



Factors predicting poor glycemic control in the first two years of childhood onset type 1 diabetes in a cohort from East London, UK: Analyses using mixed effects fractional polynomial models

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Abstract

Background/Objective: Poor early glycemic control in childhood onset type 1 diabetes (T1D) is associated with future risk of acute and chronic complications. Our aim was to identify the predictors of higher glycated hemoglobin (HbA1c) within 24 months of T1D diagnosis in children and adolescents.

Methods: Mixed effects models with fractional polynomials were used to analyze longitudinal data of patients <19 years of age, followed from T1D diagnosis for up to 2 years, at three diabetes clinics in East London, United Kingdom.

Results: A total of 2209 HbA1c observations were available for 356 patients (52.5% female; 64.4% non-white), followed from within 3 months of diagnosis during years 2005 to 2015, with a mean \pm SD of 6.2 ± 2.5 HbA1c observations/participant. The mean age and HbA1c at diagnosis were 8.9 ± 4.3 years and $10.7\% \pm 4.3\%$ (or expressed as mmol/mol HbA1c mean \pm SD 92.9 ± 23.10 mmol/mol) respectively. Over the 2 years following T1D diagnosis, HbA1c levels were mostly above the National Institute for Health, Care and Excellence (NICE), UK recommendations of 7.5% (<58 mmol/mol). Significant ($P < .05$) predictors of poorer glycemic control

Abbreviations: –2LL, –2 log likelihood; AIC, akaike information criterion; BIC, Bayesian information criterion; BMI, body mass index; DKA, diabetic ketoacidosis; HbA1c, glycated hemoglobin A1c; IMD, indices of multiple deprivations; NICE, National Institute for Health, Care and Excellence; T1D, type 1 diabetes.

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were: Age at diagnosis (12-18 years), higher HbA1c at baseline (>9.5%, ie, >80 mmol/mol), clinic site, non-white ethnicity, and period (pre-year 2011) of diagnosis. Additionally in univariable analyses, frequency of clinic visits, HbA1c at diagnosis, and type of insulin treatment regimen showed association with poor glycemic control ($P < .05$).

Conclusions: Major risk factors of poorer glycemic control during 3-24 months following childhood onset T1D are: diagnosis prior to 2011, higher HbA1c levels at baseline, age at diagnosis, non-white ethnicity, and clinic site.

KEYWORDS

HbA1c, longitudinal analyses, pediatric, predictors, type 1 diabetes mellitus

1 | INTRODUCTION

Evidence suggests that early glycemic control in childhood onset type 1 diabetes (T1D) tracks into later life¹⁻⁴ and predicts risk of future vascular complications.^{5,6} Studies in adults show a reduced risk of vascular complications and mortality in those who maintained lower HbA1c levels during early stages of the disease.^{7,8} It is therefore important to identify if this is the case or whether other factors influence glycemic trends from T1D diagnosis in children and adolescents.^{9,10}

Poor glycemic control is seen in children and adolescents soon after T1D diagnosis.¹¹ But factors influencing these outcomes are poorly understood due to studies: with small sample size, focused on older children and adolescents or investigated a limited number of demographic variables.¹² This causes a difficulty in identifying and predicting a “risk signature” of poor control during the course of the disease in young T1D patients.¹³

In order to investigate the predictors (sociodemographic, biological, and clinical) affecting the glycemic control within 24 months of T1D diagnosis in children and adolescents, we undertook a retrospective analysis of data collected prospectively from three diabetes clinics based in East London, United Kingdom.

2 | METHODS

We investigated the predictors of glycemic control (HbA1c levels) during 3 to 24 months from T1D diagnosis in young children and adolescents. Data included pediatric (<19 years of age at diagnosis) patients, recorded in the hospital database as newly diagnosed with T1D, in the period between January 1, 2005 and December 31, 2015 and receiving care from one of the three pediatric diabetes clinics of the Barts Health NHS Trust in East London, United Kingdom.

Because of increasing knowledge of more rare causes of diabetes, patients may have been misidentified during the study period as type 1 diabetes (default in the database), and may have had type 2 diabetes, maturity onset diabetes, or secondary diabetes. The records of three patients with very low HbA1c were looked at and these patients most likely did not have T1D and were excluded.

Each of the three clinics had a separate but unequal, multi-disciplinary diabetes specialist care team made up of clinicians, nurses, dietitians, psychologists, and with access to interpreters. For example, a 24-hour pediatric diabetes consultant on call service was available at only one of the clinics. The three clinics became part of a network in 2012 but care continued to be delivered by the respective care team at each clinic as per the updated care package recommended by the National Institute of Health and Care Excellence (NICE).¹⁴ Type and methods for the electronic recording of anthropometric, socio-demographic and clinical data, collected at diagnosis and at each clinic visit were not always uniform between the three clinics. For example, one of the three clinics recorded data of fewer patients in the first 3 months from T1D diagnosis (Figure S1A, B).

2.1 | Variables

We used HbA1c, a measure of average blood glucose over the previous 8-12 weeks, as our marker of diabetes control and as the dependent variable in these analyses. Venous and finger HbA1c measured using BioRad Variant II Turbo (in laboratory) and Siemens/Bayer DCA 2000 (in clinic) respectively at diagnosis and each clinic visit. The HbA1c values recorded as percentages were converted to mmol/mol using the formula: $(\text{HbA1c value in \%} - 2.15) \times 10.929$. Baseline was defined as period within 3 months of T1D diagnosis and patients with baseline measurements were eligible. HbA1c levels at diagnosis (measurement within the first month of diagnosis) and at baseline (averaged HbA1c measurements within first 3 months of diagnosis) were assessed by tertiles or categorized into low (<7.5% or <58 mmol/mol), moderate (7.5-9.5% or 58-80 mmol/mol), and high (> 9.5% or >80 mmol/mol) based on UK targets that were acceptable during the study period.

