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Presentation to primary care during the prodrome of type 1 diabetes in childhood: A case-control study using record data linkage

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Objective: To evaluate primary care presentations during the prodrome (12 months prior to onset type-1 diabetes (T1D), with or without diabetic ketoacidosis [DKA]), to identify opportunities for earlier diagnosis.

Methods: This was a case-control study, linking 16 years of data from children (≤15 years) registered at diagnosis of T1D, and routinely collected primary care records in Wales (United Kingdom). Controls (without T1D) were matched on a 3:1 ratio. Conditional logistic regression modeling was used to compare characteristics occurring in cases (children with T1D) and controls; and cases that presented with/without DKA.

Results: A total of 1345 children with T1D (19% DKA) and 4035 controls were identified. During the 12 months prior to diagnosis, cases were 6.5 times more likely to have at least one primary care contact ($P < 0.001$). One to 30 days prior to diagnosis, contacts relating to blood tests, fungal conditions, respiratory tract infections (RTIs), urinary conditions, vomiting, and weight were independently associated with T1D, as were contacts relating to blood tests, between 91 and 180 days prior to diagnosis. Children with a contact up to a month prior to diagnosis, relating to RTIs, antibiotic prescriptions, and vomiting, were more likely to present in DKA, as were boys ($P = 0.047$).

Conclusion: There are opportunities in primary care for an earlier diagnosis of T1D in childhood. These data could be used to create a predictive diagnostic tool, as a potential aid for primary care health professionals, to prevent presentation in DKA.

KEYWORDS

childhood, diabetic ketoacidosis, primary care data linkage, prodrome, type 1 diabetes mellitus

1 | INTRODUCTION

Identifying children with potential new-onset type 1 diabetes (T1D) who need further investigation, out of the many children presenting with common childhood illnesses is a key challenge for general practitioners (GPs).[1,2] Although worldwide the incidence of T1D in childhood is rising at a rate of 3% per year,[3] it continues to be a relatively rare condition. T1D is an insidious condition, which may manifest in several ways, with subtle symptoms that can be attributed to other childhood illnesses and which may change with the developmental stage of a child. The four classic symptoms of polyuria, polydipsia, weight loss, and tiredness, may present independently, not at all, or in conjunction with other health concerns such as a viral or fungal infection, increasing the potential for misdiagnosis.

Abbreviations: ALF, anonymous linking field; CI, confidence interval; DKA, diabetic ketoacidosis; GP, general practitioner; OR, odds ratio; RTI, respiratory tract infection; SAIL, secure anonymised information linkage; T1D, type 1 diabetes; WIMD, Welsh Index of multiple deprivation.

Early diagnosis of T1D is critical to avoid children developing life-threatening diabetic ketoacidosis (DKA). Delayed diagnosis was attributed as the main cause of DKA at onset of T1D in a consensus statement from the American Diabetes Association.[4] DKA is associated with significant morbidity, mortality[5–8] and health service costs.[9,10] Children presenting in DKA are likely to have poor long-term prognosis[6–8] and their parents experience greater psychological distress.[11] The rate of DKA at onset of T1D varies across the world, from 10% to 70%[12] and has an inverse relationship with the incidence of T1D.[13] In the United Kingdom, 25% of children diagnosed with T1D present in DKA,[14] which is concordant with other economically developed countries.[4,15] This rate has remained consistent in the United Kingdom over the past 20 years,[16–18] despite efforts to raise awareness of the symptoms in community and clinical settings.[16,19,20]

A systematic review found diagnostic error as a significant risk factor for delayed diagnosis.[2] However, most studies relied on retrospective parental or clinical recall once a child was diagnosed, with associated potential for bias. A Canadian study[21] explored routinely collected primary care data for the 4 weeks prior to diagnosis and showed children newly diagnosed with T1D had significantly more medical encounters in the 4 weeks prior to diagnosis than matched controls, with 33% of children having had at least one medical encounter in the week preceding diagnosis. The most common reasons for the encounter were recorded as upper respiratory infections, urinary tract disorders, and gastroenteritis. A limitation of this study was that it only looked at a 4-week period prior to diagnosis, despite parents recalling that their children displayed subtle symptoms for many months prior to diagnosis.[22] They also did not examine differences between those who presented with and without DKA.

The aim of our study was to evaluate on a country-wide basis, the extent and reasons for contact between children and primary care physicians in Wales (United Kingdom), before diagnosis of T1D, using linkage of a prospectively collected primary care dataset to a national diagnostic dataset (Brecon Group Register). By comparing data in matched controls without T1D, we explored the potential to make an earlier diagnosis, with reduced risks of DKA. To our knowledge, this is the first large-scale study to use prospectively collected primary care data to explore the pathway to diagnosis of childhood T1D, including those who present in DKA, for an extensive period prior to diagnosis.

2 | METHODS

Ethical approval was granted by London—Westminster Research Ethics Committee ref 15/LO/2054.

2.1 | Study design and data sources

We conducted a matched case-control study of children aged 15 years and under using the Secure Anonymised Information Linkage (SAIL) Databank (Swansea University). The SAIL Databank contains records of over 5 million people and holds data from about 75% of Welsh GPs over the last 15 years (period of coverage varies by primary care practice as not all practices were recruited to provide data to SAIL at the same time).

GPs record details of any symptoms, diagnoses, medications, or tests, through specific electronic patient record software systems, at the time of the consultation. This routinely collected data is stored as a series of Read codes and free text. However, it is only possible to use the Read codes recorded in subsequent analyses. GPs who agree to share their data with SAIL submit full historical extracts of all coded data to SAIL annually.

