

STUDY PROTOCOL

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# Diabetes IN develOpment (DINO): the bio-psychosocial, family functioning and parental well-being of youth with type 1 diabetes: a longitudinal cohort study design

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## Abstract

**Background:** Strict glycemic control during adolescence decreases the risk of developing complications later in life, even if this level of control is not maintained afterwards. However, the majority of adolescents with type 1 diabetes (T1D) are in poor control and so far medical or psychological interventions have shown limited success. Adolescence is characterized by major biological, psychosocial, cognitive and parent-child relationship changes and the complex interaction between these developmental trajectories, and its impact on health outcomes is still poorly understood. A specific topic of interest in this context is the timing of diagnosis. The longitudinal study DINO (Diabetes IN develOpment) aims to examine:

- 1) If and how the onset of T1D before vs. during puberty results in different outcomes of glycemic control, self-management, psychological functioning and diabetes-related quality of life.
- 2) The timing of onset of disturbed eating behavior, its risk factors and its prospective course in relation to glycemic and psychological consequences.
- 3) If and how the onset of T1D before vs. during puberty results in different family functioning and parental well-being.
- 4) If and how the cognitive development of youth with T1D relates to glycemic control and diabetes self-management.

**Methods/design:** DINO, a longitudinal multi-center cohort study is conducted in youth with T1D in the age range 8–15 years at baseline. Participants will be divided into two subgroups: pre-pubertal and pubertal. Both groups will be followed for 3 years with assessments based on a bio-psychosocial model of diabetes, scheduled at baseline, 12 months, 24 months and 36 months examining the biological, psychosocial -including disturbed eating behaviors- and cognitive development, family functioning and parental well-being.

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**Discussion:** A better understanding of how the different trajectories affect one another will help to gain insight in the protective and risk factors for glycemic outcomes and in who needs which support at what moment in time. First results are expected in 2016.

**Keywords:** Type 1 diabetes, Development, Youth, Quality of life, Well-being, Adolescence, Cognition, HbA<sub>1c</sub>, Psychosocial, Parents

