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Associations between glycaemic outcomes and BMI in Danish children with type 1 diabetes in 2000–2018: a nationwide population-based study

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What's new?

- Intensified treatment to lower HbA_{1c} with the aim of preventing late complications may be accompanied by health behaviours that lead to increased BMI in children with type 1 diabetes.
- We found a non-linear association between HbA_{1c} and BMI, with no signs of a higher BMI for those with HbA_{1c} below 60 mmol/mol.
- We suggest that low HbA_{1c} levels can be achieved without an increased BMI at the population level. The characteristics of individuals with low BMI and low HbA_{1c} levels with regard to diabetes management, including diet and physical activity, needs more attention, as do gender differences.

Abstract

Aim Type 1 diabetes is a chronic disease with a substantial increased morbidity and mortality primarily due to cardiovascular complications. Higher HbA_{1c} level is associated with late complications, however, optimizing glycaemic outcome may also be related to increased BMI, with a possible negative impact on later cardiovascular health. Over time treatment has mainly focused on lowering HbA_{1c} and avoiding severe hypoglycaemic events. Some attention has been on BMI but earlier studies report different results of the association between HbA_{1c} and BMI.

Methods We used the nationwide Danish Registry of Childhood and Adolescent Diabetes, DanDiabKids, including annual registrations, to describe HbA_{1c} and BMI over time. The association between HbA_{1c} and BMI was analysed using linear mixed-effects models with splines. The effects of gender, age, disease duration, hypoglycaemia and treatment method were also investigated. BMI z-scores were calculated for these analyses.

Results For the period from 2000 to 2018, 6097 children with type 1 diabetes were identified from the DanDiabKids database. The median (interquartile range) HbA_{1c} level was 65 (57–74) mmol/mol (8.1%) and

the median BMI z-score was 0.85 in girls and 0.67 in boys. A non-linear association was found between HbA_{1c} and BMI z-score, with the highest BMI z-score observed for HbA_{1c} values in the range of approximately 60–80 mmol/mol (7.6–9.5%). The association was modified by gender, age and diabetes duration. Severe hypoglycaemia and insulin pump treatment had a small positive impact on BMI z-score.

Conclusion The association between HbA_{1c} and BMI z-score was non-linear, with the highest BMI z-score being observed for intermediate HbA_{1c} levels; however, specific patterns depended on gender, age and diabetes duration.

Introduction

Type 1 diabetes is a serious chronic disease, causing increased morbidity and more than twice the mortality compared to the background population [1–4]. The increased mortality is primarily attributable to cardiovascular death [3], and diabetes-related late complications and mortality are associated with higher HbA_{1c} levels [2,5–7]. Enhanced metabolic control to lower HbA_{1c} often improves hyperlipidaemia which benefits cardiovascular health [8]. However, optimizing treatment in order to lower HbA_{1c} levels has been suspected to be related to increased BMI and obesity [9,10], with a possible negative effect on cardiovascular health [11,12]. In general, the effects of increased childhood BMI on cardiovascular outcomes later in life might, to some extent, be mediated through adult BMI [13]. In childhood diabetes care, continuous monitoring of BMI is important in order to balance clinical outcome variables with ensuring optimal growth. During the last decade, treatment of children with type 1 diabetes has mainly focused on optimizing HbA_{1c} levels and avoiding severe hypoglycaemic events, and decreasing trends over time in these measures are evident [14,15]. A simultaneous rise in BMI among children with type 1 diabetes can be related both to the general development of obesity caused by environmental or behavioural factors and to intensified diabetes treatment and management aimed at achieving lower HbA_{1c} goals while preventing severe hypoglycaemia [16]. Earlier studies on the association between HbA_{1c} and BMI [9,17,18] have reported conflicting results.

Large studies have generally included heterogenous populations, and few studies used repeated measurements or focused on possible non-linear effects.

Based on the unique Danish nationwide population-based registry of childhood diabetes with annual records of clinical and treatment information [14], we aimed to describe the development of HbA_{1c} and BMI over time. In addition, we aimed to investigate the association of HbA_{1c} with BMI and the influence of severe hypoglycaemia and treatment method, including other possible confounding or modifying factors, namely, gender, age and diabetes duration.

