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Adolescents with Type 1 diabetes mellitus experience psychosensorial symptoms during hypoglycaemia

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Abstract

Aim To describe mood and psychosensorial symptoms of hypoglycaemia in adolescents with Type 1 diabetes mellitus in two countries with different cultures, Turkey and the USA.

Methods We developed a 68-item questionnaire assessing physical, behavioural, mood and psychosensorial symptom frequency and ratings ['good', 'bad', or 'both' (sometimes good, sometimes bad)]. Adolescents with Type 1 diabetes were recruited from paediatric diabetes clinics at the University of North Carolina at Chapel Hill in the USA and Kocaeli University in Turkey. The percentages of participants at each clinic who endorsed individual symptoms, symptom categories and symptom ratings were calculated and compared.

Results Cronbach's α values were > 0.7 for each real symptom category. No symptom items were excluded from the questionnaire analysis based on item-total correlation results which were all > 0.2. Data were collected from 132 participants (69 from University of North Carolina, 63 from Kocaeli University, 54% male). The mean (SD) age of the participants was 14.9 (1.9) years, HbA_{1c} level was 8.7 (1.8) % and duration of Type 1 diabetes was 5.8 (3.7) years. On average, each physical symptom was experienced by 65.2% of participants, each behavioural symptom by 46.5%, each mood symptom by 42.8%, and each psychosensorial symptom by 48.9%. On average, each physical, behavioral, mood and psychosensorial symptom was rated as 'good' or 'both' by 23.0, 29.1, 36.9 and 37.2% of participants, respectively. There were no symptom differences between the groups in each country.

Conclusions In addition to the classic physical symptoms experienced during hypoglycaemia, adolescents with Type 1 diabetes report psychosensorial, mood and behavioral symptoms, and some describe them as positive experiences. Symptom experiences were similar in these two countries with different cultures.

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Introduction

Hypoglycaemia is a well-known complication of Type 1 diabetes mellitus treatment that can lead to seizure, coma, long-term neurocognitive sequelae and even death. Individuals with Type 1 diabetes experience ~2 episodes of symptomatic hypoglycaemia per week [1]. Severe hypoglycaemia (requiring help for recovery) has an annual prevalence of 30–40% among people with Type 1 diabetes and an annual incidence of 1.0–1.7 episodes per patient per year for all people with Type 1 diabetes. Since hypoglycaemia is so commonly experienced, early recognition of the symptoms is essential to prevent severe complications.

Aside from the traditionally recognized symptoms of hypoglycaemia (e.g. neuroglycopenic, autonomic and malaise symptoms) [2], some adults with Type 1 diabetes report both negative and positive mood changes [3–6] and, in children, hypoglycaemia may be manifested in behavioural changes [7,8]. Both adults and adolescents have been reported to experience pleasurable symptoms and symptoms of being 'high' [9–14], but these symptoms have never been scientifically studied before. Feelings of being 'high' may be explained by the psychosensorial experiences of derealization (distortion in how the immediate environment is perceived)

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What's new?

- There are multiple cases of people reportedly feeling 'high' during hypoglycaemia, which may be explained by psychosensorial symptoms (alterations in how one's environment and subjective self are perceived). This is the first study of psychosensorial symptoms during hypoglycaemia in adolescents with Type 1 diabetes
- Psychosensorial symptoms are common and are often reported as positive experiences during hypoglycaemia.
- There were no differences in how hypoglycaemia symptoms were reported in adolescents from two countries with different cultures.

and depersonalization (distortion in how one's own body and subjective self feel). These symptoms may contribute to episodes being perceived as positive, even desirable, rather than negative and potentially dangerous. Few paediatric studies have described the physical, mood and behavioural symptoms associated with hypoglycaemia and none have described psychosensorial experiences.