Records within SAIL are anonymized and linkable with an anonymous linking field (ALF), which allows individuals to be tracked over time and across datasets, while ensuring researchers have no access to any personal identifiable data.[23,24] Individuals are linked within SAIL using National Health Service number, name, gender, date of birth, and postcode. We obtained the Welsh Index of Multiple Deprivation (WIMD) quintile for individuals in the study.[25] WIMD is an area-based measure of socioeconomic inequality. Cases and controls were required to have GP data available in SAIL for the 12 months leading up to the index date.

Cases were defined as children 15 years old and under, with T1D, resident in Wales, at the time of diagnosis, and were identified from the Brecon Group Register (Welsh Pediatric Diabetes Interest Group). The Brecon Group Register was established in 1995 and contains consented demographic data from 98% of all newly diagnosed cases of children 15 years old and under with T1D, resident in Wales, including whether they presented in DKA (pH < 7·30).[16] There have been two major ascertainment analyses undertaken using a two-source capture-recapture model with data from pediatricians and primary care. Ascertainment of cases was 98.5% in those diagnosed from 1995 to 2005 and on a second assessment 98.1% from 1995 to 2012.[26]

A contemporary dataset was created by linking the Brecon Group Register existing diagnostic dataset to the SAIL Databank to provide a unique dataset of children aged 0 to 15 years in Wales diagnosed with T1D in a 16-year period between January 2000 and December 2015.

We aimed to identify three controls for each case. Controls were children identified from the GP data within SAIL without T1D, matched on birth date (within 1 year), gender, and primary care practice (at time of subject's diagnosis with T1D). An index date was created for the matched controls using the date of diagnosis of the children with T1D. The resulting dataset therefore contained all primary care contact records in the 12 months prior to diagnosis for children diagnosed with T1D (including those diagnosed in DKA) and a matched sample of children without T1D.

2.2 | Definition of a primary care contact

A primary care contact was defined as one primary care event per day identified by unique date and a Read code. Primary care events that did not have an interpretable Read code were included as contacts. We did not include events relating to administrative tasks, repeat prescriptions, or consultations where there was no contact with the patient.

2.3 | Grouping read codes

Read codes for presenting features that might be associated with developing T1D in childhood were grouped. The research team agreed

which symptoms, diagnoses, examinations, tests, and prescriptions should be included within each group based on clinical experience and a review of the literature (Table 1). These variables are referred to as characteristics throughout this manuscript.

Read codes associated with medications prescribed for asthma were included as a benchmark variable. Read codes included within each grouping are listed as supplementary material (Appendix S1).

2.4 | Time periods

To evaluate the prodrome, five specific time periods prior to the index date were predetermined. These were the day of diagnosis, and 1 to 30 days, 31 to 90 days, 91 to 180 days, and 181 to 366 days prior to the day of diagnosis.

2.5 | Statistical methods

Assuming a medium effect size (odds ratio [OR] = 1.5), a moderately low prevalence rate of the presenting characteristic of 30% in the control group, matching three controls per case and using a two sided 5% alpha and 80% power, we required 322 children with T1D (using the sampsi_mcc command in STATA 15).[27]

Baseline demographic data (age, gender, WIMD deprivation quintile) and number of primary care contacts in the 12 months prior to the index date were used to describe the cases and controls. A univariable conditional logistic regression model was used to compare the event of a characteristic (prodrome) associated with T1D (cases); ORs alongside 95% confidence intervals (CIs) are presented. Characteristics associated with T1D at the 10% significance level were entered into a multivariable conditional logistic regression model. Models were developed for each of the prodromal time periods. We used a cut off of less than 1% prevalence in cases to exclude characteristics from the model.

TABLE 1 Description of characteristics

Characteristic	Includes	Excludes
Abdomen	Symptoms or diagnoses (eg, colic, epigastric pain) or abdominal examination	
Antibiotics	All prescriptions for antibiotics	
Blood tests	Test requests, laboratory procedures, all test results	
Constipation	Symptoms or diagnoses (eg, constipated) or prescriptions (eg, lactulose, macrogol)	Change in bowel habit
Fungal	Diagnoses (eg, candidiasis, dermatophytosis) or prescriptions (eg, micronazole, clotrimazole)	
Headache	Symptoms or diagnoses (eg, migraine, cerebral oedema)	
Respiratory tract infection	Symptoms or diagnoses (eg, upper/lower respiratory tract infection, otitis media, temperature) or examinations (eg, rate of respiration)	
Thirst	Symptoms or diagnoses (eg, excessive fluid intake, polydipsia, advice about fluid intake)	
Tiredness	Symptoms or diagnoses (eg, tiredness, malaise, lethargy, fatigue)	
Urinary	Symptoms or diagnoses (eg, urinary tract infection, polyuria) or prescriptions (eg, nitrofurantoin, trimethoprim and desmopressin) or tests, results	
Vomiting/ nausea	Symptoms or diagnoses of nausea/vomiting	Diarrhea and vomiting combined
Weight	Symptoms or diagnoses (eg, reduced appetite, weight loss, anorexia) or measures (eg, body mass index)	Weight increasing
Benchmark variable	Includes	Excludes
Asthma	All prescriptions for asthma	

2.6 | Diabetic ketoacidosis

A secondary aim was to explore the risks associated with presenting in DKA. Given that 19% of children diagnosed with T1D were in DKA at diagnosis (260 in DKA, 1085 not in DKA) our dataset had sufficient power to observe medium effect sizes for around 20 presenting characteristics. Characteristics of presenting in DKA at diagnosis were examined and associations between the prodrome for children presenting in DKA were analyzed using the same approach as for the matched case-control study.

All analyses were performed using IBM SPSS Statistics (IBM CORP, Armonk, New York)[28] and STATA Statistical (USASTATA CORP, College Station, Texas) software, version 15.[27]

Reporting adheres to STROBE for case-controls and RECORD guidelines for reporting routine data.