Participants and methods

Study population

All children aged 0–17 years, registered with type 1 diabetes in the nationwide population-based Danish Registry of Childhood and Adolescent Diabetes, DanDiabKids [14], and who had data available from annual visits at the clinic between the years 2000 and 2018, were included. Children with a registration of maturity-onset diabetes of the young or monogenetic diabetes at baseline or at the annual follow-up visits were excluded. Data in DanDiabKids are collected as a part of the Danish national clinical quality programme and have a national coverage of >95%. Each year a comparison is performed between DanDiabKids and the Danish National Patient register (which records inpatient and outpatient visits to all hospitals in Denmark) to ensure high completeness of diabetes cases in DanDiabKids [14].

We identified 6807 type 1 diabetes cases diagnosed in individuals aged <18 years, from which seven children with missing date of diabetes onset or invalid BMI values were excluded. Data from clinical visits within the first year of diabetes diagnosis were not included to avoid remission phases and extreme values of HbA_{1c} following a diabetes diagnosis, thereby also excluding children with a total diabetes duration of <1 year. This resulted in a total of 6097 children. The adjusted analyses included data from 5925 children, with a total of 29 770 visits, who had at least one measure of the main exposure and outcome HbA_{1c} and BMI.

Measurements

HbA_{1c} was used as a marker of glycaemic control. The measure was reported in the clinical register at the childrens' annual status visit at the clinic. HbA_{1c} was determined by high-performance liquid chromatography and 90% of the samples were analysed centrally at Copenhagen University Hospital at Herlev and reported in International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units (mmol/mol). Of the remaining samples one-third were analysed locally by non-standardized immunoturbidimetric assay and two-thirds at the local laboratory using IFCC standards.

Hypoglycaemia was reported as the number of severe events occurring during the year preceding the clinical visit. Severe hypoglycaemia was defined as loss of consciousness or seizures. The episodes had to be confirmed with a measured blood glucose or be reverted by intravenous glucose or intramuscular glucagon. Because there were very few events, for the analyses, the total yearly numbers were coded into a dichotomous variable of 0 or 1+ hypoglycaemic events. Treatment method was categorized as insulin pen or insulin pump use. Insulin dose was reported as units per day and divided by the child's weight in kilograms.

From height and weight measurements, BMI was calculated as weight in kilograms divided by height in meters squared. BMI is a weight–height index that is easy to measure and correlates with later disease such as cardiovascular outcomes and mortality [13], but in children BMI varies with age and gender, and should be compared to reference values for age and gender. Therefore, BMI z-scores [BMIz; also referred to as BMI standard deviation scores (BMI-SDS)] were calculated with use of a Danish reference population based on approximately 19 000 individuals with repeated measurements [19,20].

Statistical analysis

Linear mixed-effects regression models with a child-specific random intercept were used to estimate the association between calendar year and HbA_{1c} and BMIz, respectively, separately for girls and boys (as there was a significantly different effect of gender over time) and adjusted for age at examination. We estimated the association between HbA_{1c} and BMIz also by linear mixed-effects regression, including age, gender, disease duration and calendar year as covariates in the first analysis, and severe hypoglycaemia and treatment method in a second set of analyses. We tested for non-linearity in the association between HbA_{1c}

and BMIz by comparing a model with a linear term for HbA_{1c} with a model using natural cubic splines and found a significant non-linear relationship. Age also showed non-linearity in the association with BMIz and was included as cubic spline. For the spline models, knots were set at the quartiles of the distribution of HbA_{1c} and age. Possible modifications of age, gender, diabetes duration, treatment with pen or pump and hypoglycaemic events on the HbA_{1c}–BMIz association were tested and included in the models if significant. Age, gender and diabetes duration showed statistically significant interactions with HbA_{1c}, and interaction terms were included in the model simultaneously. Results were illustrated in estimated curves separately for boys and girls and with values of the covariates set at the average of the study population (age 13 years and duration 5 years), in order to show adjusted results for these variables. For example, for age we showed the results for age 13 years (median), 10 and 16 years (quartiles). *P* values <0.05 were taken to indicate statistical significance.

The analyses were conducted with R version 3.6.11 (R Foundation for Statistical Computing, http://www.r-project.org/).