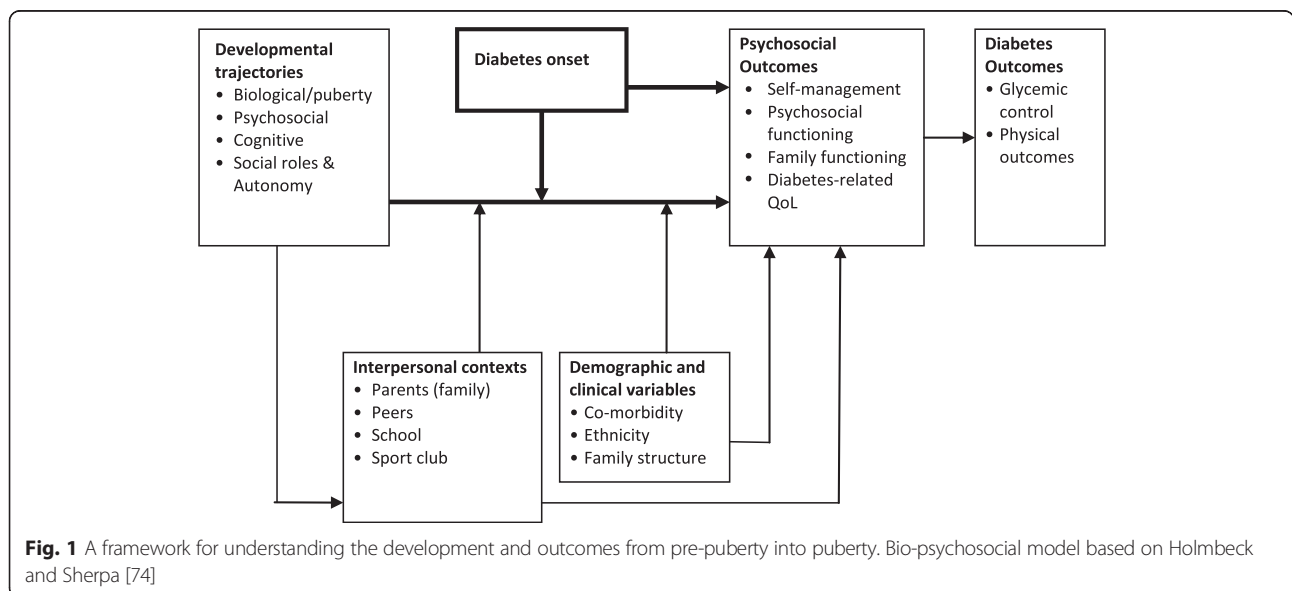
**Background**

In 2009, a report in the Lancet concluded that: “If present trends continue, doubling of new cases of type 1 diabetes in European children younger than 5 years is predicted between 2005 and 2020, and prevalent cases younger than 15 years will rise by 70 %. Adequate health-care resources to meet these children’s needs should be made available” [1]. This clearly underscores the importance of understanding the specific (changing) needs of youth with type 1 diabetes (T1D) to improve quality and efficacy of pediatric diabetes care. This holds in particular for adolescent diabetes care, as clinical data have shown repeatedly that during adolescent years patients have great difficulty reaching and maintaining optimal glycemic control [2, 3]. Less than 15 % of the young patients keep constant or reach HbA<sub>1c</sub> levels below 8 % (64 mmol/mol) from pre-puberty to young adulthood [2, 4]. In contrast to earlier belief, puberty years provide no protection against the risk of developing microvascular complications in later years as a result of prolonged hyperglycemia. In fact the reverse is true: Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study has convincingly shown that the better the glycemic control during adolescence, the lower the risk

of developing complications later on in life - even if that level of control is not maintained afterwards [5]. Adolescence is a critical period for the establishment of lifelong positive and risky health-related behaviors and, importantly, such ‘programming’ apparently applies to mental health as well [6]. In what manner biological, psychosocial and cognitive programming interact in youth with T1D is largely unknown. Of interest is the question how different trajectories develop during pre- and pubertal years, and to what extent these years offer a window of opportunity for early detection and targeted interventions to improve health outcomes. With the longitudinal cohort research DINO (Diabetes IN deVelOpment) the complex interaction of biological, psychosocial and cognitive development, family functioning and parental well-being will be studied. In order to do so, a bio-psychosocial approach is called for. The bio-psychosocial model appreciates these complex interactions, the onset and the demands of diabetes (Fig. 1).

**Biological development**

There is substantial variation between individuals in the time of onset, duration and termination of the pubertal development and these differences have social and psychological consequences [7]. In addition is known that



the onset and termination of puberty is delayed in children with diabetes compared to healthy youth [8, 9]. However, the consequences for diabetes self-management and health outcomes have not been studied. Research revealed that glycemic control tends to be better for children with shorter diabetes duration [10–12]. One study specifically showed that in T1D patients with pubertal compared to pre-pubertal onset, glycemic control was better and daily insulin doses were lower after 6 years of diabetes, irrespective of age-related factors [13]. Perhaps as a result of that, pre-pubertal onset of diabetes is found to predict earlier onset of retinopathy [14], suggesting that youth diagnosed during or after puberty do better than those diagnosed early in life. Older longitudinal studies showed that patients diagnosed before the age of 13 had better adherence to diabetes management over a 4 year follow-up period compared to patients diagnosed after this age [15]. Deterioration in adherence occurred in all age ranges as duration increased [10]. It is of note, that these longitudinal studies used age as an indicator for pubertal status and not the actual physical development such as Tanner stage, in which the based on primary and secondary sex characteristics is scaled [16]. Gender differences and individual variations in puberty onset were therefore not taken into account in these previous studies. Reviews have clearly identified the lack of prospective cohort studies in representative (pre)pubertal groups [17, 18]. Whether developing diabetes during puberty alters the duration and termination of puberty and results in psychological risks is unknown.

### **Psychosocial development**

In general, mid-adolescence appears the most vulnerable period for developing psychological problems [19]. In youth with diabetes, rates of depression, anxiety and disturbed eating behavior tend to be worrisomely elevated and are associated with poor glycemic control [20–23]. Adolescents with T1D have more emotional issues compared to healthy peers [24]. A study in female adolescents with diabetes showed that adolescents diagnosed <3 years from menarche [25], a lower overall sense of control was associated with poorer metabolic control. Hormonal fluctuations due to puberty can result in frequent ‘unexplainable’ (high) blood glucose values, easily inducing feelings of anger, frustration and discouragement, thereby contributing to poor adherence and subsequent deterioration of glycemic control and quality of life (QoL) [26]. Ten years after diagnosis, young adults with diabetes seem in general to be psychologically well adjusted, but do report lower perceived competence, including self-worth [27]. Low (diabetes specific) self-esteem is found to be associated with poor adherence and a predictor of deteriorating glycemic control in late adolescence [4, 28]. However, as stated before, the majority of these studies have not made a distinction between pre-

and pubertal onset of diabetes and can therefore not inform us on the relevance of timing of diabetes onset on psychosocial development.