3 | RESULTS

Between 15 January 2000 and 8 October 2015, 3674 children were identified in the Brecon Group Register and eligible for inclusion (Figure 1). A total of 148 children were excluded due to data errors, inability to match within SAIL, and missing data. A further 2041 (55.5%) children were excluded because they did not have 12 months of GP data leading up to diagnosis. This is because the number of primary care practices submitting data to SAIL were far fewer at the turn of this century. Eligible children were comparable with those excluded in terms of age, gender, and social deprivation.

We identified 1488 cases with T1D (19% presenting in DKA) and 4464 matched controls. We excluded 143 cases (and 429 corresponding matched controls) because they had a coded diagnosis for T1D or a prescription for insulin prior to their date of diagnosis in the Brecon Group Register data. The final study population therefore comprised 5380 children (1345 children with T1D; 260 [19%] presenting in DKA) and 4035 matched controls (Figure 1). There were 57 520 primary care events relating to the 5380 children in the study population.

Demographics for the cases and controls show that that they were well matched (Table 2). The mean age of children at the time of diagnosis of T1D was 8.7 years (SD 3.7) and there were more males

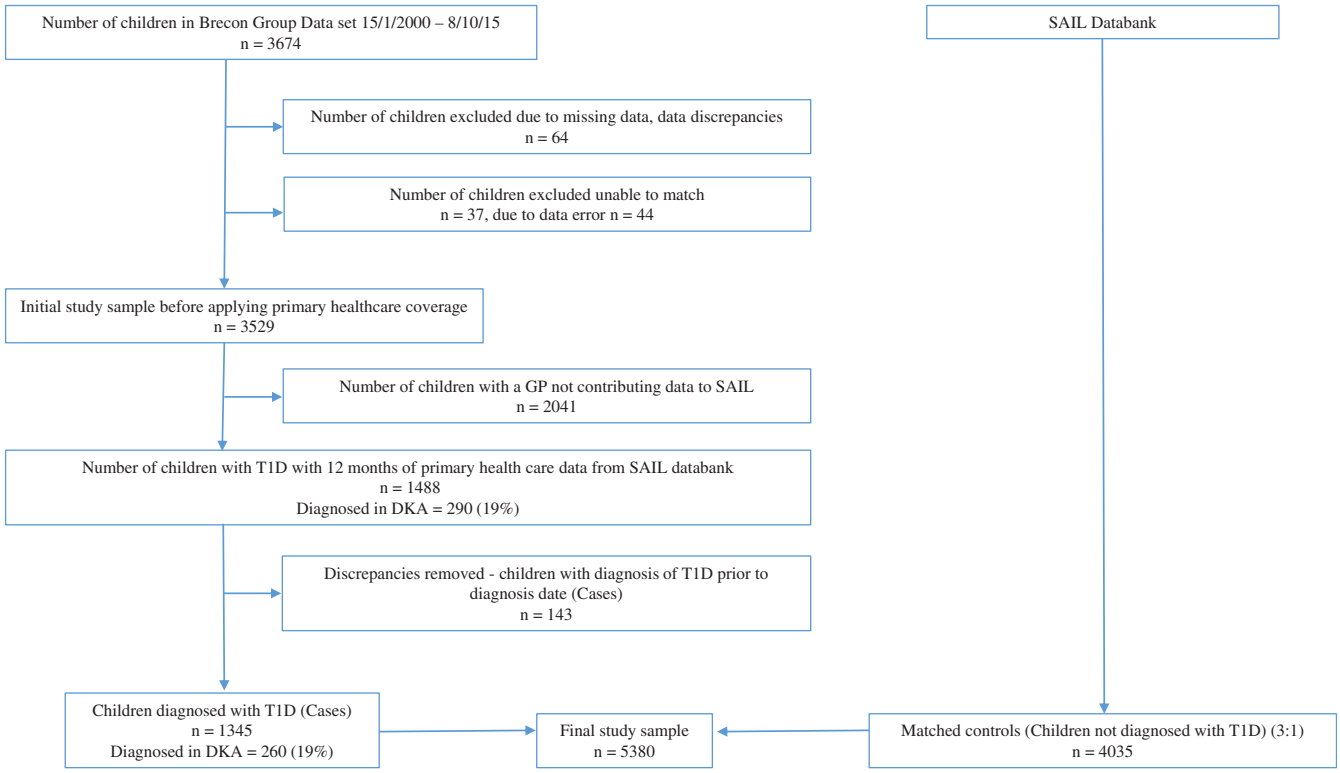

FIGURE 1 Flow diagram of individuals included in the study

(53%) than females (47%). During the 12 months prior to diagnosis, 1294 (96%) of children who developed T1D had at least one primary care contact, compared to 3261 (81%) of the matched controls (OR 6.50 [95% CI 4.84 to 8.73]; $P < 0.001$). Cases also had more contacts with a median of 4 (interquartile range: 2-8) compared to 3^{2-7} in the controls.

3.1 | Characteristics predicting T1D in children by time period

Table 3 shows the proportion of cases and controls presenting with at least one event by characteristics and by the specific time periods prior to the index date (date of T1D diagnosis) alongside unadjusted