Ethics

Use of data for this study was approved by the Danish data protection authorities under the Capital Region of Denmark (approval no: P-2019-511), which is standard for medical research including routinely collected register-based data in Denmark.

Results

Of 6097 Danish children with type 1 diabetes identified for the period 2000 to 2018, 53% were boys and 77% were aged 5–14 years at the time of diagnosis. The median [interquartile range (IQR)] diabetes duration was 6 (4–9) years, the median (IQR) HbA_{1c} was 65 (57–74) mmol/mol (8.1%) and the median BMIz was 0.85 in girls and 0.67 in boys (Table 1). A total of 1832 children (30%) had a mean HbA_{1c} <59 mmol/mol. The median (IQR) total number of visits to the clinic included in the analyses was 5 (3–8; data not shown).

HbA_{1c} decreased over calendar time ($P<0.001$; Fig. 1a). There was a different pattern between boys and girls for BMIz ($P<0.001$) over time; BMIz increased for girls, and there was a tendency towards a decrease for boys in BMIz (Fig.1b).

A non-linear association between HbA_{1c} and BMIz was found, with a statistically significant modifying effect of gender, age and diabetes duration ($P<0.001$), as shown in separate graphs for the average child and for low and high levels of these factors (Fig. 2a–c present results of adjusted analyses separately for boys and girls). Calendar year was not statistically significantly associated with BMIz in the adjusted model.

For boys, in general, the average BMIz level was almost constant at approximately 0.65 for HbA_{1c} levels below 60 mmol/mol (7.6%). For girls, the average pattern was a stable BMIz at approximately 0.75 in the HbA_{1c} range 60–80 mmol/mol (7.6–9.5%). For HbA_{1c} levels <60 mmol/mol (<7.6%), BMIz decreased with lower HbA_{1c} for girls. At levels above 75–80 mmol/mol (9–9.5%) the pattern was a negative association (lower BMIz with higher HbA_{1c}) for both genders, although with a steeper decrease for boys than for girls (adjusted analyses shown in Fig. 2a).

The general pattern was a higher BMIz with higher age in both boys and girls. For the oldest girls, the pattern of a decreasing BMIz with lower HbA_{1c} levels [in the interval < 60 mmol/mol (<7.6%)] was most pronounced, and the decrease in BMIz within the higher end of HbA_{1c} values was small, compared to the younger girls and to boys in general. Figure 2b shows the results for the oldest (dotted lines) and youngest (solid lines) quartiles of the population, adjusted for diabetes duration.

With longer diabetes duration, the BMIz was slightly higher. Figure 2c shows the age-adjusted results for children with the shortest (solid lines) and longest (dotted lines) quartiles of duration.

There was a significant positive effect of severe hypoglycaemic events on BMIz ($P<0.01$), with a slightly higher BMIz in children who experienced one or more events. In addition, a significant effect of treatment method (pump vs pen) on BMIz was observed, with slightly higher levels of BMIz for pump users ($P<0.001$; the effects were significant but small, figures not shown).

Discussion

In this study we found a non-linear association between HbA_{1c} and BMIz that was modified by gender, age and diabetes duration. Severe hypoglycaemia during the past year and treatment method (pump vs pen) was positively associated with BMIz but did not influence the HbA_{1c}–BMIz association.

Previous studies investigating the relationship between HbA_{1c} and BMI in childhood diabetes have had conflicting results. In a multicentre study among approximately 11 000 children aged <15 years from four Nordic countries, an inverse association was found between HbA_{1c} and BMI-SDS [9]. This was supported by a study of approximately 5500 teenagers from England, where lower HbA_{1c} level at enrolment was associated with overweight and obesity [10], and by a smaller study with data from a controlled trial in the USA (340 children aged 9–14 years) with repeated measures within 2 years of follow-up [21]. However, in data from Germany, Austria and the USA from more than 30 000 children (aged 2–18 years) a positive association between HbA_{1c} and BMI z-score was reported [17]. None of these studies seemed to have tested for non-linear effects of HbA_{1c} on BMI. A worldwide multicentre study including 55 paediatric centres with data from more than 34 000 children (aged 2–18 years) showed a U-shaped relationship between HbA_{1c} and BMI-SDS. In that study, a higher HbA_{1c} was associated with both underweight, overweight and obesity, and the lowest HbA_{1c} level was found in the normal-weight group [18]. Differences among the studies may partly be explained by the fact they included more heterogeneous populations, with possible differences in background characteristics or treatment access, the use of categories of HbA_{1c} or BMI and the statistical modelling; in particular, none of the large studies included repeated measures for the children in the analyses of HbA_{1c} or BMI. Using only the measurement from either the last visit in the clinic for each child or the mean values over time may level out important effects.