Based on our systematic review¹² and captured in the dataset, potential predictors of HbA1c which we used as independent variables in our analyses were sex, age at diagnosis, season/month/year/period of T1D diagnosis, ethnicity, index of multiple deprivation (IMD), clinic site, number of clinic visits, insulin regimen, body mass index (BMI), pH at diagnosis, HbA1c at diagnosis, and baseline.

We tested the accuracy of the data in a number of patients and found that the insulin treatment may have been inaccurately documented in the database. Sometimes details of insulin regimen such as dosage, injection frequency, and pump treatment were missing during the earlier years (prior to 2012) and before the individual clinics joined to form a network.

Age at diagnosis was treated as a categorical variable and stratified into the following groups: 0-5 (preschool), 6-11 (prepubertal), and 12-18 (pubertal/adolescent) years. Season of diagnosis was categorized into autumn (September to November), winter (December to February), spring (March to May), and summer (June to August). Period of diagnosis was categorized into pre-2011 and post-2011 to check for differences in outcomes between the two periods because the three diabetes clinics became part of the same network in 2012. Ethnicity was categorized into white and non-white for the main analysis. Socioeconomic status was measured using the UK IMD (2010), which gives a relative measure of neighborhood-level socioeconomic deprivation based on seven domains for small areas in England: income, employment, health and disability, education, skills and training, barriers to housing and services, living environment, and crime. IMD scores were categorized into three groups with 3 being least deprived and 1 being most deprived.¹⁵ The number of clinic visits per patient was treated as a continuous variable.

Insulin treatment (between years 2005-2015) was categorized as continuous subcutaneous insulin infusion pump, 3 or more injections per day or 1 or 2 injections per day. BMI (obtained from the records of physical examination involving measurements of height and weight) measured as kg/m² at each clinic visit, was treated as a continuous variable and was standardized to BMI (WHO) z-scores. These were further categorized into normal weight, overweight/obese, and thin.¹⁶

Whole blood pH at diagnosis was treated as a continuous variable and in a sensitivity analysis was categorized into acidotic (pH < 7.3), normal (pH 7.3 to 7.45), and alkalotic (pH > 7.45).

2.2 | Analyses

Baseline characteristics of the cohort were reported as means and SDs for continuous variables or counts and percentages for categorical variables. Baseline characteristics were compared across HbA1c categories at baseline using a global χ^2 test for categorical variables or a Wald test from linear regression for continuous variables.

Repeated measurements of the outcome HbA1c were modeled using mixed effects models. Fractional polynomials were used to account for non-linear trajectories of HbA1c over time.^{17,18} We estimated models for both 0 to 24 months (Model 1: with 253 T1D patients followed from diagnosis) and 3 to 24 months (Model 2: with 335 T1D patients followed from baseline), as data showed dramatic instability in HbA1c during the first 3 months after diagnosis, as expected. In this paper we report the results of the investigations of predictors of HbA1c levels from 3 to 24 months in the 335 patients who were followed from baseline. The trajectories and predictors of HbA1c during 0-3 months will be studied in depth and reported

separately. The polynomial terms in the model were chosen by comparing model fit amongst all fractional polynomial models with one, two or three polynomial terms with any combination of the following polynomial powers of time: (-2 -1 -0.5 0 0.5 1 2 3), where 0 represents log(t) and a repeated power (p p) indicates the functions t^p and $\log(t)t^p$. The outcome model for 0 to 24 months (Model 1) was

$$HbA1c_i(t) = \beta_0 + \beta_1 \log(t) + \beta_2 t + \beta_3 t^2 + b_{0,i} + b_{1,i} \log(t) + b_{2,i} t + b_{3,i} t^2 + \varepsilon_i$$

and the outcome model for 3 to 24 months (Model 2) was

$$HbA1c_i(t) = \beta_0 + \beta_1 \sqrt{t} + \beta_2 \log(t) \sqrt{t} + b_{0,i} + b_{1,i} \sqrt{t} + b_{2,i} \log(t) \sqrt{t} + \varepsilon_i$$

where $HbA1c_i(t)$ is the outcome of interest for individual i . $\beta_0, \beta_1, \beta_2$, and β_3 are fixed effect coefficients describing the population average trajectory of the outcome and $b_{0,i}, b_{1,i}, b_{2,i}$, and $b_{3,i}$ are normally distributed random effects describing the deviation of individual i 's trajectory from the population average. The best model was selected within each class of one-term, two-term or three-term models. Fixed effects and random effects were included in the model selection procedure. However, the expectation of the random effects was assumed to be zero. Additionally, both the Akaike information criterion (AIC) and the Bayesian information criterion (BIC) were used to assess model fit (Table S1A, B give the AIC and BIC results from each class of models). Time-dependent predictors were not included in the model. However, mean of HbA1c and BMI measurements taken during the 0-3-month period from diagnosis were used as predictors during 3-24-month follow-up.

To study the predictors of glycemic control between 3 and 24 months of diagnosis, predictor variables were included in the mixed effects model. The effect of the predictor variables represents a shift in the population average trajectory and can therefore be interpreted as a mean difference in HbA1c levels over time. Initially each predictor variable was separately added to the models 1 and 2, and significant predictor variables were then included in a multivariable model. Predictors showing significant interactions with sex, clinic site, and age at diagnosis were also included in the multivariable model. All models include $\sqrt{\cdot}$ and $\log^* \sqrt{\cdot}$ functions of time as both fixed and random effects. Results for potential predictors were reported as mean differences and 95% confidence intervals (CI). Sensitivity analyses were conducted where appropriate.

Additionally, the above initial mixed model with each predictor variable were then fitted to include interactions between the predictor variable and the polynomial time functions, allowing the shape of the HbA1c trajectory to depend on the level of the predictor variable.

