

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <https://orca.cardiff.ac.uk/id/eprint/161219/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Holman, Naomi, Woch, Emilia, Dayan, Colin , Warner, Justin, Robinson, Holly, Young, Bob and Elliott, Jackie 2023. National trends in hyperglycemia and diabetic ketoacidosis in children, adolescents, and young adults with type 1 diabetes: a challenge due to age or stage of development, or is new thinking about service provision needed? *Diabetes Care* 46 (7) , 1404–1408. 10.2337/dc23-0180

Publishers page: <http://dx.doi.org/10.2337/dc23-0180>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



National Trends in Hyperglycemia and Diabetic Ketoacidosis in Children, Adolescents, and Young Adults With Type 1 Diabetes: A Challenge Due to Age or Stage of Development, or Is New Thinking About Service Provision Needed?

Naomi Holman 1, Emilia Woch 2, Colin Dayan 3, Justin Warner 4, Holly Robinson 5, Bob Young 6, and Jackie Elliott 7 8

Affiliations

¹ School of Public Health, Imperial College London, London, U.K.

² NHS England, Leeds, U.K.

³ School of Medicine, Cardiff University, Cardiff, U.K.

⁴ Noah's Ark Children's Hospital for Wales, University Hospital of Wales, Cardiff, U.K.

⁵ Royal College of Paediatrics and Child Health, London, U.K.

⁶ Diabetes UK, London, U.K.

⁷ Sheffield Teaching Hospitals, Northern General Hospital, Sheffield, U.K.

⁸ Department of Oncology and Metabolism, University of Sheffield, Sheffield, U.K.

In young people with type 1 diabetes, hyperglycemia increases during adolescence and is still on an upward trajectory as young people move to adult services. Data from a self-selecting group in the U.S. has documented this widely recognized pattern (1), and their later report showed that, despite the increased use of technology, glycemia in people aged 15 to 18 years had deteriorated further (2). It is commonly assumed that poor communication and changes in continuity and support during the transfer from paediatric to adult services at the age of 16 to 18 years are important reasons (3) for more severe hyperglycemia at this stage of life. However, the influence of growth-related hormonal change on insulin requirements is also recognized (4) as a key factor in age-related changes. Irrespective of the causes, the long-term consequences of even 6.5 years of similar hyperglycemia in people with type 1 diabetes are evident from follow-up of the Diabetes Control and Complications Trial cohort (5).

In order to better understand this phenomenon in young people with type 1 diabetes, and thereby highlight possible areas for intervention, we combined data from childhood to early adulthood recorded in annual national paediatric and adult diabetes audits for England and Wales, with the analytical aim of exploring the age-related trajectory of changes in HbA1c measurement (as a proxy for clinic attendance and engagement with health services), HbA1c levels (as a measure of overall glucose control) and hospitalization for diabetic ketoacidosis (DKA, as a measure of failed glucose control).

RESEARCH DESIGN AND METHODS

The National Diabetes Audit (NDA) for England and Wales collates data on people of all ages with a diagnosis of diabetes from primary care records and adult specialist diabetes services and extracts data covering a 15-month period from 1 January in the first year to 31 March in the subsequent year (6). The NDA collated data from more than 97% of general practices (over 7,100 general practices) in each of the audit periods used in this analysis (7,8) and a total of 202 specialist adult diabetes

services. The National Paediatric Diabetes Audit (NPDA) collates data on children and young people receiving care from pediatric diabetes services in England and Wales for a 12-month time period covering 1 April in the first year to 31 March in the subsequent year directly from data submitted by the unit providing care (9). There is 100% participation from specialist pediatric diabetes centers. Both the NDA and the NPDA collate data on all measurements recorded in the health care record during the relevant time period. In England and Wales, young people start moving from pediatric to adult services usually around the age of 16 to 18 years old. Many pediatric centers will hold specific clinics for this cohort, which may be joined by staff from the adult team, but the frequency, timing, and content of this process is not universal. Data on hospital admissions were taken from Hospital Episode Statistics (10), which detail hospital activity in all National Health Service (NHS) Trusts in England. Hospital admission data for Wales were not available for this analysis.