In a study identifying specific trajectories of HbA_{1c} over age by using group-based trajectory modelling in 7002 children with type 1 diabetes, a lower risk of high BMI was found in the low stable HbA_{1c} group compared to the identified intermediate stable, intermediate increasing and high stable HbA_{1c} groups [22]. With similar modelling in a multicentre study from Germany, Austria and the USA in more than 15 000

children aged 8–18 years, increasing HbA_{1c} trajectories were associated with higher BMIz compared to a low stable trajectory [23]. In line with the present study, this indicates that there is a group reaching target HbA_{1c} without increasing BMI. This might be explained by endogenous insulin production, better diabetes management (precise bolusing or carbohydrate counting) or eating habits (such as not needing to over-snack to treat or prevent hypoglycaemia).

In the present study, we observed a non-linear relationship between HbA_{1c} and BMI. Although there was an increase in BMIz when reducing HbA_{1c} from the extremes (>120 mmol/mol) to approximately 60 mmol/mol, there was no further increased BMIz in the low HbA_{1c} levels. In girls, lower levels were associated with lower BMI. This is interesting since it could reflect healthy behaviour, such as healthy eating habits or physical activity, with beneficial effects on both glycaemic control and weight. There is, however, a risk that a subgroup of children may experience eating disorders that draw the BMI and HbA_{1c} down in a negative way, but this is unlikely to explain the phenomenon. Fewer than 3% of children had a diagnosis of an eating disorder after diabetes onset in Denmark according to a recent nationwide study of all children with type 1 diabetes under the age of 18 years. This does not however include children who do not exceed the threshold of clinical referral [1]. Norwegian data from self-report showed a higher prevalence of disturbed eating in older children (age >11 years), especially in girls (~28%), but this was related to higher rather than lower BMIz values [24]. A substantial proportion (30%) of our data was in the lower levels of HbA_{1c} [<59 mmol/mol (7.5%)], whereas the amount of data in the area of extremely low HbA_{1c} levels [e.g. <40 mmol/mol (<5.8%)] is very sparse and results should be interpreted with caution.

At the high end of HbA_{1c} values, the reason for the finding of increased BMI in girls compared to boys may also be related to differences in diabetes management or eating behaviours. It is known that girls have lower self-efficacy regarding coping with diabetes, and emotional capacity for diabetes management has been shown to decrease with increasing age [25]. Overeating could be one way of coping with emotional distress, and disturbed eating, including binge eating is more common in girls than boys [26] and was found particularly in overweight older girls and was related to higher HbA_{1c} [24]. Higher frequencies of insulin omissions were also found in girls [24].

Few of the mentioned studies included severe hypoglycaemia in their analyses of the association between HbA_{1c} and BMI. Two studies found presence of severe hypoglycaemia to be associated with higher BMIz [9,17]. Two multicentre studies investigated the relationship between HbA_{1c} and severe hypoglycaemia and found no association overall [27,28]. In Denmark the rate of severe hypoglycaemic events has been decreasing during the past decade to <5 events per 100 person years [14], and we hypothesized that hypoglycaemia would explain some of the association between HbA_{1c} and BMI, because intensified treatment and fear of hypoglycaemia could lead to increasing intake of carbohydrates when blood glucose is low. A severe hypoglycaemic event during the past year seemed to affect BMIz, which increased slightly independently of HbA_{1c}.

Our findings that BMIz levels were higher in girls, in older children, in children with longer disease duration and among pump users compared to pen users are supported by other studies [9,10,18,21,29]; however, the results from the present study indicate that the relationship between glycaemic outcome and BMI is complex and the diversity in results found from earlier studies points to the importance of the population included and the choice of analysis methods.