Analyses were performed using Stata 15, StataCorp. College Station, Texas, 2015. The fractional polynomial models were fitted using the stata "fp" command.

3 | RESULTS

A total of 356 T1D patients (52.5% female) with 2209 HbA1c observations (mean 6.2 ± 2.5 HbA1c observations/participant) and a

TABLE 1 Baseline^a characteristics of study population by HbA1c categories. Data are mean (±SD) or counts (%)

| Characteristic | Total | HbA1c levels at baseline (mmol/mol) | | | P value (for difference by HbA1c at baseline) |
|--|---------------|-------------------------------------|------------------|------------------|---|
| | | <58 mmol/mol | 58-80 mmol/mol | >80 mmol/mol | |
| Sex | N = 356 | N = 38 (10.67%) | N = 117 (32.87%) | N = 201 (56.46%) | 0.01* |
| Male | 169 (47.47%) | 25 (65.79%) | 63 (53.85%) | 81 (40.30%) | |
| Female | 187 (52.53%) | 13 (34.21%) | 54 (46.15%) | 120 (59.70%) | |
| Age at diagnosis (years) | N = 356 | N = 38 | N = 117 | N = 201 | 0.03* |
| | 8.9 ± 4.3 | 9.5 ± 4.7 | 8.07 ± 4.5 | 9.3 ± 4.1 | |
| Age at diagnosis | N = 356 | N = 38 | N = 117 | N = 201 | 0.14** |
| 0-5 yrs | 106 (29.78%) | 11 (28.95%) | 44 (37.61%) | 51 (25.37%) | |
| 6-11 yrs | 143 (40.17%) | 13 (34.21%) | 40 (34.19%) | 90 (44.78%) | |
| 12-18 yrs | 107 (30.06%) | 14 (36.84%) | 33 (28.21%) | 60 (29.85%) | |
| Period of T1D onset | N = 356 | N = 38 | N = 117 | N = 201 | 0.01* |
| Year 2005 to 2010 | 181 (50.84%) | 11 (28.95%) | 56 (47.86%) | 114 (56.72%) | |
| Year 2011-2015 | 175 (49.16%) | 27 (71.05%) | 61 (52.14%) | 87 (43.28%) | |
| Season of T1D onset | N = 356 | N = 38 | N = 117 | N = 201 | 0.02** |
| Spring | 93 (26.12%) | 11 (28.95%) | 38 (32.48%) | 44 (21.89%) | |
| Summer | 75 (21.07%) | 7 (18.42%) | 13 (11.11%) | 55 (27.36%) | |
| Autumn | 82 (23.03%) | 7 (18.42%) | 32 (27.35%) | 43 (21.39%) | |
| Winter | 106 (29.78%) | 13 (34.21%) | 34 (29.06%) | 59 (29.35%) | |
| Ethnicity | N = 351 | N = 38 (10.82%) | N = 116 (33.05%) | N = 197 (56.13%) | 0.05** |
| 1 White vs | 125 (35.61%) | 14 (36.84%) | 51 (43.97%) | 60 (30.46%) | |
| 2 Non-white | 226 (64.39%) | 24 (63.16%) | 65 (56.03%) | 137 (69.54%) | |
| Non-white sub groups | | | | | |
| a) Mixed | 35 (9.97%) | 2 (5.26%) | 13 (11.21%) | 20 (10.15%) | |
| b) Black | 79 (22.51%) | 9 (23.68%) | 27 (23.28%) | 43 (21.83%) | |
| c) Asian/other | 112 (31.91%) | 13 (34.21%) | 25 (21.55%) | 74 (37.56%) | |
| Indices of Multiple Deprivation | N = 354 | N = 38 (10.73%) | N = 117 (33.05%) | N = 199 (56.22%) | 0.39** |
| Most deprived | 187 (52.82%) | 18 (47.37%) | 60 (51.28%) | 109 (54.77%) | |
| Moderate | 127 (35.88%) | 13 (34.21%) | 41 (35.04%) | 73 (36.68%) | |
| Least deprived | 40 (11.30%) | 7 (18.42%) | 16 (13.68%) | 17 (8.54%) | |
| No of patients at clinics | N = 356 | N = 38 | N = 117 | N = 201 | 0.01** |
| 1 | 36 (10.11%) | 12 (31.58%) | 15 (12.82%) | 9 (4.48%) | |
| 2 | 112 (31.46%) | 9 (23.68%) | 36 (30.77%) | 67 (33.33%) | |
| 3 | 208 (58.43%) | 17 (44.74%) | 66 (56.41%) | 125 (62.19%) | |
| Insulin regimen | N = 341 | N = 37 (10.85%) | N = 112 (32.84%) | N = 192 (56.31%) | 0.60** |
| 1-2 inj./day | 92 (26.98%) | 9 (24.32%) | 31 (27.68%) | 52 (27.08%) | |
| > = 3 inj. per day | 233 (68.33%) | 25 (67.57%) | 74 (66.07%) | 134 (69.79%) | |
| Pump | 16 (4.69%) | 3 (8.11%) | 7 (6.25%) | 6 (3.13%) | |
| HbA1c at diagnosis (mmol/mol) | N = 253 | N = 13 (5.14%) | N = 62 (24.50%) | N = 178 (70.36%) | 0.01* |
| | 92.9 ± 23.10 | 49.69 ± 5.44 | 69.60 ± 6.58 | 104.17 ± 16.96 | |
| HbA1c at baseline (mmol/mol) | N = 356 | N = 38 (10.67%) | N = 117 (32.87%) | N = 201 (56.46%) | 0.01* |
| | 85.79 ± 23.75 | 49.89 ± 6.03 | 68.98 ± 6.29 | 102.36 ± 16.89 | |
| HbA1c at 1 to 3 months of diagnosis (mmol/mol) | N = 242 | N = 29 (11.98%) | N = 91 (37.61%) | N = 122 (50.41%) | 0.001* |
| | 66.11 ± 14.76 | 49.72 ± 6.19 | 63.40 ± 9.67 | 72.03 ± 15.82 | |
| HbA1c at 2 to 3 months of diagnosis (mmol/mol) | N = 127 | N = 19 (5.14%) | N = 44 (24.50%) | N = 64 (70.36%) | 0.001* |
| | 61.37 ± 15.00 | 50.89 ± 5.71 | 59.52 ± 9.91 | 65.75 ± 17.85 | |
| pH at diagnosis | N = 186 | N = 9 (4.84%) | N = 40 (21.50%) | N = 137 (73.66%) | 0.02* |
| | 7.27 ± 0.16 | 7.33 ± 0.19 | 7.33 ± 0.13 | 7.25 ± 0.16 | |