TABLE 2 - Demographics of children with type 1 diabetes and matched controls

		Cases (T1 diabetes) (n = 1345)			
Demographics	**Controls (n = 4035)**	**Total**	**No DKA n = 1085**	**DKA n = 260**	**OR (95% CI)**
Age at diagnosis (y) mean (SD)	8.7 (3.7)	8.7 (3.7)	8.7 (3.6)	8.5 (4.0)	
<2 years, N (%)			23 (2.1)	18 (6.9)	3.19 (1.67-6.09)
2 to <6			219 (20.2)	46 (17.7)	0.86 (0.59-1.24)
6 to <10			321 (29.6)	68 (26.2)	0.86 (0.62-1.20)
10 to 15			522 (48.1)	128 (49.2)	Ref
Gender					
Females	1884 (46.7)	628 (46.7)	521 (48.0)	107 (41.2)	Ref
Males	2151 (53.3)	717 (53.3)	564 (52.0)	153 (58.8)	1.32 (1.004-1.74)
Social deprivation (WIMD quintile)					
1 (least deprived)	887 (22.0)	287 (21.3)	229 (21.1)	58 (22.3)	Ref
2	863 (21.4)	287 (21.3)	235 (21.7)	52 (20.0)	0.87 (0.58-1.32)
3	823 (20.4)	273 (20.3)	219 (20.2)	54 (20.8)	0.97 (0.64-1.47)
4	676 (16.8)	223 (16.6)	181 (16.7)	42 (16.2)	0.92 (0.59-1.43)
5 (most deprived)	786 (19.5)	275 (20.4)	221 (20.4)	54 (20.8)	0.96 (0.64-1.46)
Primary care contacts over past 12 months (incl. day of diagnosis)					
None	774 (19.2)	51 (3.8)	40 (3.7)	11 (4.2)	Ref
At least one:	3261 (80.8)	1294 (96.2)	1045 (96.3)	249 (95.8)	0.87 (0.44-1.71)
Median (IQR) contacts	3 (2-7)	4 (2-8)	4 (2-8)	4 (2-7)	

For categorical variables, data are number (%).

TABLE 3 Univariable analyses of children who had at least one unique primary care contact under each characteristic by time prior to diagnosis of T1 diabetes n (%)

	Day of diagnosis				1 to 30 days prior to diagnosis				31 to 90 days prior to diagnosis				91 to 180 days prior to diagnosis				181 to 366 days prior to diagnosis			
Characteristic	T1D cases	Controls	OR (95%CI)	*P* value	T1D cases	Controls	OR (95%CI)	*P* value	T1D cases	Controls	OR (95%CI)	*P* value	T1D cases	Controls	OR (95%CI)	*P* value	T1D cases	Controls	OR (95%CI)	*P* value
Abdomen	15 (1.1)	1 (<1.0)	45.0 (5.9-340.6)	<0.001	13 (1.0)	16 (<1.0)	2.5 (1.2-5.3)	0.016	8 (<1.0)	21 (<1.0)	–	–	15 (1.1)	36 (<1.0)	1.3 (0.7-2.3)	0.468	33 (2.5)	72 (1.8)	1.4 (0.9-2.2)	0.114
Antibiotics	17 (1.3)	5 (<1.0)	1.9 (1.5-2.4)	<0.001	122 (9.1)	210 (5.2)	1.9 (1.5-2.4)	<0.001	118 (8.8)	323 (8.0)	1.1 (0.9-1.4)	0.359	151 (11.2)	481 (11.9)	0.9 (0.8-1.1)	0.483	300 (22.3)	880 (21.8)	1.0 (0.9-1.2)	0.694
Asthma meds	8 (<1.0)	10 (<1.0)	–	–	55 (4.1)	165 (4.1)	1.0 (0.7-1.4)	0.999	95 (7.1)	271 (6.7)	1.1 (0.8-1.3)	0.661	126 (9.4)	334 (8.3)	1.1 (0.9-1.4)	0.218	198 (14.7)	552 (13.7)	1.1 (0.9-1.3)	0.340
Blood tests	248 (18.4)	0 (0)	–	–	120 (8.9)	23 (<1.0)	20.7 (12.4-34.4)	<0.001	12 (<1.0)	28 (<1.0)	–	–	23 (1.7)	39 (1.0)	1.8 (1.1-3.0)	0.029	41 (3.0)	85 (2.1)	1.5 (1.0-2.2)	0.046
Blood (fasting tests only)	20 (1.5)	0 (0)	–	–	34 (2.5)	0 (0)	–	–	1 (<1.0)	1 (<1.0)	–	–	5 (<1.0)	2 (<1.0)	–	–	3 (<1.0)	5 (<1.0)	–	–
Constipation	3 (<1.0)	1 (<1.0)	–	–	13 (1.0)	17 (<1.0)	2.3 (1.1-4.7)	0.024	10 (<1.0)	37 (<1.0)	–	–	7 (<1.0)	41 (1.0)	–	–	17 (1.3)	68 (1.7)	0.7 (0.4-1.3)	0.275
Fungal	16 (1.2)	2 (<1.0)	15.1 (3.6-63.3)	<0.001	49 (3.6)	16 (<1.0)	9.7 (5.4-17.3)	<0.001	25 (1.9)	44 (1.1)	1.7 (1.0-2.8)	0.032	19 (1.4)	67 (1.7)	0.8 (0.5-1.4)	0.529	39 (2.9)	125 (3.1)	0.9 (0.7-1.3)	0.712
Headache	1 (<1.0)	0 (0)	–	–	8 (<1.0)	0 (0)	–	–	8 (<1.0)	10 (<1.0)	–	–	6 (<1.0)	12 (<1.0)	–	–	12 (<1.0)	26 (<1.0)	–	–
RTI	33 (2.5)	7 (<1.0)	14.1 (6.3-32.0)	<0.001	100 (7.4)	168 (4.2)	1.9 (1.5-2.5)	<0.001	102 (7.6)	294 (7.3)	1.0 (0.8-1.3)	0.704	121 (9.0)	438 (10.9)	0.8 (0.6-1.0)	0.046	282 (21.0)	841 (20.8)	1.0 (0.9-1.2)	0.918
Thirst	144 (10.7)	0 (0)	–	–	48 (3.6)	0 (0)	–	–	0 (0)	0 (0)	–	–	1 (<1.0)	1 (<1.0)	–	–	0 (0)	3 (<1.0)	–	–
Tiredness	14 (1.0)	0 (0)	–	–	11 (<1.0)	0 (0)	–	–	1 (<1.0)	1 (<1.0)	–	–	2 (<1.0)	3 (<1.0)	–	–	5 (<1.0)	4 (<1.0)	–	–
Urinary	320 (23.8)	0 (0)	–	–	133 (9.9)	50 (1.2)	9.0 (6.4-12.7)	<0.001	37 (2.8)	64 (1.6)	1.8 (1.2-2.7)	0.007	41 (3.0)	91 (2.3)	1.4 (0.9-2.0)	0.102	72 (5.4)	164 (4.1)	1.3 (1.0-1.8)	0.045
Nausea/vomiting	24 (1.8)	0 (0)	–	–	18 (1.3)	5 (<1.0)	10.80 (4.01-29.09)	<0.001	5 (<1.0)	13 (<1.0)	–	–	5 (<1.0)	35 (<1.0)	–	–	13 (1.0)	41 (1.0)	0.9 (0.5-1.8)	0.872
Weight	118 (8.8)	1 (<1.0)	354.0 (49.5-2533.9)	<0.001	72 (5.4)	24 (<1.0)	12.07 (7.10-20.52)	<0.001	22 (1.6)	49 (1.2)	1.4 (0.8-2.3)	0.237	30 (2.2)	71 (1.8)	1.3 (0.8-2.1)	0.248	61 (4.5)	147 (3.6)	1.3 (0.9-1.9)	0.104