The aim of the present study was to broaden the understanding of hypoglycaemic symptoms in adolescents with Type 1 diabetes by describing self-reported psychosensorial symptoms as well as the physical, behavioural and mood symptoms of hypoglycaemia. We further sought to examine whether these symptoms were rated as 'good' (i.e. positive), 'bad' (i.e. negative), or 'both' (i.e. sometimes good and sometimes bad) by the participants. Taking advantage of the relationship of one of the present authors with the paediatric endocrinology clinics at both the University of North Carolina at Chapel Hill, Chapel Hill, NC, USA and Kocaeli University, Kocaeli, Turkey, we also decided to examine if the reported symptoms were consistent in these two different cultures.

Participants and methods

Questionnaire development

A 68-item questionnaire was developed to assess previous experiences with hypoglycaemia. The first item asked participants to report at what blood glucose level they typically 'begin to feel low' and the remaining 67 items were possible symptoms divided into five different categories: physical (19 items); behavioural (five items); mood (17 items); and psychosensorial (19 items), as well as a dummy category (seven items). The physical and behavioural symptoms were assembled from those described previously in the paediatric literature [7,8] and mood symptoms consisted of a compiled list of conventionally perceived negative (e.g. 'mean') and positive (e.g. 'silly') emotions. Psychosensorial items were based on studies on panic disorders and substance abuse [15,16]. Dummy items were symptoms that are not thought to be associated with hypoglycaemia (e.g. rash), and were used to assess the integrity of each participant's responses. Dummy items were used to exclude any participant who endorsed all dummy items because of concern about the credibility of participants' answers.

A five-point Likert scale was used to assess the frequency at which each symptom had ever been experienced (0 = never, 1 = rarely, 2 = sometimes, 3 = often, 4 = always); that is, participants would indicate that during hypoglycaemic events they never, rarely, sometimes, often, or always experienced a particular symptom. Participants who ever experienced a symptom (Likert score 1, 2, 3 or 4) were then asked to rate the symptom experience as 'good,' 'bad,' or 'both' (sometimes good, sometimes bad). At the completion of data collection, the Likert scale was condensed into two categories to improve statistical power: ever experienced a symptom vs never experienced a symptom (Likert score 0 vs 1, 2, 3 or 4).

The face and content validity of the questionnaire was examined by a panel of experts including paediatric endocrinologists, child psychologists and a survey methodologist, who reviewed the questionnaire content and construct. Item-total correlation was calculated to further examine survey construct. An item-total correlation > 0.2 was considered acceptable. Cronbach's α values for each symptom category were calculated to validate the questionnaire and assess whether the symptoms in each category measured similar concepts. An α value > 0.7 was considered acceptable.

The survey was first developed in the English language and then translated into Turkish by a paediatric endocrinologist and child psychologist fluent in both English and Turkish. Forward and backward translations were used to assess the accuracy of the language translation. During the first 2 weeks of the study, participants were asked if they had any difficulty understanding or answering the questionnaire after completing it, to assess the appropriateness of the language used as well as the ease of questionnaire completion; no difficulties were reported.

Participants

Children were eligible to participate if they: 1) had Type 1 diabetes for at least 6 months (to increase the likelihood that they had experienced hypoglycaemia); 2) were 12–18 years old (children aged <12 years may not be able to independently describe their hypoglycaemia symptoms as well as older children); and 3) received care from diabetes clinics at University of North Carolina or Kocaeli University. We invited 134 consecutive patients who met the eligibility criteria to participate during routine visits between February 2010 and June 2010. Of these, 133 participants and their parent/guardian provided written informed consent and completed the questionnaire anonymously and privately without parents in the room. The study was approved by

the institutional review boards of the University of North Carolina and Kocaeli University.

Medical record review

Medical records were reviewed to obtain demographic information including age, gender, duration of diabetes, and HbA_{1c} level at the time of study participation.

Data analysis

Demographic and clinical data from the time of study participation are reported as percentages or mean (SD) values for gender, age, HbA_{1c} level at the study visit, duration of diabetes and reported blood glucose level at which the patients begin feeling hypoglycaemic. We used *t*-tests to compare continuous variables and chi-squared tests to compare proportions for categorical variables.

