categories ($p = 0.03$). Setting the cut-off at 17 years, according to the conventional distinction between child and adult, weakened the difference in remis-

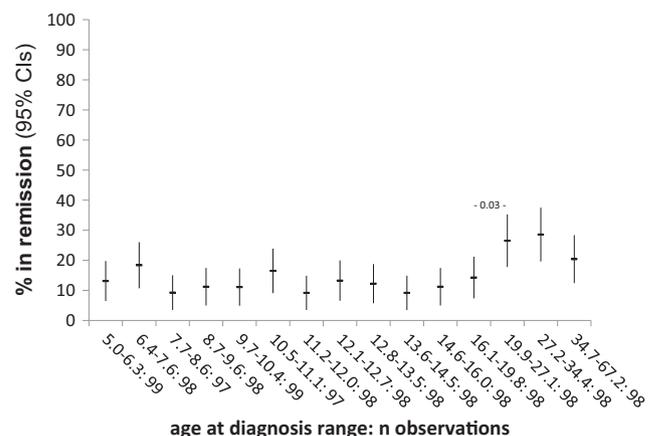


Fig. 1 – Probability of remission at first record 0–12 months after diagnosis of T1D in 15 percentile ranges of age at diagnosis. Proportions test significance between significantly different probabilities is shown.

sion prevalence between younger and older age ranges (as would be expected, given that the probability of remission for those aged 17–19 years at diagnosis was 14%, whereas between 20 and 22 years it was 34%).

3.2. Time from diagnosis and probability of remission

The discontinuity in remission prevalence at an age-at-diagnosis of around 20 years suggested markedly different remission behaviour between those aged <20 years ('younger') and those aged ≥20 years ('older'). The prevalence of remission in successive months from diagnosis was, therefore, investigated in younger and older age groups separately. In younger participants, remission prevalences were 3 and 1 percent in months 1 and 2, respectively, rising to between 10 and 20 percent in months 3–12. In older participants, prevalences were 0 and 10 percent in months 1 and 2, respec-

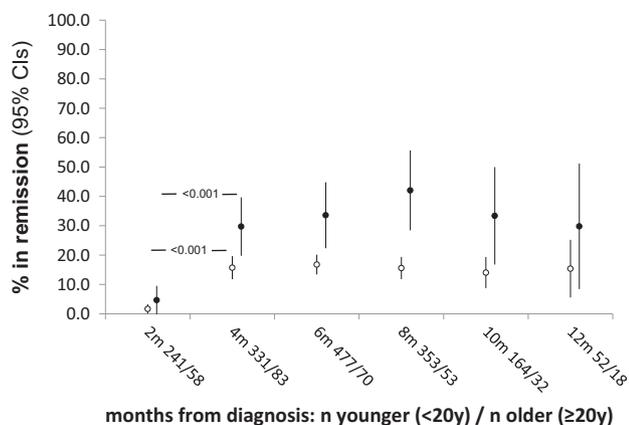


Fig. 2 – Prevalence of partial remission in younger (age <20 years: open circles) and older (≥20 years: closed circles) in 2-month periods after diagnosis. Numbers of observations contributing to each estimate are shown on the x-axis for younger/older groups. Proportions test significances between significantly different probabilities are shown.

tively, rising to between 20 and 44 percent in months 3–12. By considering 2-monthly categories of time from diagnosis, variation between categories was reduced and a significant rise in prevalence of remission ($p < 0.001$) in both younger and older participants was apparent after months 1 and 2 (Fig. 2).

3.3. Individual and presentation characteristics associated with remission

Compared with those not in remission ($n = 1250$) at first assessment (Table 1), those in remission ($n = 220$) were older (median 13.5 (95%CI 9.9,24.5) vs 12.2(9.3,15.8), $p < 0.001$), less likely to be a child (63 vs 79 percent, $p < 0.001$), more likely to be male (46 vs 37 percent, $p = 0.01$) and tended to be less likely to present with symptoms of diabetes (ketoacidosis: 35 vs 41 percent, $p = 0.09$; osmotic symptoms: 94 vs 97 percent, $p = 0.01$; fatigue: 76 vs 81 percent, $p = 0.07$).