OR and 95% CI. Figure 2 shows the results from the multivariable analyses. On the day of the diagnosis, five medical characteristics (relating to the abdomen, antibiotic prescriptions, fungal conditions, respiratory tract infections [RTIs], and weight) were shown to be more prevalent in cases with all remaining independently associated with a new diagnosis of T1D. Blood tests, thirst, tiredness, urinary conditions, and vomiting/nausea on the day of diagnosis were also more prevalent in cases but it was not possible to include these in the model as they were not present in controls and it is not possible to calculate an OR with a zero value.

One to 30 days prior to the index date, 628 (46.7%) cases and 923 (22.9%) controls had at least one primary care contact and six medical characteristics (relating to blood tests, fungal conditions, RTIs, urinary conditions, vomiting/nausea, and weight) were associated with a subsequent diagnosis of T1D, all having strong significant independent predictive value (Figure 2). Fasting blood tests and thirst were also more prevalent in cases, but it was not possible to include these in the model as they were not present in controls.

Between 31 and 90 days, 91 and 180 days, and 181 and 360 days prior to diagnosis, having at least one primary care contact were similar in cases and controls (557 [41.4%] vs 1473 [36.5%], 649 [48.3%] and 1913 [47.4%], and [68.1%] and 2642 [65.5%] respectively). Between 31 and 90 days prior to diagnosis, two characteristics (fungal and urinary conditions) were higher in cases (Table 3) but only urinary conditions was independently associated with a diagnosis of T1D (Figure 2). For the time period of 91 to 180 days both blood tests and RTIs were associated with T1D but only blood tests were independently predictive. For 181 to 360 days prior to diagnosis, blood tests and urinary conditions were both associated with T1D, but neither was independently predictive.

3.2 | Characteristics predicting children who present in DKA at diagnosis by time period

Table 2 shows the characteristics of the individual patients by DKA at diagnosis or not. For children presenting in DKA, children under 2 years old were significantly more likely to present in DKA than older age categories and more males presented in DKA.

Table 4 shows presenting characteristics by the specific time periods prior to the date of diagnosis for children with T1D in DKA or not at diagnosis. Independent of age and gender, children with a primary care contact on the day of diagnosis relating to RTIs or vomiting/nausea were significantly more likely to present in DKA than children who did not (Figure 3). Children with a primary care contact relating to blood tests, thirst, and urinary conditions on the day of diagnosis were significantly less likely to present in DKA.

One to 30 days prior to the date of diagnosis, children with a primary care contact relating to antibiotics, and vomiting/nausea were significantly more likely to present in DKA. Children with a primary care contact relating to urinary conditions were significantly less likely to present in DKA.

In the 31 to 90, and 91 to 180 days period prior to diagnosis, children prescribed antibiotics were significantly less likely to present in DKA than children who did. In the 181 to 366 days period prior to diagnosis, children attending a primary care contact relating to urinary

conditions were significantly less likely to present in DKA than those who did not.

4 | DISCUSSION

This study of prospectively collected primary care data linked to a population-based pediatric diabetes diagnostic register has shown that for up to 12 months prior to diagnosis, children who went on to be diagnosed with T1D, were more likely to have contact with primary care for a range of specific reasons, than children who were not diagnosed with T1D. Furthermore, up to 30 days prior to diagnosis, children who presented in DKA, were more likely to have a primary care contact relating to RTIs, vomiting and a prescription for antibiotics. These findings together can be used to develop a prediction model for use in primary care to promote an earlier diagnosis of diabetes while reducing the risk of presentation in DKA.

4.1 | Strengths and weaknesses of the study

By analyzing data from 12 months prior to diagnosis, we have identified a longer prodrome of symptoms (up to 6 months) than is usually assumed. Our data from the Brecon Group Register is a robust, country-wide hospital recorded dataset (98% complete coverage of all known childhood-onset cases),[29] and our prospective collection of this diagnostic dataset likely provides an accurate date of diagnosis, as it is recorded by diabetes healthcare professionals at the time of diagnosis. Another strength of our study is that it uses prospectively collected primary care data and therefore the results will be less prone to the bias and inaccuracies of recall which influence many other studies on this topic.[2]

One limitation of the primary care dataset is the lack of control over the quality of the data collected. In our contemporary dataset, a discrepancy in the date of diagnosis affected 10% of the sample. However, the DKA rate was unaltered by removal of these children from the analyses, so it seems unlikely that these individuals had differing characteristics which would have affected the findings. In addition, we had to exclude 55.5% of the children registered on the Brecon Cohort dataset because their GP was not submitting data to SAIL preceding diagnosis. However, all children excluded from the study were comparable with eligible children, in terms of age, gender, and social deprivation.