Next, the percentage of participants who experienced each symptom was calculated, and a mean percentage of participants reporting symptoms was calculated for each symptom category. Similarly, the percentage of participants who rated a symptom (having reportedly experienced the symptom) as 'good,' 'bad,' or 'both' was calculated, and a mean percentage of participants was calculated for each category rating. To determine what percentage of participants endorsed the symptoms as ever being a positive experience, the percentage of participants that described symptoms as 'good' or 'both' was also calculated. To compare the ratings between symptom categories, a mixed-effects logistic regression model was used in order to avoid over-dispersion of a sequence of binary outcomes within the same symptom category by a participant. The odds ratio and its 0.95 CI were calculated based on the coefficient estimation and its Wald-type coverage in the logistic model.

Results at each site were analysed for differences using *t*-tests for continuous variables and chi-squared tests for categorical variables, and the results of the sites were combined after determining that there were no differences between sites for symptom category endorsements or ratings.

All statistical tests were two-tailed with an α value of 0.05 significance level. R software (R Development Core Team, Vienna, Austria) and IBM SPSS v. 19 (SPSS Inc., Chicago, IL, USA) were the statistical packages used for analyses.

Results

Cronbach's α values were > 0.7 for each symptom category except for the dummy items, demonstrating the reliability with which each real symptom category measured similar concepts (physical 0.81, behavioural 0.78, mood 0.82, psychosensorial 0.89, dummy 0.60). No symptom items were excluded from the questionnaire analysis based on item-total correlation results which were all > 0.2.

Of the 133 eligible and consenting participants, one participant's results were excluded from analysis because of having endorsed all dummy items, leaving a total sample size of 132 participants, 69 from the University of North Carolina and 63 from Kocaeli University. The study populations included slightly more boys (54%) than girls, and the mean (SD) age of the participants was 14.9 (1.9) years (Table 1). The sites differed with regard to duration of diabetes, mean HbA_{1c} level and blood glucose level at which symptoms began, such that participants at University of North Carolina had a higher mean HbA_{1c} level, a higher mean reported blood glucose level at which symptoms began and longer duration of diabetes at the time of study participation.

In examining the percentage of participants who ever experienced the symptoms presented in the questionnaire (i.e. reported a Likert score indicating 'rarely' to 'always'), we found that the most commonly reported symptom category was physical, with a mean of 65.2% of participants reporting each symptom (Table 2). The physical symptoms experienced by the most participants were trembling, weakness, feeling run down, headache and feeling 'awful'. Psychosensorial symptoms (depersonalization and derealization) were experienced on average by 48.9% of participants, and the most experienced symptoms were difficulty concentrating, lightheadedness, confusion, feeling 'spaced out', and 'feeling like you don't care'. A mean of 46.5% of participants reported behavioural symptoms. The most frequently experienced behavioural symptoms were odd behaviour, argumentativeness and aggressiveness. Mood symptoms were experienced by a mean of 42.8% of participants. The most experienced mood symptoms were jitteriness, unhappiness, edginess, uneasiness, and moodiness/feeling as though on an emotional roller coaster.

Table 1 Participant characteristics

	Overall *N*= 132	University of North Carolina *n* = 69	Kocaeli University *n* = 63
Male, %	53.8	53.6	54.0
Mean (SD) age, years	14.9 (1.9)	15.0 (±1.9)	14.7 (±1.9)
Mean (SD) HbA_{1c}* mmol/mol%	72 (19)	80 (18)	63 (17)
	8.7 (1.8)	9.4 (1.7)	7.9 (1.5)
Mean (SD) blood glucose level at which hypoglycaemia symptoms begin*, mmol/l	3.7 (0.9)	4.2 (0.7)	3.21 (0.8)
Duration of Type 1 diabetes <5 years†, %	48.7	39.4	58.8

*$P < 0.001$.
†$P = 0.022$.