3.4. Independent discriminators of remission status

The difference in prevalence of remission between months 1–2 after diagnosis and months 3–12 in both younger and older participants suggested a further discreet difference in remission behaviour as well as the difference associated with age at diagnosis. Accordingly, in regression analysis of predictors of remission, as well as analysing younger and older participants separately, an additional categorical variable was included that distinguished whether or not a remission assessment had been made in the first 2 months after diagnosis. In mixed effects regression analysis in younger participants (Table 2), individual predictors of being less likely to be in remission were female gender ($p = 0.01$), presenting with ketoacidosis ($p = 0.01$), osmotic symptoms ($p = 0.02$) or weight loss ($p = 0.03$) and having 2 or more of the presentation symptoms: osmotic symptoms, weight loss or fatigue ($p = 0.004$). In multivariable analysis, with entry of individual predictors significant at $p < 0.05$, females were less likely to be in remission (Odds ratio 0.55 (95%CI 0.33,0.93), $p = 0.02$) as were those pre-

Table 1 – Comparison between participants not in partial remission at record 1 with those in remission at first record of remission status 0–12 months post-diagnosis: median (IQR), % (n).

	not in remission (n = 1250)	in remission (n = 220)	p
age, years	12.2 (9.3,15.8)	13.5 (9.9,24.5)	<0.001
female	46 (571)	37 (81)	0.01
child	79 (983)	63 (138)	<0.001
bmi z-score child (zbfa1, n = 1041)	0.42(−0.26,1.24)	0.54(−0.15,1.21)	0.4
bmi adult (bmi1, n = 328)	23.7 (21.0,26.9)	23.8 (21.4,26.5)	1.0
overweight or obese	32 (374)	33 (69)	0.7
white	90 (1122)	93 (205)	0.1
autoimmune disease	6 (68)	5 (10)	0.8
parent with DM	14 (168)	10 (21)	0.1
sibling with DM	6 (69)	6 (12)	0.9
ketoacidosis	41 (512)	35 (77)	0.09
osmotic symptoms	97 (1208)	94 (207)	0.01
weight loss	84 (1030)	80 (174)	0.1
fatigue	81 (997)	76 (166)	0.07
symptom duration, mean (SD) (weeks)	5.7 (9.5)	6.3 (10.4)	0.6
autoantibody positive % (n) (n = 670)	88 (489)	87 (101)	0.7

Table 2 – AGE < 20 YEARS: univariable and multivariable (including univariable predictors at $p < 0.05$) predictors of being in remission relative to not in remission. All analyses included as a confounder whether or not a remission assessment had been carried out during the 2 months after diagnosis when the probability of being in remission was low.

	n	Univariate OR (95%CI) ^P	Multivariable OR (95%CI) ^P (n = 1566)
Female	1625	0.53 (0.32,0.87) ^{0.01}	0.55 (0.33,0.93) ^{0.02}
Overweight	1529	1.25 (0.74,2.10) ^{0.3}	
White	1625	1.43 (0.61,3.38) ^{0.4}	
Autoimmune disease	1600	1.01 (0.34,3.01) ^{0.9}	
Parent with DM	1604	0.80 (0.35,1.81) ^{0.5}	
Sibling with DM	1465	1.21 (0.39,3.76) ^{0.7}	
Ketoacidosis	1609	0.51 (0.30,0.85) ^{0.01}	0.53 (0.30,0.92) ^{0.02}
Osmotic symptoms	1617	0.24 (0.07,0.84) ^{0.02}	
Weight loss	1600	0.51 (0.27,0.97) ^{0.03}	
Fatigue	1593	0.58 (0.32,1.04) ^{0.06}	
2 or 3 symptoms	1576	0.27 (0.12,0.60) ^{0.002}	0.31 (0.14,0.69) ^{0.004}
Symptom duration (weeks)	1559	1.01 (0.98,1.03) ^{0.6}	
Autoantibody positive	594	0.67 (0.20,2.21) ^{0.5}	

senting with ketoacidosis (0.53 (0.30,0.92), $p = 0.02$) or 2 or more of the symptoms (0.31 (0.14,0.69), $p = 0.004$). In older participants none of these characteristics predicted remission status.

3.5. Individual and presentation characteristics and transition to remission

In a further analysis of the subgroup of participants with both a first and second record of remission status, participants not in remission at record 1 and record 2 ($n = 349$) were compared with those not in remission at record 1 who transitioned to remission at record 2 ($n = 57$). Among participants in the younger age category (<20 years), 13 percent transitioned to remission, whereas among those in the older age category (≥ 20 years), 32 percent transitioned (chi squared $p = 0.008$). The equivalent figures for children (age < 17 years) and adults

(age ≥ 17 years) were 13 and 27 percent ($p = 0.03$). Among those not in remission at record 1 and record 2 and those not in remission at record 1 who transitioned to remission at record 2, there were only 25 participants in the older age category. Comparisons between those not transitioning and those transitioning were, therefore, restricted to the younger age category ($n = 381$). Among the younger participants, those transitioning to remission tended to have had their first remission record in months 1–2 after diagnosis and to have a shorter symptom duration, but no difference reached statistical significance (Table 3). In multivariable logistic regression analysis, including as predictors individual and presentation characteristics that differed between those remaining not in remission and those transitioning to remission at $p \leq 0.1$ (namely first remission record in months 1–2 after diagnosis; gender, non-White, parent with DM and symptom duration), only first remission record in months 1–2 after diagnosis

Table 3 – Participants aged <20 years with 2 records who were not in partial remission at records 1 or 2 compared with those who transitioned from not in remission at record 1 to in remission at record 2.. First and second remission assessments were within made 12 months of diagnosis. Median (IQR) or % (n) are shown.