A final weakness of analyzing prospective, routinely collected data is that it is not possible to ascertain certain details of consultations, such as why a test was conducted, what dialogue took place at the time of the consultation, and whether a primary care physician had a suspicion of any particular condition.

4.2 | Results of the study in context

The study was conducted in a UK-context. However, early recognition of T1D in primary care, to prevent presentation in DKA at diagnosis, remains a global issue. Therefore, the results of this study are likely relevant to physicians world-wide, regardless of models of primary

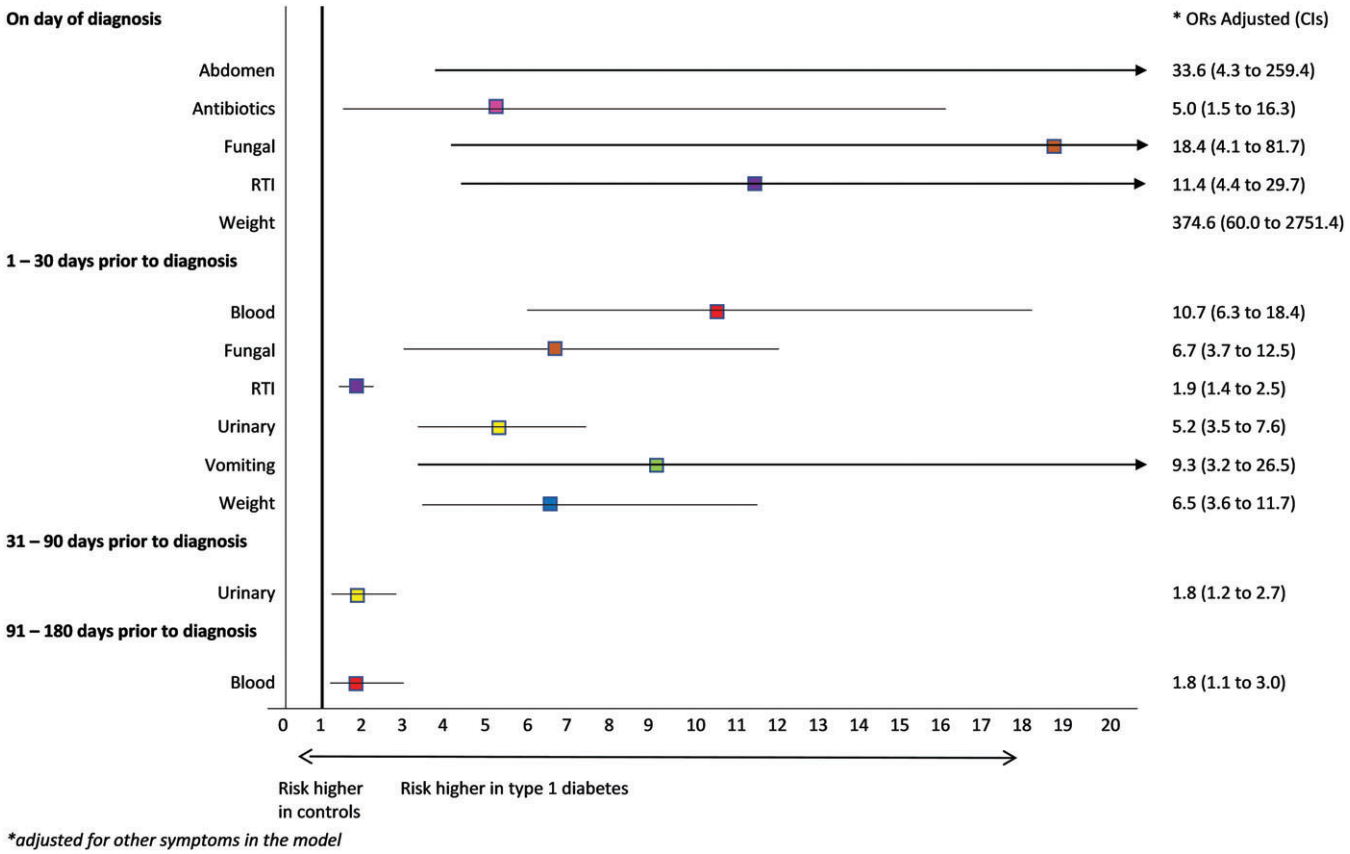

FIGURE 2 Characteristics associated with new diagnosis of type 1 diabetes vs matched controls in children: by time period prior to diagnosis of type 1 diabetes

TABLE 4 Univariable analyses of children presenting in DKA or not in DKA, with at least one contact with primary care for each characteristic n (%)