Adolescents with T1D are at an increased risk of disturbed eating behavior (DEB) compared to healthy peers [29–33] due to hormonal changes [3], the focus on food, issues around control and autonomy in diabetes care. This ‘Diabulimia’ has been frequently reported among adolescents with T1D; 33–53 % reported to engage in unhealthy eating behaviors and insulin restriction for weight purposes was prevalent in up to 30 % of patients [31, 34–39]. DEB increases the risk for poorer glycemic control, earlier complications from diabetes, particularly retinopathy and nephropathy as well as mortality [32–37, 40–43]. In T1D, it is suggested that in most cases the DEB developed after diabetes onset [44]. Although the peak of onset of DEB is in adolescence only one study assessed risk factors for the onset of DEB in adolescent girls [45]. Currently, diabetes teams are hesitant to discuss DEB with their patients [46], because they are afraid they might bring the association between insulin and weight control to mind of the adolescent. It is important to know the timing of onset of DEB, who is at risk, how to address these behaviors and to be able to identify those at risk for DEB [40].

### **Cognitive development**

Neuropsychological research shows that children with T1D, especially those with early-onset diabetes ( $\leq 6$  years of age), have mild impairment of cognitive functioning [47] including poorer academic achievement [48], lower verbal intelligence, and worse performance on measures of attention, executive function, mental flexibility, and psychomotor speed [47] compared to healthy controls. This challenges adolescents’ diabetes adherence behaviors, since these tasks are of great importance to organize and plan the diabetes management.

In general, adolescence is a critical period for brain maturation, essential for the development of higher cognitive functions. Significant improvements in cognitive processing speed and intellectual functioning are evident throughout adolescence and mature in young adulthood, with the most dramatic improvements occurring in the development of executive functions including abstract thought, organization, decision making, planning, and response inhibition [19, 49]. This implies that later on in adolescence the ability to critically outweigh the costs and benefits of (non) adherence behaviors increases [50]. However, until that time the adolescent’s brain is inclined to engage in risk taking behavior and prefers immediate rather than long term satisfaction [49]. Given their stage of cognitive development and the challenges facing adolescents might challenge their ability to manage their diabetes on a daily basis.

### Family functioning and parental well-being

The way the family of T1D youth functions is important, both as determinant and consequent of poor diabetes control. A negotiating parent–child environment is beneficial for children with diabetes. In addition, shared responsibility for diabetes management tasks is shown to be associated with better psychological health, self-care behavior and metabolic control [51–53]. A lack of collaboration between children and parents can result in conflicts which are often associated with poor glycemic control and QoL [54, 55], however, this seems to be related to ethnicity [56]. Shared responsibility regarding diabetes tasks between parents and adolescents (rather than complete/sudden transfer of parental control) for diabetes management may serve as a way to achieve autonomy for self-care. Youth with an inordinate self-care autonomy relative to their psychological maturity are at greater risk of poor treatment adherence, worse diabetic control and more hospitalizations [57]. Inconsistencies regarding competence and independence between parents and children with T1D is associated with poorer diabetes outcomes [58]. Furthermore, the better parents are able to adopt youth's perspectives the better the glycemic control [59]. Recent research reveals that parental involvement [60] in diabetes care and greater overall parental support [61] are associated with better health [60] and service use [61], and greater parental motivation is related to child's healthier diet [62]. These findings highlight the importance of parenting practices. One of the major tasks for parents is to be responsive to adolescents' needs for increasing responsibility and decision making power while at the same time maintaining a high level of cohesiveness in the family. However, parental well-being influences the way this task proceeds. Recent research reveals that parents with T1D children were more anxious and perceived less family cohesion than the parents of healthy youth [63]. The diagnosis, hypoglycemic events, as well as the chronic nature of diabetes and its demands all contribute to anxiety and depressive symptoms in parents [64, 65]. Importantly, worse parental well-being is shown to be associated with poorer glycemic control of the children [66, 67] and maternal depression is found to be associated with acute hospitalization [68]. Of interest is how family functioning and parental well-being influences adolescents' diabetes outcomes and development, and how parental well-being influences youths' diabetes and psychosocial outcomes.