Sequential cohorts of people with type 1 diabetes aged 5 to 30 years old and included in the 2017/2018, 2018/2019, and 2019/2020 data collections for the NDA and NPDA were identified. Age was calculated in years at 1 April of each audit period. These sequential cohorts for the two audits were combined using the NHS number as a unique patient identifier to create a pooled cohort. People were identified as having type 1 diabetes if they had a diagnosis code of type 1 diabetes recorded in their NDA or NPDA data and treatment records consistent with the use of an insulin pump, basal-bolus insulin, or fixed-mix insulin.

For each year of age, the latest valid HbA1c measurement recorded in either the NDA or the NPDA was identified. Hospital admissions to English NHS hospitals in England between 1 April 2017 and 31 March 2020 for DKA (ICD-10 codes E10.1, E11.1, E12.1, E13.1, and E14.1) were identified from Hospital Episode Statistics. Hospital admissions for DKA that occurred in the same year of diagnosis were excluded to ensure the admissions did not reflect clinical presentation at diagnosis.

The median and interquartile ranges (IQRs) for HbA1c measurements were calculated for all the measurements across the entire cohort taken at each single year of age. The statistical significance of differences in median HbA1c between male and female individuals and across different ages were calculated using Kruskal-Wallis tests. The skewness and kurtosis of the distribution of HbA1c by age and sex were calculated. The proportion of people who had one or more hospital admissions for DKA by single year of age was calculated. The statistical difference in the prevalence of hospitalization for DKA was tested using χ^2 tests. Logistic regression models stratified by sex were created for HbA1c of 7.5% (58 mmol/mol) or less and HbA1c of 10% (86 mmol/mol) or greater. Age, self-reported ethnicity as recorded in the electronic health record, social deprivation quintile based on the Indices of Multiple Deprivation (11,12), and duration of diabetes were included as explanatory variables. Odds ratios associated with each year of age were converted to relative risks to aid interpretation (13).

In order to comply with the NDA information governance, all counts of people are rounded to the nearest five, and all percentages reported are based on rounded figures.

RESULTS

A total of 93,125 individuals were included in the pooled cohort. Of these, 11,650 (12.5%) contributed 1 year of data, 12,025 (12.9%) contributed 2 years of data, and 69,450 (74.6%) provided data from all 3 years. The characteristics of those included in the cohort are shown in Table 1. The proportion of records without an HbA1c measurement in the year from April to March varied by age; it was consistently low up to age 16 years (5%), then rose quickly, peaking at the age of 21 years for men (22.3%) and 19 to 20 years for women (17.3%) before falling gradually to 17.9% for men and

13.1% for women at the age of 30 years (males significantly higher than females, $P < 0.005$) (Supplementary Table 1).

	<i>n</i>	%
Sex		
Male	42,335	45.5
Female	50,790	54.5
Ethnicity		
Asian	5,005	5.4
Black	3,115	3.3
Mixed	1,990	2.1
Other	1,790	1.9
White	76,555	82.2
Unknown/not stated	4,670	5.0
Age at diagnosis		
<2 years	1,730	1.9
2 to <5 years	9,780	10.5
5 to <10 years	22,550	24.2
10 to <15 years	27,875	29.9
15 to <20 years	15,020	16.1
≥20 years	15,715	16.9
Unknown	450	0.5

Across the whole of the pooled cohort, median recorded HbA1c rose steadily from the age of 9 years in male individuals (median 7.6% [60 mmol/mol] IQR 7.1–8.4%, 54–68 mmol/mol) and female individuals (median 7.7% [61 mmol/mol] IQR 7.1–8.4%, 54–68 mmol/mol), peaking at 19 years of age (men: 8.7% [72 mmol/mol], IQR 7.5–10.3%, 59–89 mmol/mol; women: 8.9% [74 mmol/mol] IQR 7.8–10.6%, 62–92 mmol/mol). By the age of 30 years, median HbA1c had fallen to 8.4% (68 mmol/mol [IQR 7.4–9.7%, 57–83 mmol/mol]) for men and 8.2% (66 mmol/mol [IQR 7.3–9.7%, 56–82 mmol/mol]) for women. From the age 16 to 22 years, median HbA1c was consistently higher for women than for men ($P < 0.005$) (Fig. 1 and Supplementary Table 1). Between ages 5 and 30 years, those aged 20 years had the smallest proportion with a recorded HbA1c of 7.5% (58 mmol/mol) or lower. The greatest proportions with a very high HbA1c (more than 10.0% [86 mmol/mol]) were among men aged 17 years (31.4%) and women aged 18 years (35.8%) (Supplementary Table 1). These age-related patterns persisted after adjustment for ethnicity, social deprivation, and duration of diabetes (see Supplementary Figs. 1 and 2).