	No remission (n = 332)	Transition to remission (n = 49)	p
1st record in months 1–2 post-diagnosis	30 (101)	43 (21)	0.08
age (years)	10.9 (8.2,13.1)	10.4 (8.7, 13.1)	0.7
female	49 (162)	37 (18)	0.1
BMI z-score	0.42 (–0.27,1.24)	0.68 (–0.34,1.46)	0.2
Overweight	32 (101)	36 (17)	0.5
Non-white	11 (36)	4 (2)	0.1
Autoimmune disease	6 (18)	6 (3)	0.8
Parent with DM	9 (30)	17 (8)	0.1
Sibling with DM	6 (19)	5 (2)	0.6
Ketoacidosis	43 (142)	35 (17)	0.2
Osmotic symptoms	97 (323)	98 (47)	0.8
Weight loss	85 (281)	78 (35)	0.2
Fatigue	78 (254)	77 (37)	0.8
Symptom duration (mean, SD: weeks)	5.2 (8.6)	3.4 (2.9)	0.07
Antibody positive (n = 148)	89 (99)	89 (17)	0.9

was significant (OR 2.1 (95%CI 1.2, 3.9), $p = 0.01$). With inclusion of the 25 participants in the older age category who had either remained not in remission or transitioned to remission, age ≥ 20 years also emerged as a significant predictor of transition to remission (OR 3.4 (95%CI 1.3, 8.9), $p = 0.01$).

3.6. Early HbA1c and transition to remission

Using the second remission assessments, a further analysis was undertaken to test the possibility that a lower HbA1c soon after diagnosis among those not in remission might increase the probability of subsequent partial remission. For those with a first record of HbA1c at least 1 month post-diagnosis, prior to the second remission assessment and not in remission (i.e. insulin dose >0.4 units/kg body weight/day or HbA1c ≥ 53 mmol/mol or both), the HbA1c concentration was entered in logistic regression analysis as a predictor of remission at record 2. Among the 335 participants aged <20 years with a qualifying post-diagnosis record of HbA1c (mean time from diagnosis 110 days, range 42–295 days) and a second remission assessment (mean time from diagnosis 207 days, range 89–358 days), HbA1c was a significant negative predictor of remission at the second remission assessment (OR 0.96 (95% CI 0.94, 0.99), $p = 0.008$). In the two lowest quintiles of HbA1c (32–56 mmol/mol), prevalence of subsequent remission was 18–19 percent but fell to 5–6 percent in the two upper quintiles (64–139 mmol/mol). This analysis was not undertaken in those aged ≥ 20 years because only 17 had a qualifying HbA1c measurement.

4. Discussion

Rather than continuous variation in the relationship between age at diagnosis and remission, our cross-sectional analysis by month from diagnosis up to 12 months demonstrated a step increase in the prevalence of remission at 20 years. Likewise there was a discontinuous relationship between remission and time from diagnosis, with a step increase at 3 months. Among younger participants (age <20 years), being male, not having DKA and having fewer of the classical symptoms of T1D at presentation were each independently associated with remission. Among older participants (age ≥ 20 years) none of these characteristics were associated with remission. Moreover, in those with two remission assessments, transition to remission was associated only with being aged 20 years or more, with having a first assessment in months 1–2 after diagnosis and having a relatively low post-diagnosis early HbA1c level. In accord with other studies, we found no evidence for influence on remission of adiposity [11] or ethnicity [14] and we also found no associations with a history of autoimmune disease, a parental or sibling history of diabetes or duration of symptoms. Importantly, we also assessed islet autoantibody status for an association with partial remission but found none, which is consistent with the majority [8,16,17] although not all [25,26] previous studies.

In younger participants, we found the prevalence of remission in months 3–12 after diagnosis to range between 10 and 20 percent, on average 15 percent, whereas among older participants, the equivalent figures were 21–44 percent and 34

percent. One study with follow-up over the course of 36 months after diagnosis reported that 18 percent of participants experienced partial remission, with periods of remission lasting for a median of 6 months [9]. Otherwise, reported proportions experiencing remission have ranged between 26 and 72 percent [5,8,10–12,16,17]. These studies generally involved assessments of remission status at intervals of 3 months with a median time of remission between 6 and 9 months. In contrast to these studies, which provided an estimate of the proportion of participants experiencing remission within the time period of follow-up, our cross-sectional analysis provided estimates of the prevalence of remission within monthly or 2-monthly periods based on one or two assessments over the first year following diagnosis. Therefore, although our analysis could not distinguish the overall proportion of participants experiencing remission, it was able to illustrate the average time course of partial remission, with remission unlikely in the first 2 months following diagnosis and relatively likely and constant thereafter up to 12 months.