Table 2 Percentage of participants endorsing hypoglycaemia symptoms

Physical category		Behavioral category		Mood category		Psychosensorial category		Dummy category	
Overall	65.2	Overall	46.5	Overall	42.8	Overall	48.9	Overall	10.5
Trembling	95.7	Odd behaviour	62.0	Jittery	68.8	Difficulty concentrating	79.9	Pain in joints	20.3
Weak	88.3	Argumentativeness	60.0	Unhappy	62.1	Lightheaded	78.4	Runny nose	12.1
Run down	86.1	Aggressiveness	54.0	Edgy	59.1	Confused	70.1	Itchy	10.9
Feeling awful	84.3	Meanness	39.4	Uneasy	54.7	Spaced out	62.8	Sneezing	9.5
Sweating	83.2	Naughtiness	17.3	Agitated	52.6	Just don't care about things	60.1	Stuffy nose	9.4
Tired	82.5			Moody/Emotional roller coaster	52.6	Things feel different	55.1	Cough	8.7
Sleepy	78.4			Irritable	49.6	Dazed/In a fog	51.4	Rash	2.2
Uncoordinated	77.9			Gloomy	49.6	Loosened up	45.3		
Dizziness	76.3			Calm	46.4	Things look different than normal	45.3		
Restless	60.4			Aggravated	46.3	Buzzed	42.1		
Sick	59.4			Sorrowful/Sad	37.8	Things sound different than normal	41.6		
Pounding heart	59.0			Jolly/Silly	34.5	Floating/Moving through the world differently	41.0		
Blurred vision	58.3			Excited	31.4	Free/Having let go from normal self	41.0		
Headache	57.1			Full/Rush of energy	30.0	World slightly strange/ unreal	39.9		
Warmness	55.1			Cheerful	19.0	Outside of body	38.4		
Slurred speech	40.6			Revved up	17.5	Mellow/Chilled out	38.0		
Yawning	40.3			Elated	14.9	Distant/Separate from real world	36.8		
Tingling lips	33.1					Daydreaming	34.8		
Tummy pain	22.6					Alert	26.6		

Generally, symptoms were reported as 'good' or 'both' by one-quarter to one-third of the participants. Of participants who ever experienced physical symptoms, 23.1% reported them as 'good' or 'both'. The physical symptoms most commonly reported as 'good' or 'both' were yawning, sleepiness, warmness, tiredness and restlessness. Of participants who ever experienced behavioural symptoms, 29.2% reported them as 'good' or 'both'. The behavioural symptoms most commonly reported as 'good' or 'both' were naughtiness, meanness and odd behaviour. Of participants who ever experienced mood symptoms, 36.9% reported them as 'good' or 'both'. The mood symptoms most commonly reported as 'good' or 'both' were feeling jolly/silly, cheerful, revved up, full/rush of energy and excited. The psychosensorial symptom category had the most positive responses, with 37.2% of participants reporting the symptoms as 'good' or 'both'. The psychosensorial symptoms most commonly reported as 'good' or 'both' were dreaming, feeling free/having let go of self, mellow/chilled out, alert and floating/moving through the world differently. The psychosensorial and mood categories had the highest odds of positive endorsement compared with other symptom categories [psychosensorial compared with physical: odds ratio 2.8 (95% CI 2.3, 3.4); psychosensorial compared with behavioural: odds ratio 1.7 (95% CI 1.2, 2.3); psychosensorial compared with mood: odds ratio 1.1 (95% CI 0.9, 1.4); mood compared with physical: odds ratio 2.5 (95% CI 2.1, 3.1); and mood compared with behavioural: odds ratio: 1.5 (95% CI 1.1, 2.1)]. The symptoms according to frequency and ratings for mood and psychosensorial categories are shown in Figs 1 and 2, respectively.

There was no statistically significant relationship for any symptom category endorsement frequency or ratings with study location, age, gender, HbA_{1c} level, reported blood glucose level at which hypoglycaemia symptoms begin, or duration of Type 1 diabetes at the time of study participation.