The shapes of the distributions of HbA1c levels by age and sex are in some ways similar but actually differ significantly (Fig. 2A and B). The distributions for female individuals are all slightly shifted to the right (higher HbA1c). By age, the most left-shifted (low HbA1c) patterns are for age 15 years, the most right shifted (high HbA1c) are for age 19 years, and, at age 25 years, there is a leftward shift without fully regaining the high peak of low HbA1c or losing the shoulder of high HbA1c.

A total of 87,970 individuals in the cohort (94.4%) were registered with a general practice and/or a diabetes specialist service in England and were analyzed for hospital admissions. Fig. 1 shows the annual prevalence of one or more hospital admissions for DKA rose from 1.4% for girls and 2.0% for boys aged 6 years old, peaking at 18 years old for women (12.7%) and 19 years old for men (7.9%). Thereafter, the proportion of people having one or more hospital admissions for DKA per year fell and, by age 30 years, was 4.3% for men and 5.4% for women. Each year, from the age of 9 years, the proportion of female individuals with one or more hospitalizations for DKA was higher than in male individuals ($P < 0.005$).

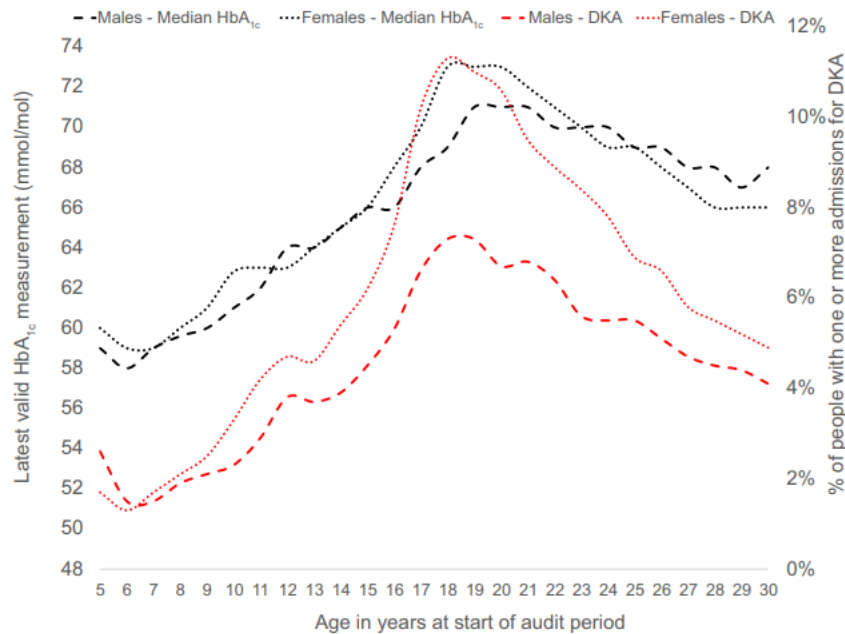


Figure 1—Median HbA_{1c} and percentage of people with one or more hospital admissions for DKA by age and sex.