The median BMIz was 0.76, suggesting that the average child with type 1 diabetes has a higher BMI than the reference child from the background population. Behavioural explanations related to diabetes include extra calorie intake to treat or prevent hypoglycaemia or ingestion of a bedtime snack containing carbohydrates and protein to reduce risk of nightly hypoglycaemia. Higher peripheral insulinaemia than that which is normally secreted by the pancreas of children without diabetes could also promote the disposition of fat [18]. Our finding of a higher BMIz in children with type 1 diabetes compared to the background population, and further increased levels in girls compared to boys is consistent with the findings of other studies [9,17], and excessive fat storage in the abdomen of girls with type 1 diabetes has been suggested [16].

In girls we also found a small but increasing BMIz over calendar time, which was suspected given the general trend of increasing BMI over time due to changes in health behaviour, such as more sedentary lifestyles and fatty food intake. However the trend towards an increased prevalence of overweight and obesity seems to have been leveling off over the recent decade in Denmark [30], and we suggest that our

finding of a stable increase among girls also in recent years points to changes in both behaviours related to the diabetic disease and to more general health behaviours, such as levels of physical activity, that are different for boys and girls.

We chose a Danish reference for calculating BMIz [19,20], which was based on older data. Other international references exist, including those of the WHO or the American Centre for Disease Control and Prevention. Choice of reference population depends on the research question under study, and the background data used in Nysom *et al*., based on approxiately 14 000 children, is a valid reference for comparing with a Danish population with suspected normal growth. Another more recent Danish study exists [31], but this was based on fewer children (~2800), had very few measurements from children in the teenage group, and has also been criticized for the data regarding the youngest group of children [32]. Further, we suggest that the results regarding the association between HbA_{1c} and BMI do not depend on choice of reference for calculating BMI scores.

Our finding of elevated BMI in childhood is important considering the lifelong consequences of this with regard to cardiovascular health. There is evidence of associations between childhood BMI and hypertension and coronary heart disease from a systematic review [13], however, there were attenuated effect sizes in the few studies examining associations independently of adult BMI [13]. Excess gain in BMI during childhood and from child to adult ages was also found to increase cardiovascular risk factors and coronary heart disease [33], and childhood obesity was found to be positively associated with adult blood pressure and total cholesterol [12]. Although adult BMI might be a mediator, increased childhood BMI is a serious concern in children in general as well as in children with type 1 diabetes.

Limitations of the present study include the fact that we only had one measurement per year of the variables included and that there were no patient-reported outcomes included in our data, i.e. information about health behaviours that could possibly mediate the associations. In addition, only reports of severe hypoglycaemic events were included, which makes the results derived from this variable less sensitive. Strengths of this study include its homogenous population, covering all age groups of children with type 1 diabetes diagnosed

in Danish hospitals across the whole country, and the mandatory registration of repeated measures each year into a nationwide clinical register which has a very high coverage of data [14]. We used all the longitudinal data measurements available, modelled with splines, which allows non-linear associations to be identified and included interactions with covariates.

In conclusion, the finding that the association between HbA_{1c} and BMI appears to be non-linear and varies with gender and age is important. In girls we found a trend of increasing BMI over time. In general, it seems possible to aim for low levels of HbA_{1c} and not experience a higher BMI for some children, which is interesting and should be explored further.

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Competing interests

The authors report no conflicts of interest in relation to this work. P.F.R. has received research grants from Amgen and from the Danish Diabetes Academy for other projects. D.V., P.F.R. and J.S. own shares in Novo Nordisk. J.S. serves as an adviser to Medtronic, Janssen and Novo Nordisk, and has received fees for speaking on behalf of Medtronic, Sanofi, Novo Nordisk and Bayer AG.

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FIGURE 1 Estimated curves for (a) HbA_{1c} and (b) BMI z-score over calendar time for children Danish children with Type 1 diabetes with clinical visits between 2000 and 2018. Age set at 13 years for boys (blue) and girls (red). Shaded areas are 95% CIs.