People presenting with T1D as adults have greater residual beta cell function than those presenting as children [13,18] and, in accord with this and with our observations, the majority of studies of relationships between partial remission and age at diagnosis have found partial remission to occur more frequently in older individuals [10,12,26,27]. Interestingly, the transition towards a greater probability of remission did not coincide with the conventional dividing line of 17 years between child and adult, but slightly later at 20 years.

Among younger participants, we found evidence for male gender being associated with a higher probability of being in partial remission. A number of previous studies have found no significant association between partial remission and gender [5,9–11,13,14,16,17]. By contrast, others have reported a higher incidence of partial remission both in boys [25–27] and men [8]. Also, despite finding no overall association between occurrence of partial remission and gender, two studies have noted an increased duration of remission in males [5,11].

Also among younger participants, we distinguished absence of DKA at presentation and a lower frequency of classical symptoms as positive factors in partial remission, which could also suggest less severe beta cell destruction. Previous studies have focused on ketoacidosis as a presentation symptom and have generally reported an association between absence of ketoacidosis at diagnosis and subsequent partial remission [5,10,12,16,17,21,26] although there are exceptions [14]. Importantly, the proportion of participants who presented at diagnosis with ketoacidosis (41 percent) was roughly comparable with other European studies, in which proportions have ranged between 14 and 48 percent [12,14,16,26,28]. Adults may present with less disease severity or metabolic decompensation than children [13,29]. Nevertheless, in the present analysis, absence of ketoacidosis and having fewer presentation symptoms predicted remission in younger not older participants. This observation raises the possibility that diagnosis and initiation of insulin treatment prior to development of DKA might increase the probability of early remission in the young and it is noteworthy that in

our data, among younger participants, an HbA1c below 57 mmol/mol, one month or more post-diagnosis in those not in remission significantly predicted an increased probability of subsequent remission relative to those with higher HbA1c.

Novel aspects of our analysis included the large number of participants evaluated in the context of routine clinical practice at a national level. Treatment of T1D in the UK National Health Service is according to rigorous national guidelines so, although no analysis of variation according to recruiting centre has been carried out for ADDRESS-2, we may expect generally homogenous outcomes between the 134 centres contributing information. Both children and adults with a broad age range were included, enabling a discriminatory analysis of variation in the prevalence of remission with age. Our study also included, a small sample of non-White European individuals. Moreover, a substantial number of potential predictors of remission was considered, including autoantibody status. Despite these strengths, in order to provide a basic overview of remission predictors in the ADDRESS-2 cohort, our analyses were necessarily limited: for example, the structure of data collection for ADDRESS-2 did not allow for the intensive, sequential follow-up of participants that would be needed to gain insight into duration of remission. Nevertheless, as numbers of ADDRESS-2 recruits accumulate, a range of further, more restricted and focused, analyses may be anticipated. In particular, the lack of variation with ethnicity we observed was based on very small numbers and will need to be re-investigated as more observations become available. Moreover, comparison between younger and older participants of predictors of transition to remission will require more follow-up evaluations of remission in adults. Also the roles of different insulin regimens, different definitions of partial remission, relationships with islet autoantibody types and titres and investigation of the use of plasma C-peptide concentrations in the evaluation of remission status may all be considered in future studies of remission in the ADDRESS-2 cohort. It should also be noted that a broad range of MDI dosing regimens, including use of short, intermediate and long acting insulin, was encountered among ADDRESS-2 participants, reflecting the variety of dosing regimens employed in routine clinical practice. Further analyses could compare remission according to different MDI dosing regimens and CSII insulin dosing.

In conclusion, the weight of evidence from this analysis supports a transition at around 20 years of age at diagnosis and at 3 months after diagnosis after which partial remission becomes more likely. Predictors of partial remission identified in this analysis focus attention on females <20 years of age, with ketoacidosis, more presentation symptoms at diagnosis and an HbA1c of 57 mmol/mol or more at least one month after diagnosis for future investigations into interventions for sparing or restoring beta cell function in early T1DM.

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Declaration of Competing Interest

There are no competing interests.

Authorship statement

Analysis planning: VB, IFG, DGJ, NO.

Data collection: AK, HCW, DGJ.

Analysis: AH, VB, HCW, IFG, NO.

Manuscript development and writing: AH, VB, AK, HCW, IFG, SM, DGJ, NO.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.diabres.2019.107789>.

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