Discussion

As anticipated, we found that adolescents commonly experience physical and behavioural symptoms during hypoglycaemia, but this is the first study to report that many adolescents with Type 1 diabetes also experience psychosensorial symptoms of depersonalization and derealization and mood changes during hypoglycaemia. Surprisingly, hypoglycaemia symptoms are also sometimes described as positive experiences, particularly the psychosensorial and mood symptoms. The reported symptom experiences were similar in both the University of North Carolina and Kocaeli University samples, suggesting no difference between these two cultural settings.

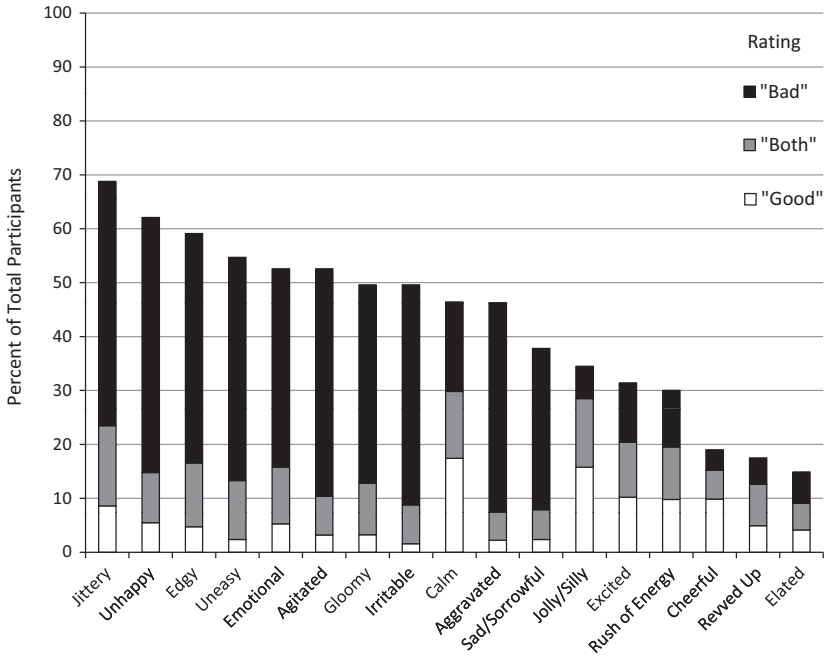

FIGURE 1 Percentage of participants reporting mood symptoms and how these symptoms were rated.

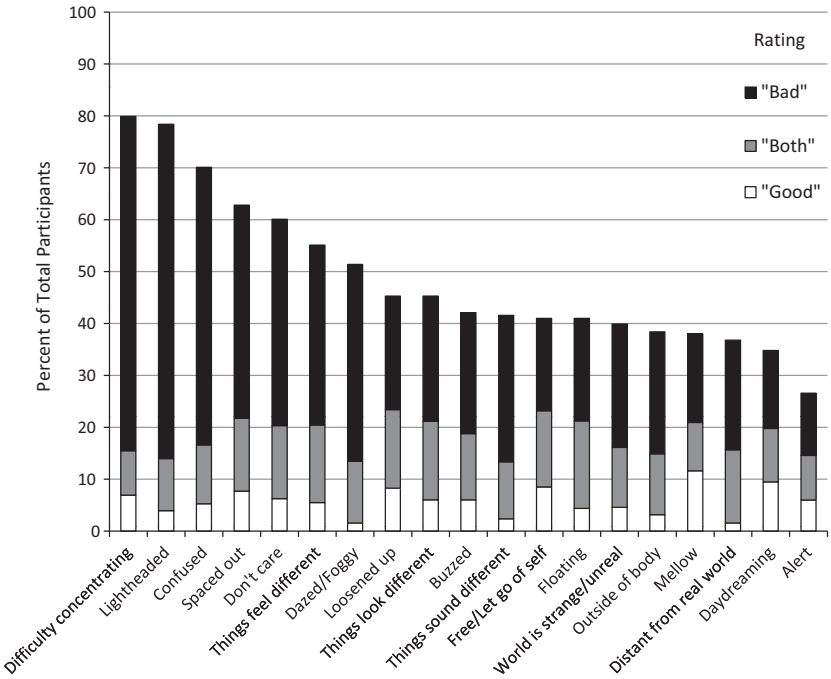

FIGURE 2 Percentage of participants reporting psychosensorial symptoms and how these symptoms were rated.