FIGURE 2 Estimated curves for the associations between HbA_{1c} and BMI z-score in children with type 1 diabetes according to (a) gender, (b) first and third quartile of age and (c) first and third quartile of diabetes duration. (a) Association between HbA_{1c} and BMI z-score for age 13 years and diabetes duration 5 years (median of study population). (b) Association between HbA_{1c} and BMI z-score for age 10 years (solid lines) and age 16 years (dotted lines). Diabetes duration 5 years. (c) Association between HbA_{1c} and BMI z-score

for duration 3 years (solid lines) and 8 years (dotted lines). Age 13 years. Girls (red) and boys (blue), shaded areas are 95% CIs.

Table 1 Descriptive statistics of children with type 1 diabetes under age 18 in the national Danish Registry of Childhood and Adolescent Diabetes (data from yearly visits in the clinic between year 2000 and 2018)

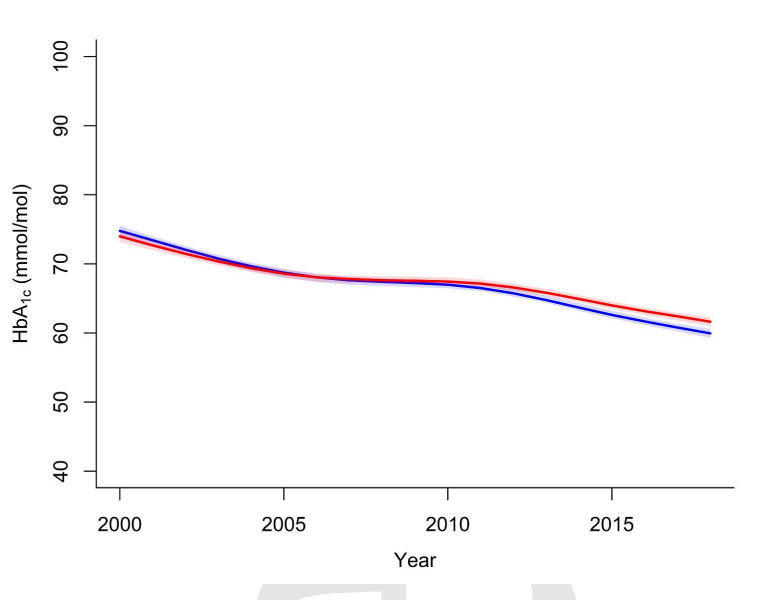
Characteristics			
Number of children			
Girls	2895		
Boys	3202		
Total	6097		
Age at diabetes onset, *n* (%)			
1–4 years	562 (19)	644 (20)	1206 (20)
5–9 years	1112 (38)	1053 (33)	2165 (36)
10–14 years	1138 (39)	1374 (43)	2512 (41)
≥15 years	83 (3)	131 (4)	214 (4)
Median (IQR) age at annual visit, years	13.3 (10.5–15.9)	13.9 (10.6–16.0)	13.6 (10.6–15.9)
Median (IQR) age at first included annual visit, years	11.2 (8.1–14.1)	12.1 (8.3–14.9)	12.0 (8.2–14.2)
Calendar year at diabetes onset, *n* (%)			
1980–1989	35 (1.2)	43 (1.3)	78 (1)
1990–1999	541 (19)	616 (19)	1157 (19)
2000–2009	1251 (43)	1327 (41)	2578 (42)