Overall, studies integrating the biological, psychosocial and cognitive developmental trajectories, family functioning and parental well-being are lacking [18] with a few positive exceptions. Wiebe *et al.* examined the relationship between self-efficacy, parental responsibilities, pubertal maturation and adherence [69]. Luyckx *et al.*

determined developmental classes of glycemic control in young people with T1D throughout adolescence and emerging adulthood, in relation to general family climate and self-concept [4]. King *et al.* used latent growth class analysis to look at trajectories of metabolic control in relation to autonomy, diabetes management and hospitalizations [60]. These studies used a person-centered approach that is uniquely suited to capture diversification in glycemic control, looking for meaningful subgroups characterized by unique developmental pathways.

### Overall aims and research question

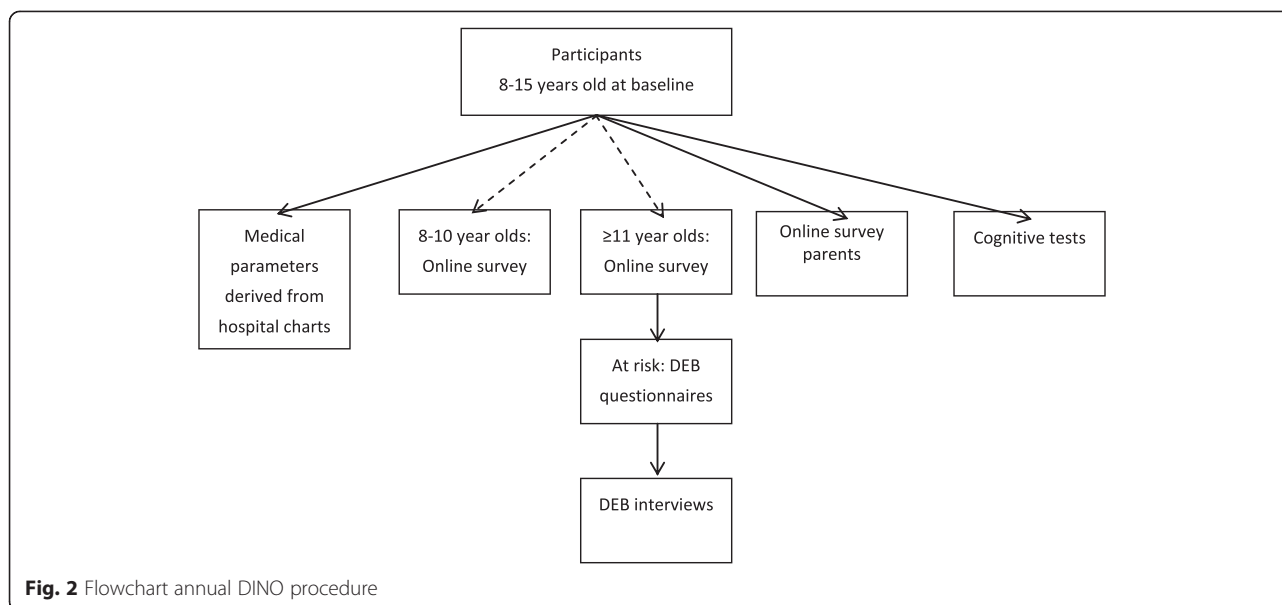
There is paucity of evidence with regard to the question if and how (living with) diabetes during pre-pubertal years and early adolescence predict glycemic control, self-management, psychosocial functioning and diabetes-related QoL during later years. The importance of being diagnosed with diabetes before versus during puberty has hardly received attention in past decades, while the mechanisms and role of puberty could give important information for (well-timed) future interventions.