(Continues)

TABLE 1 (Continued)

| Characteristic | Total | HbA1c levels at baseline (mmol/mol) | | | P value (for difference by HbA1c at baseline) |
|---------------------------------------|--------------|-------------------------------------|------------------|------------------|---|
| | | <58 mmol/mol | 58-80 mmol/mol | >80 mmol/mol | |
| pH at diagnosis | N = 186 | N = 9 | N = 40 | N = 137 | 0.01** |
| Normal 7.3-7.45 | 98 (52.69%) | 5 (55.56%) | 31 (77.50%) | 62 (45.26%) | |
| Acidotic <7.3 | 80 (43.01%) | 2 (22.22%) | 8 (20.00%) | 70 (51.09%) | |
| Alkalotic >7.45 | 8 (4.30%) | 2 (22.22%) | 1 (2.50%) | 5 (3.65%) | |
| BMI at diagnosis (kg/m ²) | N = 232 | N = 11 (4.74%) | N = 56 (24.14%) | N = 165 (71.12%) | 0.01* |
| | 18.29 ± 3.62 | 21.26 ± 5.48 | 18.03 ± 2.83 | 18.18 ± 3.65 | |
| BMI WHO z-score at baseline | N = 330 | N = 33 (10.00%) | N = 109 (33.03%) | N = 188 (56.97%) | 0.02** |
| Thin | 70 (21.21%) | 5 (7.14%) | 19 (27.14%) | 46 (65.71%) | |
| Normal weight | 103 (31.21%) | 6 (5.83%) | 30 (29.13%) | 67 (63.05%) | |
| Obese/overweight | 157 (47.58%) | 22 (14.01%) | 60 (38.22%) | 75 (47.77%) | |

Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin; N, number of patients; pH, measure of acidity; WHO, world health organization.

^aBaseline: Period within 3 months of T1D diagnosis.

*Wald test (χ^2).

**Global Wald test (χ^2).

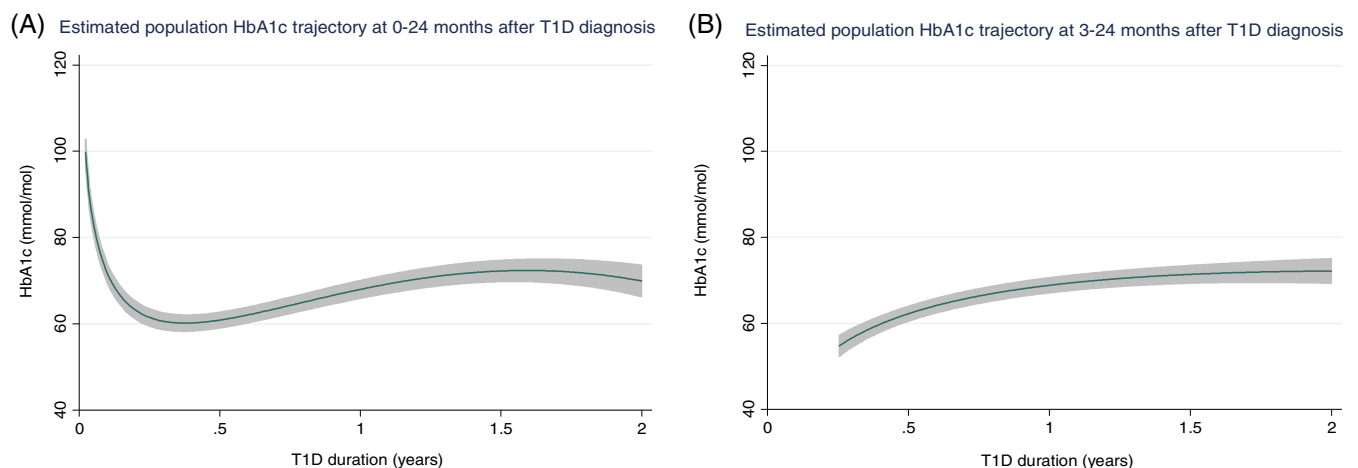


FIGURE 1 PANEL 1: Estimated HbA1c trajectories based on fractional polynomials. A, Estimated HbA1c trajectory of 253 patients followed from diagnosis. B, Estimated HbA1c trajectory of 335 patients followed from baseline

follow-up of 2 years from T1D diagnosis at the three sites, during the study period (2005-2015) were eligible for inclusion in our study at baseline.

However, in the analyses of data covering the 3-24 months period from diagnosis, a total of 335 patients (53.4% female) with 1627 HbA1c observations (mean 7.4 ± 2.0 HbA1c observations/participant) were eligible. Of these, 253 (75.5%) patients were followed from and had HbA1c measurements within first month of T1D diagnosis (See Table 1 for baseline characteristics). Insulin regimen may have been inaccurately documented for some patients and data on insulin dosage was missing, which restricted the analysis of this variable against our objectives. pH at diagnosis (mean \pm SD, 7.27 ± 0.16) was available for only 186/356 (52.25%) patients and 80 out of these 186 (43%) patients were acidotic. Mean BMI at diagnosis was 18.3 ± 3.6 (BMI WHO z-score at diagnosis

and at baseline was 0.46 ± 1.2 and 0.53 ± 1.3 respectively) and frequency of clinic visits from diagnosis ranged from 1 to 13. (See Table S2 for baseline characteristics by HbA1c tertiles).