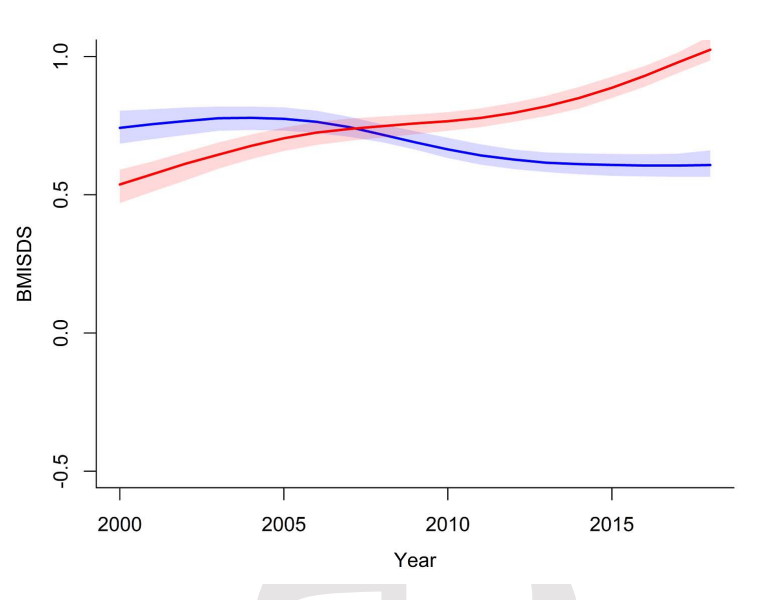
2010–2018	1068 (37)	1216 (38)	2284 (37)
Calendar year of first yearly visit included (from 2000 to 2018), *n* (%)			
2000–2004	939 (32)	1035 (32)	1974 (32)
2005–2009	654 (23)	713 (22)	1,367 (22)
2010–2014	702 (24)	78 (24)	1,484 (24)
2015–2018	600 (21)	672 (21)	1,272 (21)
Median (IQR) duration of disease, years from onset to last visit	6.2 (3.8–9.4)	5.8 (3.5–9.1)	5.9 (3.7-9.2)
HbA_{1c}*			
Median (IQR), mmol/mol	65 (57–74)	65 (57–74)	65 (57–64)
Median, %	(8.1)	(8.1)	(8.1)
Missing, *n* (%)	74 (3)	54 (2)	128 (2)
BMI*			
Median (IQR), kg/m^2	20.0 (17.5–22.9)	19.3 (17.3–21.8)	19.6 (17.4–22.3)
Missing, n (%)	77 (3)	45 (1)	122 (2)
BMI z-score*			
Median (IQR)	0.85 (0.18–1.46)	0.67 (0.00–1.36)	0.76 (0.08–1.42)
Missing	77 (3)	45 (1)	122 (2)

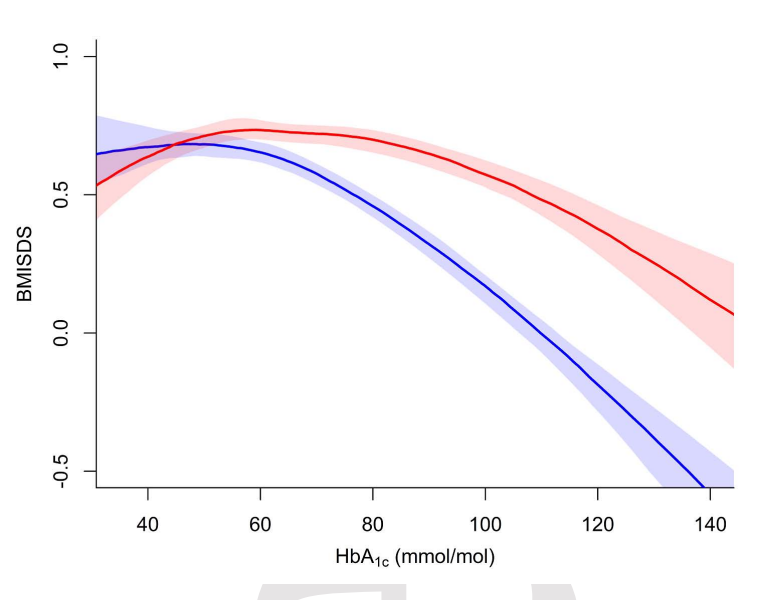
Blood pressure*, mmHg			
Systolic, median (IQR)	114 (106–121)	115 (107–124)	114 (106–123)
Diastolic, median (IQR)	68 (62–74)	66 (60–72)	67 (61–73)
Missing, *n* (%)	161 (6)	150 (5)	311 (5)
Puberty (at end of follow-up), *n* (%)	1934 (67)	2077 (65)	4011 (66)
Treatment type (ever use), *n* (%)			
Insulin pen	2048 (71)	2323 (73)	4371 (72)
Insulin pump	1610 (56)	1553 (49)	3163 (52)
Insulin dose*, units/kg/day			
Median (IQR)	0.9 (0.7–1.1)	0.9 (0.7–1.1)	0.9 (0.7–1.1)
Missing	85 (3)	52 (2)	137 (2)
Self-measured plasma glucose, times per week (last reported measure), *n* (%)			
7–21	720 (25)	921 (29)	1641 (27)
28–35	979 (34)	1041 (33)	2020 (33)
> 35	1094 (38)	1134 (35)	2228 (37)
Missing	102 (4)	106 (3)	208 (3)
Severe hypoglycaemic event (ever), *n* (%)	555 (19)	650 (20)	1205 (20)