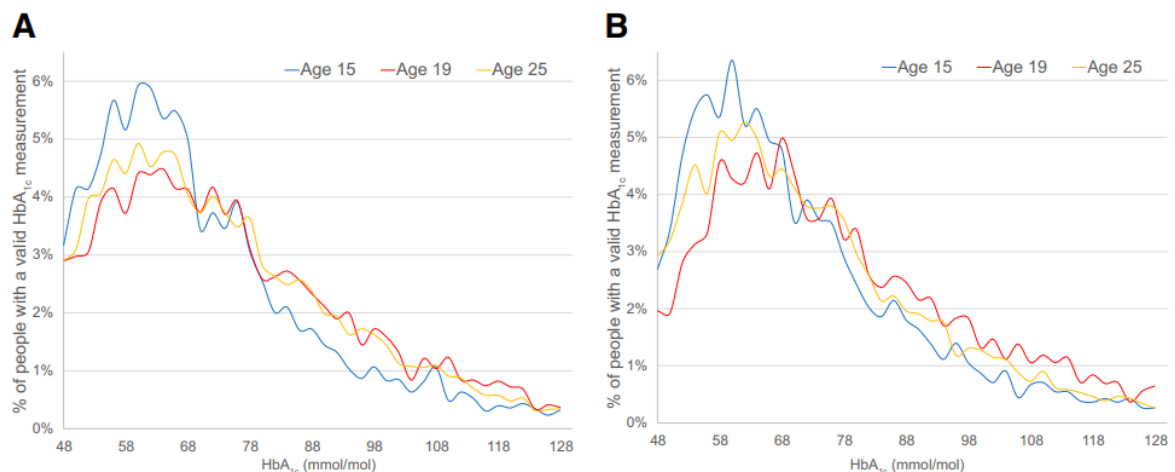


Figure 2—A: Distribution of HbA_{1c} in males aged 15 years, 19 years, and 25 years. Kurtosis at 15 years, -1.16 ; at 19 years, -1.43 ; at 25 years, -1.41 . Skewness at 15 years, 0.58 ; at 19 years, 0.12 ; at 25 years, 0.18 . B: Distribution of HbA_{1c} in women aged 15 years, 19 years, and 25 years. Kurtosis at 15 years, -1.01 ; at 19 years, -1.10 ; at 25 years, -1.37 . Skewness at 15 years, 0.64 ; at 19 years, 0.36 ; at 25 years, 0.31 .

CONCLUSIONS

This analysis of over 93,000 individuals with type 1 diabetes in England and Wales highlights the changes in measurement of HbA_{1c}, hyperglycemia, and risk of hospitalization for DKA throughout childhood, adolescence, and early adulthood. Almost all children have annual records of HbA_{1c}, but, during the ages of transfer to adult services (16 to 20 years old), the proportion drops abruptly to

about 80%. Median HbA1c and the prevalence of hospitalization for DKA start to rise earlier but peak over the same ages. Median HbA1c increases progressively from the age of 9 to 19 years, before decreasing, though not reattaining childhood levels, up to the age of 30 years, meaning that the phenomenon starts before and continues after the period of transitioning from pediatric to adult services. This follows the pattern found in the SWEET project, which compiled data on 66,418 individuals with type 1 diabetes from 22 centers across 19 countries and found that, in 2016 to 2018, adjusted HbA1c rose steadily from the age of 6 to 18 years (14). The scale of the rise in HbA1c from age 9 to 18 years in this analysis (12 mmol/mol for male individuals, 13 mmol/mol for female individuals) is similar to the 11 mmol/mol increase in HbA1c reported over the same age period in a combined cohort of individuals living in Germany or Austria and the U.S. (15). The prevalence of hospitalization for DKA in our study follows a trajectory similar to HbA1c levels but peaks slightly earlier at 18 years old. Hyperglycemia and the prevalence of DKA are significantly higher in females than males at most ages.

The sudden increase at ages 17 to 19 years in the proportion of people with no annual records of HbA1c suggests that attendance at either a pediatric clinic, a general practitioner-led diabetes service, or an adult hospitalbased clinic dramatically reduces at the time of changing service provision from pediatric to adult. This is also a time when psychological and social pressures are increasing. This study does not allow analyses that might precisely distinguish age effects from service transfer effects, but the different time trajectories (gradual increase in hyperglycemia and DKA throughout adolescence, sudden change in HbA1c measurement at the age of transfer) make it likely that the changes are due to a combination of personal and organizational factors. Previous allage analyses have shown that people for whom routine care processes have not been recorded are at increased risk of future morbidity and mortality (16,17), so the evidence of fourfold higher rates of irregular engagement in routine care is of notable concern in itself.