The fractional polynomial model 1 fitted to HbA1c measurements taken 0-24 months post T1D diagnosis revealed that the initial, high HbA1c levels of the cohort dropped rapidly after diagnosis due to initiation of insulin treatment. However, subsequently after around three months of diagnosis, the population mean HbA1c levels rose steadily above the then (2005-2015) NICE recommended targets and remained high throughout the entire duration of follow-up. The model 2 fitted to HbA1c measurements 3-24 months gave similar results for that period (Figure 1).

We then examined the association of various predictor variables with HbA1c trajectories from 3 to 24 months of T1D diagnosis. At

TABLE 2 Predictors of glycemic control in children and adolescents from 3 to 24 months post-T1D diagnosis (MVA with predictor HbA1c at baseline)

| Predictor | Univariable analysis | | | Multivariable analysis (MVA) without interaction terms | | | MVA (with predictors showing significant interaction with sex, age at diagnosis or clinic) | | |
|--|----------------------|-------------------------|---------|--|------------------------|---------|--|-------------------------|---------|
| | N | Estimate (95% CI) | P-value | N | Estimate (95% CI) | P-value | N | Estimate (95% CI) | P-value |
| Sex (ref female) | 335 | 0.46 (-2.79 to 3.72) | 0.78* | | | | | | |
| Age at diagnosis (Ref 0-5 yrs) | 335 | | 0.01** | 330 | | 0.02** | 330 | | 0.04** |
| 6-11 yrs | | 0.96 (-2.92 to 4.84) | | | 0.59 (-3.11 to 4.28) | | | 0.44 (-3.23 to 4.11) | |
| 12-18 yrs | | 5.84 (1.65 to 10.02) | | | 5.05 (1.07 to 9.03) | | | 4.49 (0.53 to 8.45) | |
| Year of diagnosis (Ref pre 2011) 2011-2015 | 335 | | 0.001* | 330 | | 0.001* | 330 | | 0.001* |
| | | -7.47 (-10.63 to -4.31) | | | -6.09 (-9.17 to -3.01) | | | -9.43 (-13.63 to -5.23) | |
| Season of diagnosis (Ref Spring) | 335 | | 0.45** | | | | | | |
| Summer | | 1.71 (-3.08 to 6.51) | | | | | | | |
| Autumn | | 1.82 (-2.82 to 6.47) | | | | | | | |
| Winter | | 3.58 (-0.73 to 7.89) | | | | | | | |
| Ethnicity (Ref White) | 331 | | 0.002* | 330 | | 0.02* | 330 | | 0.01* |
| Non-white | | 5.46 (2.07 to 8.85) | | | 3.89 (0.66 to 7.13) | | | 5.37 (1.28 to 9.45) | |
| IMD (Ref 1 most deprived) | 333 | | 0.59** | | | | | | |
| 2 (moderate) | | 0.89 (-2.65 to 4.42) | | | | | | | |
| 3 (least deprived) | | -2.06 (-7.47 to 3.34) | | | | | | | |
| Clinic (ref clinic 3) | 335 | | 0.001** | 330 | | 0.02** | 330 | | 0.01** |
| 1 | | -0.53 (-6.05 to 4.99) | | | 2.43 (-3.12 to 7.97) | | | 11.48 (2.42 to 20.55) | |
| 2 | | 6.55 (3.08 to 10.02) | | | 4.66 (1.34 to 7.98) | | | 6.09 (0.12 to 12.06) | |
| Number of clinic visits ^a | 335 | 0.22 (0.03 to 0.41) | 0.02* | | | | | | |
| Insulin regimen(Ref > =3 inj. per day) | 333 | | 0.02** | | | | | | |
| 1-2 inj./day | | 0.62 (-2.13 to 3.36) | | | | | | | |
| Pump | | -7.64 (-13.18 to -2.10) | | | | | | | |
| HbA1c at diagnosis | 238 | 0.15 (0.07 to 0.23) | 0.001* | | | | | | |
| HbA1c at diagnosis (ref <58 mmol/mol) | 238 | | 0.02** | | | | | | |
| 58 to 80 | | 5.74 (-3.60 to 15.09) | | | | | | | |
| >80 mmol/mol | | 10.36 (1.59 to 19.14) | | | | | | | |
| HbA1c at baseline | 334 | 0.25 (0.17 to 0.33) | 0.001* | | | | | | |
| HbA1c at baseline (ref <58 mmol/mol) | 334 | | 0.001** | 330 | | 0.003** | 330 | | 0.001** |
| 58 to 80 | | 2.47 (-2.57 to 7.51) | | | 3.02 (-1.88 to 7.93) | | | 3.07 (-1.75 to 7.90) | |
| >80 mmol/mol | | 8.80 (3.84 to 13.76) | | | 7.55 (2.61 to 12.48) | | | 8.21 (3.30 to 13.12) | |

(Continues)