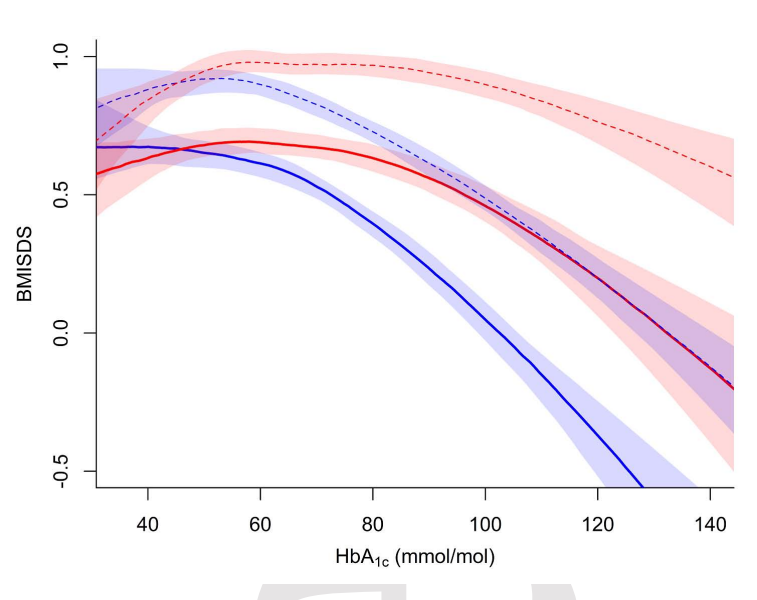
IQR, interquartile range.

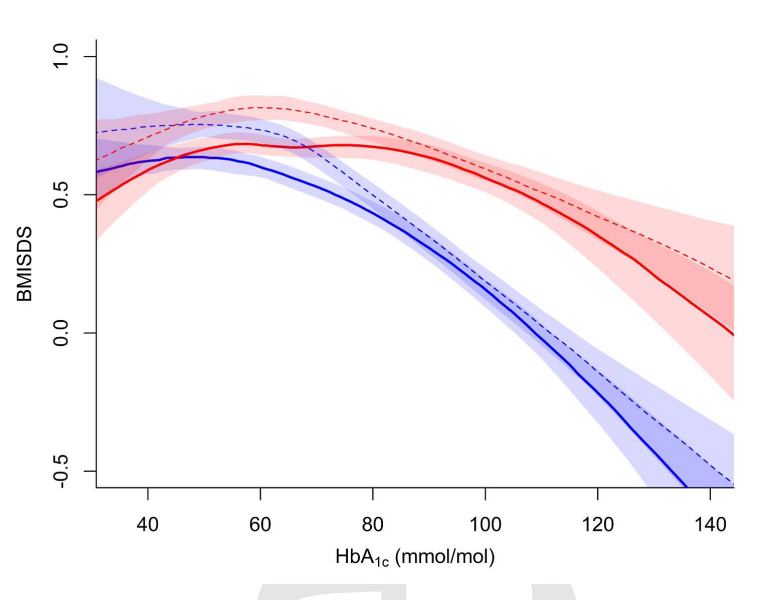
*****All measurements included over time from the children's first annual visit after diagnosis to last visit.


100
90
80
70
60
50
40
HbA1c (mmol/mol)
2000
2005
2010
2015
Year


BMISDS
1.0
0.5
0.0
-0.5
2000
2005
2010
2015
Year


BMISDS
1.0
0.5
0.0
-0.5
40
60
80
100
120
140
HbA1c (mmol/mol)


BMISDS
1.0
0.5
0.0
-0.5
40
60
80
100
120
140
HbA1c (mmol/mol)


BMISDS
1.0
0.5
0.0
-0.5
40
60
80
100
120
140
HbA1c (mmol/mol)