Characteristic	Day of diagnosis				1 to 30 days prior to diagnosis				31 to 90 days prior to diagnosis				91 to 180 days prior to diagnosis				181 to 366 days prior to diagnosis			
	Not in DKA	DKA	OR (95%CI)	*P* value	Not in DKA	DKA	OR (95%CI)	*P* value	Not in DKA	DKA	OR (95%CI)	*P* value	Not in DKA	DKA	OR (95%CI)	*P* value	Not in DKA	DKA	OR (95%CI)	*P* value
Abdomen	12 (1.1)	3 (1.2)	1.0 (0.3-3.7)	0.947	11 (1)	2 (<1)	–	–	8 (0.7)	0 (0)	–	–	15 (1.4)	0 (0)	–	–	33 (3)	0 (0)	–	–
Antibiotics	12 (1.1)	5 (1.9)	1.8 (0.6-5.0)	0.296	85 (7.8)	37 (14.2)	1.9 (1.3-2.9)	0.001	105 (9.7)	13 (5.0)	0.5 (0.3-0. 9)	0.019	132 (12.2)	19 (7.3)	0.6 (0.3-0.9)	0.028	243 (22.4)	57 (21.9)	1.0 (0.7-1.4)	0.869
Asthma meds	8 (0.7)	0 (0)	–	–	42 (3.9)	13 (5)	1.3 (0.7-2.5)	0.410	79 (7.3)	16 (6.2)	0.8 (0.5-1.5)	0.524	103 (9.5)	23 (8.8)	0.78 (0.5-1.2)	0.247	168 (15.5)	30 (11.5)	0.7 (0.5-1.1)	0.108
Blood tests (fasting only)	216 (19.9) 18 (1.7)	32 (12.3) 2 (<1)	0.6 (0.4-0.8)	0.005	108 (10) 33 (3)	12 (4.6) 1 (<1)	0.4 (0.2-0.8) –	0.008 –	9 (0.8) 1 (0.1)	3 (1.2) 0 (0)	1.4 (0.4-5.2) –	0.619 –	21 (1.9) 5 (0.5)	2 (<1) 0 (0)	–	–	33 (3)	8 (3.1)	0.4 (0.1-1.7)	0.209
Constipation	2 (0.2)	1 (<1%)	–	–	8 (0.7)	5 (1.9)	2.6 (0.9-8.1)	0.091	9 (0.8)	1 (<1)	–	–	7 (0.6)	0 (0)	–	–	16 (1.5)	1 (<1)	–	–
Fungal	15 (1.4)	1 (<1)	–	–	35 (3.2)	14 (5.4)	1.7 (0.9-3.2)	0.099	19 (1.8)	6 (2.3)	1.3 (0.5-3.4	0.552	18 (1.7)	1 (<1)	–	–	33 (3)	6 (2.3)	0.2 (0.0-1.7)	0.152
Headache	0 (0)	1 (<1)	–	–	6 (0.6)	2 (<1)	–	–	7 (0.6)	1 (<1)	–	–	6 (0.6)	0 (0)	–	–	12 (1.1)	0 (0)	–	–
RTI	17 (1.6)	16 (6.2)	4.1 (2.1-8.3)	<0.001	70 (6.5)	30 (11.5)	1.9 (1.2-3.0)	0.006	83 (7.6)	19 (7.3)	1.0 (0.6-1.6)	0.852	97 (8.9)	24 (9.2)	1.0 (0.7-1.7)	0.883	226 (20.8)	56 (21.5)	1.0 (0.7-1.7)	0.883
Thirst	133 (12.3)	11 (4.2)	0.3 (0.2-0.6)	<0.001	40 (3.7)	8 (3.1)	0.8 (0.4 to 1.8)	0.635	0 (0)	0 (0)	–	–	1 (0.1)	0 (0)	–	–	0 (0)	0 (0)	–	–
Tiredness	11 (1.0)	3 (1.2)	–	–	8 (0.7)	3 (1.2)	1.6 (0.4-6.0)	0.507	1 (0.1)	0 (0)	–	–	2 (0.2)	0 (0)	–	–	4 (0.4)	1 (<1)	–	–
Urinary	278 (25.6)	42 (16.2)	0.6 (0.4-0.8)	0.001	124 (11.4)	9 (3.5)	0.3 (0.1-0.6)	<0.001	32 (2.9)	5 (1.9)	0.7 (0.3-1. 7)	0.367	40 (3.7)	1 (<1)	–	–	66 (6.1)	6 (2.3)	0.4 (0.2-0.9)	0.020
Vomiting/nausea	8 (0.7)	16 (6.2)	8.8 (3.7-20.9)	<0.001	9 (0.8)	9 (3.5)	4.3 (1.7-10.9)	0.002	5 (0.5)	0 (0)	–	–	3 (0.3)	2 (<1)	–	–	10 (0.9)	3 (1.2)	2.8 (0.5-16.8)	0.261
Weight	94 (8.7)	24 (9.2)	1.1 (0.7-1.7)	0.772	61 (5.6)	11 (4.2)	0.7 (0.4-1.4)	0.372	21 (1.9)	1 (<1)	–	–	26 (2.4)	4 (1.5)	0.6 (0.2-1.8)	0.404	52 (4.8)	9 (3.5)	0.6 (0.2-1.8)	0.404

care or health service provision. Our findings are consistent with a Canadian study that found children were more likely to be diagnosed with a RTI, urinary tract infections and disorders, or gastrointestinal disorder in the 4 weeks prior to diagnosis of T1D.[21] In addition, in the Canadian study, almost 50% of the children did not see their physician within a month of diagnosis, which is comparable to 53% in our UK-based study. Similar findings have just been reported from an analysis of primary care consultations in England, in which 35% of children had an encounter in the 7 days prior to diagnosis.[30] This study focused on the classical warning signs of T1D,[31] whereas by contrast, our study evaluated a much wider range of characteristics, reflecting the clinical challenge GPs face when trying to recognize this deceptive condition.

Our study is unique in exploring a prolonged period prior to diagnosis, in terms of numbers of contacts, as well as, the characteristics of consultations children have with primary care. This is especially novel with regards to looking at the differences of children who presented in DKA and those that did not. Children who presented in DKA, were more likely to have had a consultation relating to RTIs, antibiotic prescriptions, and vomiting, in the 30 days prior to diagnosis. It is surprising that these particular differences presented some considerable time before diagnosis and are unlikely to be a misinterpretation of the well-recognized signs of DKA, including Kussmaul breathing, which are only likely to arise once the patient has become significantly acidotic and clinically ill in the final hours before presentation.