The present findings are supported by adult studies evaluating mood symptoms of hypoglycaemia, which have shown that low blood glucose is often associated with negative mood states, but also occasionally with positive mood states [1,17–19]. There have also been case reports of adults and adolescents who misuse insulin to achieve a euphoric or 'high' effect [7,8,14,20–22]. In a study by Schober et al. [14], 35% of adolescents who overdosed with insulin reported that feeling 'high' during hypoglycaemia was one of the reasons for their actions, in addition to suicidal intentions or attention seeking; therefore, we believe the present findings that adolescents experience mood changes

and psychosensorial symptoms, in addition to the well-known physical and behavioural symptoms of hypoglycaemia, and that these symptoms are sometimes positively experienced are valid.

Limitations of the present study include its relatively small sample size and reliance on recall of previous hypoglycaemic experiences. In addition, we were not able to report the frequency with which participants experienced hypoglycaemia. Nevetheless, based on the present work, further studies can now be designed in the knowledge that some adolescents endorse psychosensorial symptoms and that hypoglycaemia symptoms are sometimes reported as good. In addition, while our questionnaire categories demonstrated excellent internal consistency, as evidenced by high Cronbach's α values, further validation techniques would be needed before application to other populations.

Hypoglycaemia is known to cause a considerable burden to families of children with diabetes through increased anxiety, poor sleep and a high number of hospitalizations, while also leading to excessive lowering of insulin doses and worsening glycaemic control [21]. Prompt hypoglycaemia symptom recognition is important for reducing diabetes-associated morbidity and mortality such as the hypoglycaemia-associated decrease in neurocognitive function and structural brain changes found in some studies in young children with Type 1 diabetes [17–20,23,24]. Considering that negative symptoms of hypoglycaemia have been the focus of traditional diabetes education and that positive symptoms are likely to be more desirable and better tolerated, it is possible that some hypoglycaemia unawareness may be attributable to predominantly positive hypoglycaemic experiences that are not being recognized as possible symptoms of hypoglycaemia. An understanding of the array of hypoglycaemia symptoms reported in the present study, therefore, may help providers educate patients and their families regarding the variety of possible symptoms, including the potential for positive experiences. In turn, children with diabetes and their families may improve their recognition of hypoglycaemia, which could lead to faster treatment and prevention of complications.

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Competing interests

None declared.