The steady rise and then fall in median HbA1c and DKA throughout childhood, adolescence, and early adulthood straddles the period before and after transfer from pediatric to adult services, implying that the change is not simply due to turbulence associated with changing health care provider. Adolescence is a time of difficult psychological change for all young people, but even more so for those with a chronic condition like diabetes. The relentless need for continual self-care is, itself, burdensome. Both very high HbA1c levels and DKA are often related to insulin omission and/or psychological stress. The additional challenge, both personal and clinical, is the compounding effect of the surge in pubertal associated growth hormones. This demands physiologically matched adjustments in insulin of a magnitude and rate of change equaled only in the middle trimester of pregnancy. The age-related HbA1c profiles suggest the need to focus particularly on those with the highest HbA1c levels if the surge and associated higher rates of DKA are to be attenuated. In the long run, it is these metabolic risks that will be most detrimental to health (6).

Our data show greater adverse changes in young women, who are less likely to achieve the glycemic target of 7.5% (58 mmol/mol) or less, are more likely to have an HbA1c of greater than 10% (86 mmol/mol), and, when aged 15 to 25 years, are approximately 50% more likely to have at least one episode of DKA compared with men of the same age. One of the reasons behind this inequality may be the higher prevalence of disordered eating among women (18). Psychological and societal pressures including approaches to body image, peer pressure, and risk-taking behavior may also exert themselves differently between men and women in this age group.

The strength of this analysis lies in the use of data from two national audits that collate data on children and young people receiving care from specialist pediatric diabetes services and from primary care records across the whole population of England and Wales. For the data collection

periods used in the analyses, population coverage of the NDA was over 97%, and the NPDA included data from all pediatric services providing diabetes care. The novel use of sequential cohorts provides the statistical power to identify changes in hyperglycemia and the prevalence of hospitalization for DKA by age and sex, while using data from a relatively short time period.

However, there are several limitations. The use of data collated from routine health records means the information on HbA1c is limited to those individuals who are engaging with the health services and misses those who are potentially at greatest risk. Records of HbA1c measurement may be incomplete because measurements made by specialist services, particularly point-of-care tests, may not be submitted to the NDA or reliably communicated to the primary care provider. The age at which the percentage of people without a valid HbA1c recorded coincides with the peak in measured hyperglycemia. While it is not known for certain, it is likely that, on average, nonattenders have high HbA1c. This means that the scale of the increase in HbA1c in the late teenage years and early twenties may well be even greater than we report. At the time of analysis, hospital admission data were only available for England, and therefore the data on the prevalence of hospitalization for DKA does not include admissions to hospitals in Wales. However, people receiving care in Wales account for approximately 5% of the cohort, and age-related patterns of hospitalization are unlikely to differ substantially (8). In this analysis, we have allocated deprivation scores on the basis of the individual's home postcode at each age for which they contribute data to the analysis. It is possible that the association between deprivation and health outcomes varies by age; in particular, the geographical location of young adults as they move into independent accommodation may not reflect their life experiences and health risk.

Our data suggest the need for novel approaches to the support of children and young adults with type 1 diabetes. Rates of very high HbA1c >10% (>86 mmol/mol) peak for around a third of the measured population at a time of life when another fifth have not had their HbA1c level recorded. The overall aims should be to flatten the rise in HbA1c throughout the teenage years, which are independent of duration of diabetes, ethnicity, and social deprivation, and to reduce the peak in hospital admissions for DKA across the same ages. Further evidence on the type of interventions and service structures that will address these issues is needed, but it is clear that improved, innovative, and appropriately resourced age-appropriate service designs oriented to the delivery of optimal care during this period of life are warranted.

Acknowledgments. The authors would like to thank all the health care providers that provide data for the NDA and the National Diabetes Paediatric Audit.

Funding. N.H. was funded by NHS England and Diabetes UK. No other specific funding was used for this work.