TABLE 2 (Continued)

| Predictor | Univariable analysis | | | Multivariable analysis (MVA) without interaction terms | | | MVA (with predictors showing significant interaction with sex, age at diagnosis or clinic) | | |
|---|----------------------|------------------------|---------|--|-------------------|---------|--|--------------------------|---------|
| | N | Estimate (95% CI) | P-value | N | Estimate (95% CI) | P-value | N | Estimate (95% CI) | P-value |
| HbA1c during 1 to 3 months after diagnosis | 230 | 0.37 (0.25 to 0.49) | 0.001* | | | | | | |
| HbA1c during 1 to 3 months after diagnosis (ref <58 mmol/mol) | 230 | | 0.001** | | | | | | |
| 58 to 80 | | 7.19 (3.01 to 11.36) | | | | | | | |
| >80 mmol/mol | | 14.26 (8.88 to 19.63) | | | | | | | |
| HbA1c at 2 to 3 months after diagnosis | 124 | 0.56 (0.40 to 0.71) | 0.001* | | | | | | |
| HbA1c at 2 to 3 months after diagnosis (ref <58 mmol/mol) | 124 | | 0.001** | | | | | | |
| 58 to 80 | | 12.87 (7.84 to 17.91) | | | | | | | |
| >80 mmol/mol | | 21.15 (13.05 to 29.26) | | | | | | | |
| pH at diagnosis (Ref normal pH 7.3–7.45) | 175 | | 0.71** | | | | | | |
| Acidotic <7.3 | | 1.80 (–2.84 to 6.44) | | | | | | | |
| Alkalotic >7.45 | | 2.65 (–8.43 to 13.74) | | | | | | | |
| BMI (WHO) z score at baseline (ref normal weight) | 309 | | 0.22** | | | | | | |
| Overweight/obese | | –2.27 (–6.26 to 1.73) | | | | | | | |
| Thin | | 1.41 (–3.38 to 6.20) | | | | | | | |
| Year of diagnosis # sex (Ref Females) | 330 | | | | | | | | 0.04** |
| Pre 2011 # Males | | | | | | | | –1.88 (–6.07 to 2.31) | |
| 2011–2015 # Males | | | | | | | | 5.38 (0.91 to 9.84) | |
| Ethnicity # clinic (Ref white # clinic 3) | 330 | | | | | | | | 0.05** |
| Non-white # Clinic 1 | | | | | | | | –13.84 (–24.94 to –2.75) | |
| Non-white # Clinic 2 | | | | | | | | –2.49 (–9.63 to 4.66) | |

Note: All models include ν and $\log^2 \nu$ functions of time as both fixed and random effects.

Abbreviations: BMI, Body mass index; HbA1c, glycated hemoglobin; IMD, Indices of multiple deprivation; pH, measure of acidity; Ref, reference group; WHO, World health organization.

^aClinic visits (range 2–13).

*Wald test (χ^2).

**Global Wald test (χ^2).

the univariable level, pubertal age (12-18 years) at diagnosis, year of diagnosis pre-2011, non-white ethnicity, clinic site, frequency of clinic visits, insulin regimen type, and higher HbA1c levels at diagnosis and during 0-3 months after diagnosis were significant predictors of higher mean HbA1c over the follow-up period (Table 2).

After adjustment for predictors that were statistically significant in univariable analyses, the following predictors of glycemic control remained statistically significant in a multivariable analysis (Table 2): age at diagnosis (12-18 years), earlier years of diagnosis (pre 2011), non-white ethnicity, HbA1c during the first 3 months after diagnosis, and clinic site.

The results were similar when the multivariable analyses were repeated in the sensitivity analyses with predictors: HbA1c tertiles at baseline (Table S3A) and HbA1c at diagnosis (Table S3B).

Additional univariable and multivariable sensitivity analyses for predictor variables from 1 to 3 months after diagnosis consistently revealed the following as significant predictors of poor glycemic control: year of diagnosis (pre-2011), clinic site, HbA1c, and BMI (WHO z score) at 1-3 months after diagnosis.

There was no effect modification when interaction with age at diagnosis, sex, or clinic site were added to the mixed initial (with each predictor variable) and multivariable models. However, interaction with ethnicity by clinic site showed some significance in both univariable ($P = .04$) and multivariable ($P = .05$) analyses. The interaction year of diagnosis by gender seems to have an effect of borderline significance in multivariable analyses ($P = .04$). Age at diagnosis by clinic interaction showed some significance ($P = .05$) in the univariable analyses and $P = 0.03$ in the sensitivity analyses when predictor HbA1c at diagnosis was added to the multivariable analyses (Table S3B).

We then examined the following predictors by including interactions with polynomial terms in time since diagnosis in the initial mixed models with each predictor variable: sex, age at T1D diagnosis, year of diagnosis, ethnicity, clinic site, insulin regimen, HbA1c level at diagnosis and baseline (also tertiles at baseline), and BMI (WHO) z score at baseline (Table S4). The interaction with polynomial time terms

allowed for the shapes of the HbA1c trajectories to differ between the compared groups. The following predictors had significant interactions with polynomial time terms: age at diagnosis, HbA1c at diagnosis (Figure 2) and HbA1c at baseline.

Interaction between age at diagnosis and polynomial time terms showed that prepubertal (6-11 years) and pubertal children (12-18 years) experienced a sharper increase in HbA1c after 3 months than preschool (0-5 years) aged children, leading to higher levels throughout the study period ($P = .001$) (Figure 2A).

There was a significant difference in HbA1c trajectories between those with low, moderate, and high HbA1c levels at diagnosis (Figure 2B) and baseline ($P = .001$ and $P = .01$ respectively). All children had a similar starting point at 3 months but, the glycemic control steadily deteriorated in those children with HbA1c levels above 7.5% (58 mmol/mol) at diagnosis or at baseline. But, there is some uncertainty in the HbA1c trajectory of those who had HbA1c levels <7.5% (<58 mmol/mol) at diagnosis or at baseline as there were only 13 (5.14%) and 38 (10.67%) patients in these groups at diagnosis and baseline respectively and the diagnosis details of these patients could not be verified. However, we found that the difference between HbA1c trajectories was of significance ($P = .02$) when the analyses were repeated by HbA1c tertiles at baseline (Figure S2)

4 | DISCUSSION

Our longitudinal, retrospective, cohort study of glycemic control during 3-24 months after T1D diagnosis in 356 children and adolescents of multi-ethnic backgrounds, receiving care; between January 1, 2005 and December 31, 2015; at a network of three diabetes clinics located in East London, United Kingdom. We used fractional polynomial modeling to estimate the non-linear mean HbA1c trajectories to identify the predictors (sociodemographic, biological and clinical) of glycemic control during the first 2 years of T1D diagnosis. We found that the partial remission period ends at around 3 months from diagnosis,