The primary goal of DINO is to further our understanding how the onset of diabetes impacts the biological, psychosocial and cognitive development and family functioning and parental well-being during pre-pubertal and pubertal years in Dutch youth with T1D. With DINO we will examine:

- 1) If and how the onset of T1D before vs. during puberty results in different outcomes of glycemic control, self-management, psychological functioning and diabetes-related quality of life.
- 2) The timing of onset of disturbed eating behavior, its risk factors and its prospective course in relation to glycemic and psychological consequences.
- 3) If and how the onset of T1D before vs. during puberty results in different family functioning and parental well-being.
- 4) If and how the cognitive development of youth with T1D relates to glycemic control and diabetes self-management.

### Methods/Design

A prospective multi-center cohort study will be conducted in youth with T1D in the age range 8–15 years at baseline. For 3 years, participants' biological, psychosocial and cognitive development will annually be assessed (at baseline, 12 months, 24 months and 36 months), as represented in Fig. 2. During the course of the study, newly diagnosed youth will be included 6 months after diagnosis -when diabetes regimen is habituated- and follow the scheduled assessments. By consequence, not all newly diagnosed will have the same



number of assessments. Participants will be divided into two subgroups:

- A) Pre-Pubertal Onset of Diabetes (Tanner stage 1) and
- B) Pubertal Onset of Diabetes (Tanner stage 2–5).

Group A will provide information on the effects of puberty on the developmental trajectories in relation to diabetes outcomes in youth already diagnosed with diabetes. Group B will provide information on how the onset of diabetes affects the developmental trajectories.

#### Procedure and participants

Five Dutch pediatric diabetes care clinics agreed to participate. Pediatricians will recruit youth diagnosed with T1D and their parents. Exclusion criteria are: other types of diabetes than Type 1 (e.g. type 2 or MODY), younger than 8 years or older than 15 years at baseline, not speaking the Dutch language, and mental retardation. All medical parameters are taken from hospital charts and no extra tests will be performed. As represented in Fig. 2, youth between 8 and 15 years at baseline with T1D who consent to participate will complete an online survey regarding their psychosocial development. If a paper survey is preferred or participants do not respond to the e-mail, a paper version is sent to their home address. Due to the age difference, 8–11 year olds will complete a shorter and more simple survey than participants 11 years and older. To gain better insight in the perspectives of the adolescents about DEB, we will conduct interviews with a selection of youth. Only youth at risk (based on their answers on the online survey) will be invited for the interview. The interviews will take place at the adolescent's residence or at the outpatient

clinic, depending on the adolescent's preference. Parents will report on family functioning and parental well-being by an online survey as well, unless the paper version is preferred. A neuropsychological test battery will be used to assess the cognitive development. Most test results will be compared to normative data, however, three measures will also be administered to a gender and age matched sample of 100 healthy controls as reference values are not yet available for these tasks. These healthy controls are derived from schools in the Netherlands and will be measured cross-sectional.

#### Ethical considerations

The study protocol was approved by the medical ethical committee of VU University Medical Centre (date: December 19th, 2012). Youth and parents are provided with written information about the study and are asked to provide written informed consent (both parents -if applicable- and youth  $\geq 12$ ) prior to the data collection.

#### Study measures

An overview of study measures is shown in Tables 1, 2 and 3.

A full description of these measures is presented in the online text Additional file 1.

#### Data analyses

Using descriptive statistics, baseline data are analyzed cross-sectionally and scores are compared with reference values when applicable. Uni-variate analysis ANOVA will be used to explore differences between boys and girls and Tanner stages. Pearson or Spearman correlation is used to explore associations between several outcomes (such as age, cognitive development, social-emotional

**Table 1** Overview of study measures – Socio-Demographic and clinical data

	History	Baseline	12 months	24 months	36 months
Socio-Demographic data					
Date of birth		H			
Gender		H			
Ethnicity		P			
Education level child		P + C	P + C	P + C	P + C
Socioeconomic status		P			
Family structure		C	C	C	C
Family related life events	P	P	P	P	P
Clinical data					
History of medical and psychological co-morbidity	H	H	H	H	H
Treatment regime		H	H	H	H
Care consumption	H	H	H	H	H
Tanner stage at time of diagnosis [16]		H			
Current Tanner stage [16]		H	H	H	H
Blood pressure		H	H	H	H
Weight and Height		H	H	H	H
Hemoglobin A1c (HbA1c)	H	H	H	H	H
Number of diabetes related hospitalizations	H	H	H	H	H
DKA	H	H	H	H	H
Indicators for complications	H	H	H	H	H
Severe hypoglycemic episodes	P	P	P	P	P

H Hospital, P Parent, C Child, HC Healthy control

development, glycemic control, psychological functioning, QoL, diabetes management and DEB). To examine whether associations are mediated by other variables, multiple mediation analysis will be used [70].