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References

1 Frier BM. The incidence and impact of hypoglycemia in type 1 and type 2 diabetes. *Int Diabetes Monitor* 2009; **21**: 210–218.
2 Deary IJ, Hepburn DA, MacLeod KM, Frier BM. Partitioning the symptoms of hypoglycaemia using multi-sample confirmatory factor analysis. *Diabetologia* 1993; **36**: 771–777.
3 Gonder-Frederick LA, Cox DJ, Bobbitt SA, Pennebaker JW. Mood changes associated with blood glucose fluctuations in insulin-dependent diabetes mellitus. *Health Psychol* 1989; **8**: 45–49.
4 Hermanns N, Scheff C, Kulzer B, Weyers P, Pauli P, Kubiak T, Haak T. Association of glucose levels and glucose variability with mood in type 1 diabetic participants. *Diabetologia* 2007; **50**: 930–933.
5 McCrimmon RJ, Frier BM, Deary IJ. Appraisal of mood and personality during hypoglycemia in human participants. *Physiol Behav* 1999; **67**: 27–33.
6 Hermanns N, Kubiak T, Kulzer B, Haak T. Emotional changes during experimentally induced hypoglycaemia in Type 1 Diabetes. *Biol Psychol* 2003; **53**: 15–44.
7 McCrimmon RJ, Gold AE, Deary IJ, Kelnar CJ, Frier BM. Symptoms of hypoglycemia in children with IDDM. *Diabetes Care* 1995; **18**: 858–861.
8 Ross LA, McCrimmon RJ, Frier BM, Kelnar CJ, Deary IJ. Hypoglycaemic symptoms reported by children with type 1 diabetes mellitus and by their parents. *Diabet Med* 1998; **15**: 836–843.
9 Odei ELA. Insulin habituation and psychopathy. *Br Med J*. 1968; **2**: 346.
10 Retsas S. Insulin abuse by a drug addict. *Br Med J* 1972; **4**: 792–793.
11 Scarlett JA, Mako ME, Rubenstein AH, Blix PM, Goldman J, Horwitz DL *et al*. Factitious hypoglycemia. Diagnosis by measurement of serum C-peptide immunoreactivity and insulin-binding antibodies. *N Eng J Med* 1972; **297**: 1029–1032.
12 Scaramuzza A, Castellani G, Lorini R. Insulin abuse in an adolescent with insulin-dependent diabetes mellitus. *Eur J Pediatr* 1996; **155**: 526.
13 Cassidy EM, O'Halloran DJ, Barry S. Insulin as a substance of misuse in a patient with insulin dependent diabetes mellitus. *BMJ* 1999; **319**: 1417–1418.
14 Schober E, Wagner G, Berger G, Gerber D, Mengl M, Sonnenstatter S *et al*. Prevalence of intentional under- and overdosing of insulin in children and adolescents with type 1 diabetes. *Pediatr Diabetes* 2011; **12**: 627–631.
15 Márquez M, Sequí J, García L, Canet J, Ortiz M. Is panic disorder with psychosensorial symptoms (depersonalization-derealization) a more severe clinical subtype. *J Nerv Ment Dis* 2001; **189**: 332–335.
16 Somer E. Opioid use disorder and dissociation. In: Dell PF, O'Neil JA eds. *Dissociation and the dissociative disorders: DSM-V and beyond*. New York: Routledge/Taylor & Francis Group, 2009: 511–518.

17 Rovet JF, Ehrlich RM, Czuchta D. Intellectual characteristics of diabetic children at diagnosis and one year later. *J Pediatr Psychol* 1990; **15**: 775–788.
18 Ryan C, Vega A, Drash A. Cognitive deficits in adolescents who developed diabetes early in life. *Pediatrics* 1985; **75**: 921–927.
19 Northam EA, Anderson PJ, Jacobs R, Hughes M, Warne GL, Werther GA. Neuropsychological profiles of children with type 1 diabetes 6 years after disease onset. *Diabetes Care* 2001; **24**: 1541–1546.
20 Ho MS, Weller NJ, Ives FJ, Carne CL, Murray K, Vanden Driesen RI *et al*. Prevalence of structural central nervous system abnormalities in early-onset type 1 diabetes mellitus. *J Pediatr* 2008; **153**: 385–390.
21 Tupola S, Rajantie J, Akerblom HK. Experience of severe hypoglycaemia may influence both patient's and physician's subsequent treatment policy of insulin-dependent diabetes mellitus. *Eur J Pediatr* 1998; **157**: 625–627.
22 Deary IJ, Hepburn DA, MacLeod KM, Frier BM. Partitioning the symptoms of hypoglycaemia using multi-sample confirmatory factor analysis. *Diabetologia* 1993; **6**: 771–777.
23 Northam EA, Rankins D, Lin A, Wellard RM, Pell GS, Finch SJ *et al*. Central nervous system function in youth with type 1 diabetes 12 years after disease onset. *Diabetes Care* 2009; **32**: 445–450.
24 Lin A, Northam EA, Rankins D, Werther GA, Cameron FJ. Neuropsychological profiles of young people with type 1 diabetes 12 yr after disease onset. *Pediatr Diabetes* 2010; **11**: 235–43.