Another surprising result from our study is that boys were more likely to present in DKA, in contrast to other studies which found no gender differences.[21,32] This might be explained by the fact that in the month preceding diagnosis boys had less contact with primary care, perhaps reflecting a possible cultural belief that boys are more resilient than girls, and therefore less likely to be taken by their parents for assessment. Other studies have also reported that older adolescent boys are less likely to seek clinical support when experiencing ill-health.[33,34]

4.3 | Implications for future research

Overall our results suggest that for some children there may be a prolonged opportunity for an earlier diagnosis. These results have important public health implications. They provide robust evidence to inform development of interventions to raise awareness in primary care about how a child may present with new-onset T1D.[35] This information may be used to refine previous interventions that have been developed to raise public and primary care professional awareness of the symptoms of T1D.[20] Furthermore, using appropriate modeling techniques, the results will allow development of a robust, potentially automated diagnostic aid, which might be used when electronic data are collected in primary care and which could alert GPs to consider the need to screen children for the development of T1D. However, further imputation work is required to develop this equation, as for some time points and for some characteristics there were no controls recorded as having a primary care contact for specific symptoms/diagnoses. This meant that we were unable to calculate odd ratios, and include these important characteristics (blood tests,

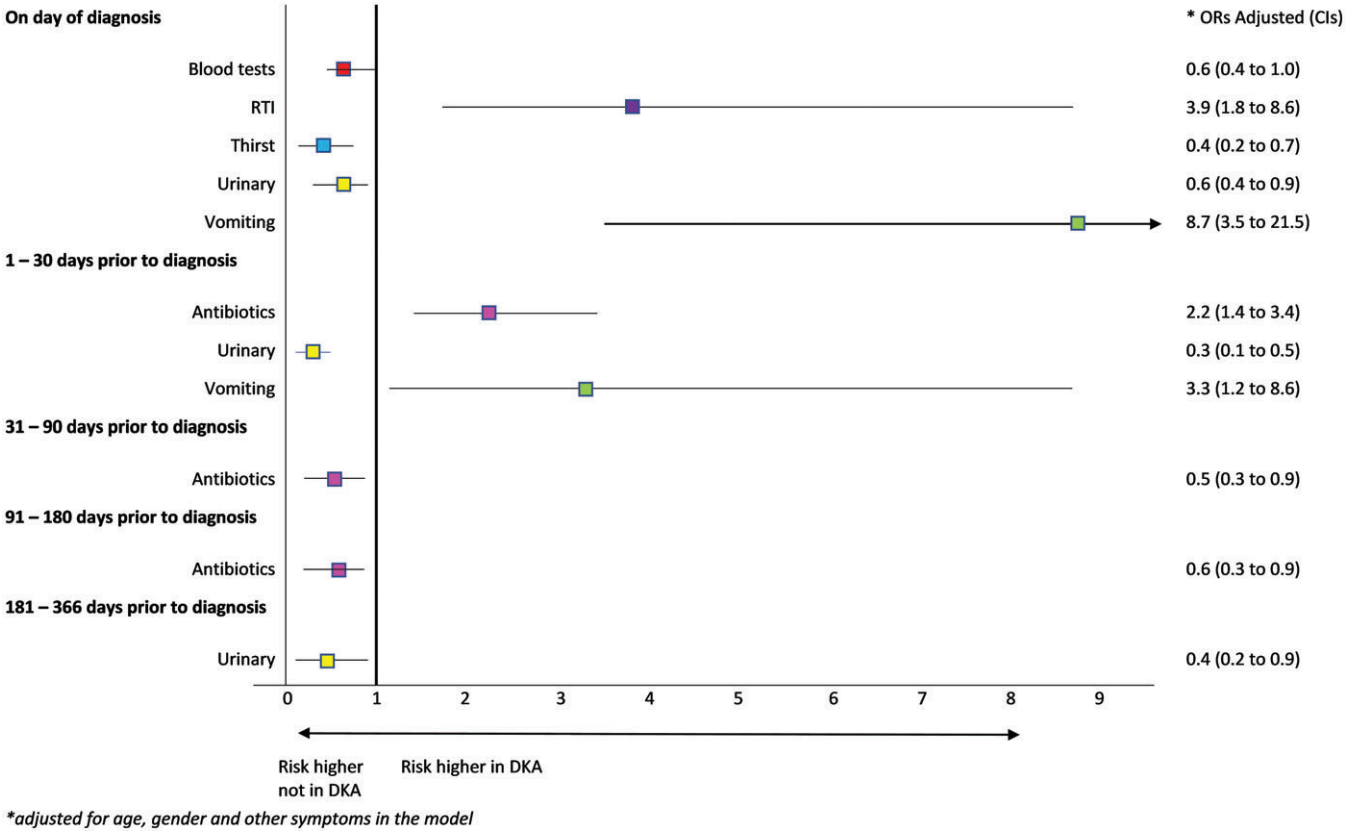

FIGURE 3 Characteristics associated with presenting in DKA at diagnosis vs not presenting in DKA: by time period prior to diagnosis of type 1 diabetes

thirst, tiredness, urinary conditions, and vomiting/nausea) in the modeling.

5 | CONCLUSION

We conclude that there are opportunities in primary care for an earlier diagnosis of T1D in children, given their presentation with medical contacts relating to abdomen symptoms, antibiotic prescriptions, fungal conditions, RTIs, weight, urinary conditions, vomiting, and blood tests, up to 6 months prior to diagnosis. Those with primary care contacts relating to RTIs, vomiting, antibiotic prescriptions, and in particular boys, are more likely to present with DKA. This information can now be used to create a diagnostic tool for primary care physicians to help predict which children are more likely to develop T1D, thus preventing presentation in DKA.

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CONFLICTS OF INTEREST

The authors declare that no conflicts of interest associated with this manuscript.

Author contributions

All authors designed the study. D.T. conducted the matching and linking of the dataset within the SAIL databank. J.T., R.C.-J., and D.T. had full access to all the data in the study. J.T. and R.C.-J. analyzed the data. J.T. wrote the first draft of the report. All authors contributed to revision of the report and agreed to its publication. J.G. together with others established the Brecon Group Register. J.T. is the guarantor of this work, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the analysis.

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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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