With regard to the cognitive development, performance on the computerized measures will be administered to a gender and age matched sample of 100 healthy controls. Because of the longitudinal nature of this study, Generalized Estimation Equations (GEE) is used to examine the differences between the two groups diagnosis pre-puberty vs puberty on glycemic control, self-management, psychological functioning and diabetes related QoL. The differences between the two groups on family functioning and parental well-being and the development of DEB are investigated by GEE as well. GEE adjusts for the correlation between repeated observations taken in the same patient and has the advantage of handling longitudinal data on subjects with varying numbers of unequally spaced observations. The latter is important, because the assessments are scheduled within routine care and as a consequence, the time between the consultations will differ. Longitudinal linear regression analyses, using GEE, enables us to examine the association between the developmental trajectories in relation to diabetes onset and outcomes.

Data are controlled for demographic and clinical variables and examined for associations with and predictors of biological and social-emotional developmental outcomes. Latent class growth analysis is used to identify developmental trajectories of glycemic control and psychological, cognitive and family functioning.

For the analyses of the interviews, a framework approach is used [71, 72]: interviews are transcribed verbatim and key words and codes extract content from the text is assigned by two researchers, at least for the first few transcripts using Atlas.Ti.

#### Sample size

Sample size calculations indicate that a sample of 86 patients is sufficient to detect a statistically clinically difference of  $\geq 0.5\%$  HbA<sub>1c</sub> (sd = 1.1 %) at a significance level of 5 % with a power of 80 %, given three follow-up measurements using GEE analyses and taking into account the within-subject correlation ( $\rho = 0.7$ ). Sample size calculations for psychological functioning (as measured with the SDQ) indicate that a sample of 40 patients is sufficient to detect a difference of 20 % in the proportion likely “cases” with mental health disorders (assuming  $p = 0.33$  [73]) at a significance level of 5 % with a power of 80 %, given three follow-up measurements using longitudinal

**Table 2** Overview of study measures – Psychosocial development, DEB, Cognitive development

Psychosocial development					
Strengths and Difficulties Questionnaire (SDQ) [75]		P + C ≥11	P + C ≥11	P + C ≥11	P + C ≥11
Revised Children's Quality of Life Questionnaire (KINDL-R) self esteem subscale [76]		C	C	C	C
KIDSCREEN Autonomy subscale [77, 78]		C ≥11	C ≥11	C ≥11	C ≥11
Diabetes Family Responsibility Questionnaire (DFRQ) [79]		P + C ≥11	P + C ≥11	P + C ≥11	P + C ≥11
MIND Youth Questionnaire (MY-Q) [80]		C	C	C	C
Adapted version for 8–10 year olds					
Confidence in Diabetes Self-care Youth (CIDS-youth) [81]		C ≥11	C ≥11	C ≥11	C ≥11
Mismanagement scale – renewed [82]		C ≥11	C ≥11	C ≥11	C ≥11
Adherence	H	H	H	H	H
Disturbed Eating Behavior (DEB) <sup>a</sup>					
2 questions regarding dieting status and frequency			C ≥11	C ≥11	C ≥11
Diabetes Eating Problems Scale-Revised (DESP-R) [36, 43]			C ≥11	C ≥11	C ≥11
Questions of the AHEAD study [35]			C ≥11	C ≥11	C ≥11
DEB semi structured interview			C ≥11		
2 MY-Q subscale body and weight [80]			P	P	P
Cognitive development					
Wechsler Intelligence Scale for Children III (WISC-III) subtests Information; Picture Arrangement; Arithmetic; Block Design; Digit Span [83, 84]		C + HC	C	C	C
Attention Network Task (ANT)-adapted version [85, 86]		C + HC	C	C	C
Eriksen Flanker Task [87, 88]		C + HC	C	C	C
Klingberg Task – adapted version [86, 89, 90]		C + HC	C	C	C
Behavior Rating Inventory of Executive Functioning questionnaire (BRIEF) [91, 92]		C + HC	P	P	P

H Hospital, P Parent, C Child, HC Healthy control

<sup>a</sup>DEB is assessed in a step-wise manner in order to minimize the burden in adolescents with no DEB and younger participants. Kindly note the online text Additional file 1

logistic regression analyses and taking into account the within-subject correlation ( $\rho = 0.2$ ). This means that in order to detect differences in HbA<sub>1c</sub> and likely cases of psychological dysfunction between youth with pre vs. pubertal onset of diabetes, both groups should contain at least 43 patients. Given an expected drop-out rate of 10 %, we will include at least an additional 4 patients in each group. Therefore, we aim to include a minimum of 100 boys and 100 girls ( $N = 200$ ).