Duality of Interest. B.Y., N.H., and C.D. are members of the NDA Research Advisory Group. J.W. and H.R. are members of the NPDA Project Board. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. The study was designed by all the authors. N.H. and E.W. undertook the statistical analysis. All authors reviewed the methods, assisted in writing the article, and reviewed the final manuscript. N.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Wood JR, Miller KM, Maahs DM, et al. T1D Exchange Clinic Network. Most youth with type 1 diabetes in the T1D Exchange Clinic Registry do not meet American Diabetes Society or International Society for Paediatric and Adolescent Diabetes Clinical Guidelines. *Diabetes Care* 2013;36:2035–2037
2. Foster NC, Beck RW, Miller KM, et al. T1 Diabetes Exchange. State of type 1 diabetes management and outcomes from the T1D Exchange in 2016–2018. *Diabetes Technol Ther* 2019;21:66–72
3. Ladd JM, Reeves-Latour J, Dasgupta K, Bell LE, Anjachak N, Nakhla M. Toward a better understanding of transition from paediatric to adult care in type 1 diabetes: a qualitative study of adolescents. *Diabet Med* 2022;39:e14781
4. Acerini CL, Williams RM, Dunger DB. Metabolic impact of puberty on the course of type 1 diabetes. *Diabetes Metab* 2001;27:S19–S25
5. DCCT/EDIC Research Group. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. *Diabetes Care* 2014;37:9–16
6. Holman N, Knighton P, Wild SH, et al. Cohort profile: National Diabetes Audit for England and Wales. *Diabet Med* 2021;38:e14616
7. National Health Service. NHS Digital National Diabetes Audit Report 1 - Care Processes and Treatment Targets 2018-19, Short Report, updated 12 December 2019. Accessed 5 January 2023. Available from <https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-audit/report-1-care-processes-and-treatment-targets-2018-19-short-report>
8. National Health Service. NHS Digital Report 1: Care Processes and Treatment Targets 2019-20, Full Report, updated 3 November 2021. Accessed 5 January 2023. Available from <https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-audit/report-1-care-processes-and-treatment-targets-2019-20>
9. Royal College of Paediatric and Child Health. National Paediatric Diabetes Audit Annual Reports. Accessed 23 January 2023. Available from <https://www.rcpch.ac.uk/resources/npda-annual-reports>
10. National Health Service. NHS Digital Hospital Episode Statistics (HES) - NHS Digital, updated 22 June 2022. Accessed 5 January 2023. Available from <https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospitalepisode-statistics>
11. Ministry of Housing. Communities and Local Government English indices of deprivation 2019, updated 26 September 2019. Accessed 5 January 2023. Available from <https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019>
12. Government of Wales. Welsh Indices of Multiple Deprivation. Accessed 5 January 2023. Available from <https://www.gov.wales/welsh-index-multiple-deprivation-full-index-update-ranks-2019>
13. Grant RL (2014) Converting an odds ratio to a range of plausible relative risks for better communication of research findings. *BMJ* 2014;348:f7450
14. Gerhardsson P, Schwandt A, Witsch M, et al. The SWEET Project 10-year benchmarking in 19 countries worldwide is associated with improved HbA1c and increased use of diabetes technology in youth with type 1 diabetes. *Diabetes Technol Ther* 2021;23:491–499

15. Hermann JM, Miller KM, Hofer SE, et al. T1D Exchange Clinic Network and the DPV initiative. The Transatlantic HbA1c gap: differences in glycaemic control across the lifespan between people included in the US T1D Exchange Registry and those included in the German/Austrian DPV registry. *Diabet Med* 2020;37:848–855
16. Holman N, Knighton P, O’Keefe J, et al. Completion of annual diabetes care processes and mortality: a cohort study using the National Diabetes Audit for England and Wales. *Diabetes Obes Metab* 2021;23:2728–2740
17. Valabhji J, Barron E, Gorton T, et al. Associations between reductions in routine care delivery and nonCOVID-19-related mortality in people with diabetes in England during the COVID-19 pandemic: a population-based parallel cohort study. *Lancet Diabetes Endocrinol* 2022;10:561–570
18. Young V, Eiser C, Johnson B, et al. Eating problems in adolescents with type 1 diabetes: a systematic review with meta-analysis. *Diabet Med* 2013;30:189–198