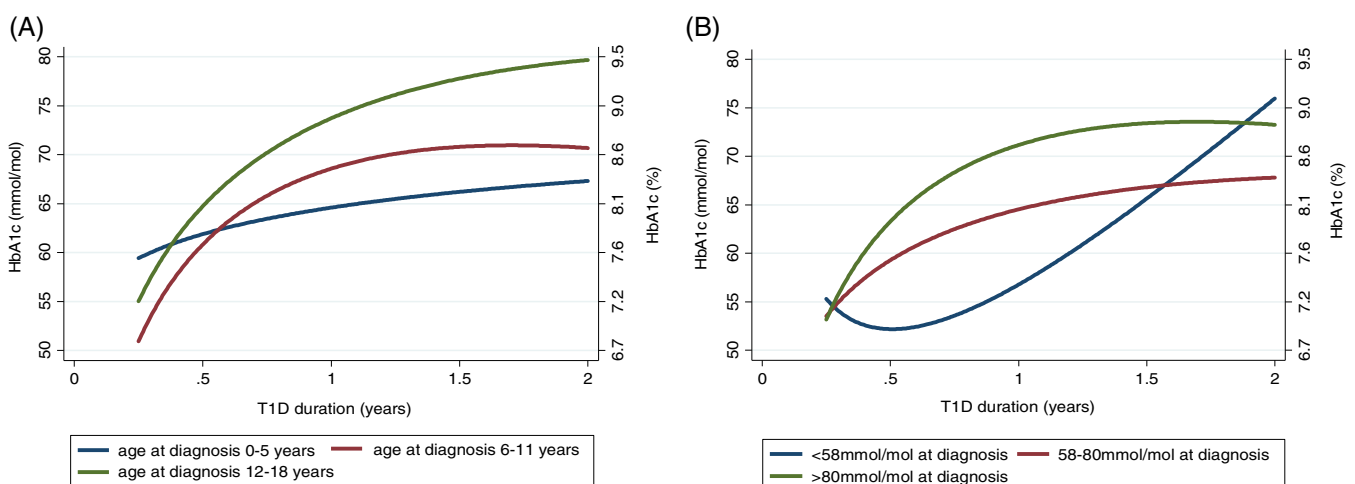


FIGURE 2 PANEL 2: Estimated HbA1c trajectories based on fractional polynomials by A, Age at diagnosis. B, HbA1c at diagnosis

and that independent risk factors of poorer glycemic control during the 2005-2015 study period were higher levels of HbA1c at baseline, higher age at diagnosis (12-18 years), non-white ethnicity, year of diagnosis (pre-year 2011), and clinic factors.

It is important to ensure good glycemic control from T1D onset, but lack of evidence on predictors of glycemic control restricts prediction of future glycemic trends and risk of complications in children and young people, thus hampering the proactive prognosis and management of glycemic control in high risk patients. Furthermore, glycemic control is an important outcome and an exposure and/or mediator of later-life outcomes. Previously, NICE recommended HbA1c targets below 7.5% (58 mmol/mol).¹⁹ However, since year 2015, NICE recommends achieving a target of HbA1c levels of 6.5% (48 mmol/mol) or below including during the honeymoon phase (period shortly after T1D diagnosis) when the existing beta cells of the pancreas continue to produce some insulin to help control blood glucose. Our study found that it was challenging for the cohort to achieve recommended blood glucose and HbA1c levels after the honeymoon period and during the first 24 months of T1D diagnosis during the study period (2005-2015) as indicated by other studies.^{20,21}

In this cohort of young children and adolescents with T1D, we found that higher HbA1c levels (>9.5%, ie, >80 mmol/mol) at diagnosis/baseline were associated with higher HbA1c levels during the first 24 months of T1D diagnosis. Elevated HbA1c levels at diagnosis may be due to delayed access to medical treatment and/or delayed T1D diagnosis but evidence suggests that better glycemic control can be achieved during this sensitive period through disease awareness and change of behaviors in diagnostic and care practice.^{22,23}

Children diagnosed at an older age (12 to 18 year olds) had significantly poorer glycemic control during the study period. Adolescence has proven to be yet another sensitive period which influences formation of enduring behaviors and diabetes self-management habits.²⁴ This may relate to a complex interaction of factors such as increased insulin resistance, eating disorders, psychological disturbances, and the psychosocial demands of adolescence leading to decreased adherence to management plans.^{25,26}

Children diagnosed pre-2011 had poorer glycemic control which may be due to older diagnostic testing, treatment, and recording strategies as reported by other studies.^{13,27} Additionally, it may indicate that being part of a network improved the glycemic outcomes of the patients registered at the three clinics, as the three clinics became part of a network only from 2012. However, this is a causal hypothesis which the currently reported data and analyses cannot address.

We also found that overweight or obese children had better glycemic control, although this effect was statistically non-significant. This is likely to reflect the association of weight gain during T1D treatment with better adherence to insulin regimens and therefore BMI may represent an indirect marker of good glycemic control. However, there is uncertainty in the HbA1c trajectory of underweight/thin children in our study as there were <10% children in this group. Evidence from other studies on the association of BMI with HbA1c is also inconclusive.²⁸⁻³⁰ Also, a small minority of patients may have been misclassified during the study period and may have had T2D, MODY or secondary diabetes.

Non-white ethnicity was associated with elevated HbA1c levels. This association is consistent with other studies and may be due to biological, cultural and lifestyle differences, sub-optimal treatment prescription or reluctance to try new therapy.³¹⁻³³ Also, some ethnicities may have an inherent genetic predisposition to adverse health outcomes from T1D.³⁴ The role of clinic in improving glycemic control in children with T1D (particularly ethnic minorities) and whether more frequent clinic visits would result in better care and adherence to treatment among the T1D patients from ethnic minority remains unclear.