## Discussion

To the best of our knowledge, only a few studies have examined the effect of diabetes onset during pubertal vs. pre-pubertal years and little longitudinal research is available in children and teenagers with T1D, although a

lot changes during pubertal years. There is large individual variability in glycemic and psychological trajectories. The way youth and families cope with puberty and the developmental changes differ as well. In our research project DINO we aim to assess the different developmental trajectories (biological, psychosocial -including disturbed eating behaviors- and cognitive) and family functioning and parental well-being. This will provide insight in protective and risk factors for glycemic outcomes and in who needs which support at what moment in time. Better understanding contributes to the optimization of pediatric diabetes care. This might include the use of more sensitive screening instruments, for example to assess cognitive functioning in relation to self-management, risk factors for DEB and other psychological problems. This would enable diabetes teams to better personalize their care for adolescents with diabetes. Better understanding can contribute to the development of new interventions aimed at, for example, prevention and/or treatment of depressive symptoms and better tailoring of self-management education to the developmental phase of the child. First results of DINO are expected in 2016.

**Table 3** Overview of study measures – parental assessment

Parental assessment				
Problem Areas In Diabetes-Parents Revised (PAID-PR) [93, 94]	P	P	P	P
WHO-Five Well-being Index (WHO-5) [95–97]		P	P	P
Diabetes Family Behavior Checklist (DFBC) [98]		P	P	P

H Hospital, P Parent, C Child, HC Healthy control

### Limitations of this comprehensive study

A selection bias and the adolescents lost to follow up might influence the external validity of the results. However, this is almost unavoidable in longitudinal research studies. In addition, the newly diagnosed youth are not followed the entire 3 years of the study. To assess psychological development and family functioning and parental well-being self-report measures are used. With regard to the cognitive development, there can be an interviewer or observers bias as multiple test leaders will perform the neuropsychological assessments throughout the Netherlands. With a standardized training program we try to minimize the bias. The use of neuroimaging techniques such as functional Magnetic Resonance Imaging (fMRI) might provide a more objective, additional source of information, nonetheless this was not an option within the current budget. As seen in the biopsychosocial model (Fig. 1) the T1D adolescent functions in a broad social network. School and friends for example play an important role in youth's development, yet we did not include these factors because of the feasibility of the study.

### Additional file

**Additional file 1: Study measures online text supplement.**

### Abbreviations

T1D: Type 1 diabetes; DCCT/EDIC: Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications; DINO: Diabetes IN developMent; QoL: Quality of Life; DEB: Disturbed eating behavior; HbA1c: Hemoglobin A1c; SDQ: Strengths and difficulties questionnaire; KINDL-R: Revised children's quality of life questionnaire; DFRQ: Diabetes family responsibility questionnaire; MY-Q: MIND youth questionnaire; CIDS-youth: Confidence in diabetes self-care youth; DESP-R: Diabetes eating problems scale-revised; WISC-III: Wechsler Intelligence Scale for Children-III; ANT: Attention network task; BRIEF: Behavior rating inventory of executive functioning questionnaire; PAID-PR: Problem areas in diabetes-parents revised; WHO-5: WHO-five well-being index; DFBC: Diabetes family behavior checklist.

### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

ME conducted the design of the study, collect and research data, and wrote manuscript. MdW conducted the design of the study, and reviewed and edited the manuscript. JR reviewed and edited the manuscript. HJA reviewed and edited the manuscript. WMBvW reviewed and edited the manuscript. ECAMH reviewed and edited the manuscript. ML conducted the cognitive tests and reviewed and edited the manuscript. JO conducted the cognitive tests and reviewed and edited the manuscript. PW reviewed and edited the manuscript. FS reviewed and edited the manuscript. All authors read and approved the final manuscript.

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