However, we did find that patients at one of the clinics had better glycemic control than others and that more frequent clinic visits (univariable analyses) were associated with higher HbA1c levels. More frequent appointments for children with poor control may have been offered in some clinics. Other studies have indicated associations with glycemic control and clinic related factors.^{2,28,35} Some studies have also highlighted the active role of diabetes teams in achieving glycemic targets.^{36,37} Frequency of clinic attendance may be high in those patients living closer to the diabetes clinics. Poor or non-attendance is associated with elevated diabetes complications risk due to non-adherence to treatment in the high risk groups.³⁸

Details of insulin regimen such as injection frequency, pump treatment, dosage and treatment changes were missing which meant that we were restricted in our investigations of this variable against our research objectives, although, pump regimen (univariable analyses) was associated with lower HbA1c levels. However, sensitivity analysis with and without adjusting for insulin regimen did not affect our conclusions. It would be useful to investigate the benefits of intensive insulin treatment earlier on in the course of the disease management and whether early HbA1c levels tracks in later years and reduces the risk of vascular complications.

In our study we found that sex showed no association (univariable analyses) with glycemic control although interaction with year of diagnosis by sex (univariable and multivariable analyses) showed some association. This is contrary to the findings of some studies^{5,13,30}, whilst there are others who have reported no association^{28,35} between sex and HbA1c levels.

No association was seen between pH at diagnosis (proxy for DKA) and HbA1c levels during the 3-24 months from T1D diagnosis. Although this was also the conclusion of some studies,^{28,30,35} others have shown an association.³⁹⁻⁴¹ It was not clear if the general practitioners (GPs) managed the T1D symptoms in any of these patients prior to referral to the diabetes clinics for specialist care. We did not have access to GP prescription data to confirm if any form of glycemic control started prior to clinic diagnosis date although it would be extremely unusual in the United Kingdom for a GP to commence insulin treatment in a child with diabetes.

5 | STRENGTHS AND LIMITATIONS

Historically, mixed effects modeling have been used to describe trajectories of repeated outcomes within and between clustered individuals. But because glycemic trajectories are often non-monotonic and

non-linear, they require more flexible models to accurately investigate the factors which influence the HbA1c levels or the outcomes it is associated with. To our knowledge this is the first longitudinal study to investigate predictors of HbA1c during the first 24 months of T1D duration using mixed effects multilevel models with fractional polynomial time terms which allowed flexibility and parsimony in the modeling of non-linear trajectories. The application of fractional polynomials requires the comparison of many models for model selection and represents a situation of multiple testing. The modest sample size was suitable for the two step approach using fractional polynomials in multilevel modeling. However, the sample size limitation precluded the enhancement of complexity of fitting models with all covariates. Assessment of predictors of HbA1c was performed in a two-step approach, with polynomial terms selected in the first step and predictor selection performed in the second step. The effect estimates of present models may be biased due to the two-step procedure, and no adjustment has been made for multiple testing. Data were abstracted from routinely collected electronic medical records, thus limiting selection and recall bias. It was not possible to ascertain that the primary outcome or exposure was not associated with loss to follow-up. The total sample size was modest but exceeded the minimum ($N > 100$) suggested for multilevel modeling and may have limited the power to detect weaker associations. The study cohort was rich in ethnic diversity and an unusually high proportion of socially deprived population, which enabled us to study these predictors in greater detail but was also a limitation because there was less contrast.

Data was limited to patients receiving care between 2005 and 2015 at three diabetes clinics which formed a network in 2012. So the methods of data collection and recording may have differed and changed over the study period and may not be generalizable to other populations. The data used were from a dataset maintained for ongoing clinical use across the three clinic sites, and, as with most clinical datasets, was not subject to the detailed data checking that would be expected in a research dataset. We verified data where possible in association with the clinic physicians. However it was not practicable to examine and verify each individual clinical record. Additionally, it was not possible to investigate whether the disparity in the number of clinic visits and treatment across the study population was due to individual and/or clinic factors. This is a retrospective analysis of an observational study and residual confounding cannot be ruled out. Details of laboratory methods and instruments used across clinics between 2005 and 2015 could not be confirmed.

6 | CONCLUSIONS

Our study identified higher HbA1c levels at baseline, non-white ethnicity, clinic site, BMI, and year of diagnosis as major risk factors of poor glycemic control during the first 24 months of children diagnosed with T1D. Because higher HbA1c at T1D diagnosis is associated with poorer subsequent HbA1c levels and is associated with increased risk of developing complications, these findings could help clinicians, policy makers and researchers better understand the characteristics of type 1 diabetes and encourage quick identification of

high risk patients for consideration of appropriate individualized treatment strategy to meet the HbA1c targets during the 24 months following the diagnosis of T1D. These findings will also help explore the underlying explanations for poor glycemic outcomes so further efforts are made to overcome these differences.

7 | FUTURE RESEARCH

Further research into the reasons for differences in HbA1c outcomes is required. Also predictors of glycemic control in the first 3 months of diagnosis and beyond 2 years of diagnosis need further investigation.

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CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

AUTHOR CONTRIBUTIONS

V.M.P. designed the study, analyzed the data, and wrote the first draft of the manuscript. J.B. advised on the statistical plan and analyses. E.G. coordinated the acquisition of data and clarified data related queries. J.B., D.D., R.V., E.G., D.T.R., and T.S. contributed to the study

plan, analyses, and critical revision of the manuscript. All authors approved the final version. T.S. is the principal investigator on the funding from the National Institute for Health Research Policy Research Programme and lead for the Long Term Conditions theme of this work. T.S. and V.M.P. are guarantors of this work, and as such had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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