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DISSERTATION

Health-related Quality of Life of Children and Adolescents with Chronic Conditions: Evaluation and Application of the Kids-CAT in Clinical Practice

zur Erlangung des akademischen Grades

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Abstract

Background: Health-related quality of life (HRQL) is an important patient-reported outcome in health research and health policy. However, regular assessment of HRQL is not well established in clinical routine. The Kids-CAT, a computer-adaptive test to assess the HRQL of children and adolescents, comprises five health domains and belongs to a new generation of patient-reported outcome measures that minimises the process-related challenges of implementation in clinical practice.

Objective: This thesis aimed to investigate the experience of paediatricians and young patients using the Kids-CAT in clinical practice and to explore the HRQL of children and adolescents with three chronic conditions (such as asthma, diabetes mellitus, and juvenile arthritis) and the associations between HRQL and clinical data.

Methods: The Kids-CAT study was a longitudinal observational study including clinical and home assessments at eight time points over one year. The user-friendliness of the Kids-CAT was assessed using three items presented to young patients. The experiences of paediatricians using the Kids-CAT in clinical practice were evaluated in focus group interviews. The HRQL of 312 young patients was measured using the Kids-CAT. Clinical data were reported by the treating paediatricians. Associations between HRQL and clinical data were explored on the domain level using linear regression analysis. Trajectories of HRQL were assessed for the diabetic sub-sample including 203 young patients using linear mixed-effect models. Path analysis were conducted in the same sub-sample to assess the associations between HRQL and glycated haemoglobin (HbA1c) levels over six months.

Results: Completion of the Kids-CAT was perceived as easy by 89.4% of the young patients. Focus groups suggested that the Kids-CAT data were valued as meaningful additional information that facilitated the identification of important aspects regarding HRQL of their patients. Overall, young patients achieved good scores in all five Kids-CAT domains; however, only minimal cross-sectional and longitudinal association were found between HRQL and clinical data. Sociodemographic and clinical data explained between 4.7-18.5% of the variance in the five Kids-CAT domains. Path analyses indicated minimal negative temporal associations between certain Kids-CAT domains and HbA1c levels.

Conclusion: The Kids-CAT is a user-friendly and practicable tool to assess the HRQL of children and adolescents in clinical practice. Minimal association between self-reported HRQL and clinical data indicate that HRQL cannot be derived from sociodemographic and clinical data and should be monitored as a distinct treatment goal. Self-reported HRQL data provides important information that has to be addressed in clinical practice.

Abstract in German

Hintergrund: Die gesundheitsbezogene Lebensqualität (LQ) ist ein wichtiges patienten-berichtetes Ergebnis in der Gesundheitsforschung und Gesundheitspolitik. Allerdings ist die routinemäßige Erfassung der LQ in der klinischen Routine noch nicht etabliert. Der Kids-CAT, ein computer-adaptiver Test zur Erfassung der LQ von Kindern und Jugendlichen, umfasst fünf Gesundheitsdomänen und gehört zu einer neuen Generation von Instrumenten zur Erfassung von patientenberichteten Ergebnissen, welche prozessbezogene Herausforderungen bei der Implementierung in der klinischen Praxis minimieren.

Ziel: Das Ziel dieser Dissertation war es die Erfahrungen von Pädiatern und jungen Patienten bezüglich der Nutzung des Kids-CAT in der klinischen Praxis zu untersuchen. Des Weiteren sollte die LQ von Kindern und Jugendlichen mit Asthma, Diabetes mellitus und juvenile Arthritis sowie der Zusammenhang von LQ und klinischen Daten exploriert werden.

Methoden: Die Kids-CAT Studie war eine längsschnittliche Beobachtungsstudie mit acht klinischen und häuslichen Erhebungszeitpunkten über den Zeitraum von einem Jahr. Mittels drei Fragen wurde die Nutzerfreundlichkeit des Kids-CAT von den Patienten bewertet. Die klinische Praxiserfahrung der Pädiater mit dem Kids-CAT wurde durch Fokusgruppeninterviews evaluiert. Die LQ von 312 Patienten wurde mittels des Kids-CAT erhoben und klinische Daten durch die behandelnden Pädiater berichtet. In Anwendung linearer Regressionen wurde auf Domänebene der Zusammenhang zwischen LQ und klinischen Daten untersucht. In einer Subgruppe (203 Kinder mit Diabetes mellitus) wurden mittels linearer gemischter Modelle die zeitlichen Verläufe von LQ untersucht. Pfadanalysen wurden in der gleichen Subgruppe durchgeführt, um den Zusammenhang zwischen LQ und HbA1c über den Zeitraum von sechs Monaten zu untersuchen.

Ergebnisse: Die Beantwortung des Kids-CAT wurde von 89.4% der jungen Patienten als leicht wahrgenommen. In den Fokusgruppen wurden die zusätzlichen Informationen durch den Kids-CAT als bedeutsam beschrieben. Diese ermöglichten es, wichtige Aspekte in Bezug auf die LQ der Patienten zu identifizieren. Insgesamt erzielten die Patienten gute Werte in allen fünf Kids-CAT Domänen. Allerdings wurden nur minimale querschnittliche sowie längsschnittliche Zusammenhänge zwischen der LQ und den klinischen Daten gefunden. Soziodemographische und klinische Daten konnten zwischen 4,7-18,5% der Varianz in den fünf Kids-CAT Domänen aufklären. Die Pfadanalysen zeigten minimale negative zeitliche Zusammenhänge zwischen einzelnen Kids-CAT Domänen und HbA1c Werten.

Schlussfolgerung: Der Kids-CAT ist ein nutzer-freundliches Instrument zur Messung der LQ von Kindern und Jugendlichen in der klinischen Praxis. Der minimale Zusammenhang zwischen selbstberichteter LQ und klinischen Daten weist darauf hin, dass LQ nicht aus soziodemographischen und klinischen Daten abgeleitet werden kann und daher als eigenständiges Behandlungsziel nachverfolgt werden sollte. Selbstberichtete LQ Daten liefern wichtige Informationen die in der klinischen Praxis adressiert werden sollten.

Introduction

The assessment of health-related quality of life (HRQL) aims to transform health care by including the patients' perspective in health policy, health research, and clinical practice. HRQL data, referred to as *patient-reported outcomes* (PROs), are usually collected directly from the patient (1). HRQL is a multidimensional latent construct related to the three broad dimensions of physical, mental, and social health (2). PROs are reported by patients themselves without being interpreted by a third person and are measured using patient-reported outcome measures (PROMs) (2). These data can be used for screening, evaluation, and monitoring that in turn can aid health care decision making (3-5). In light of the increasing burden of chronic conditions, improvement or maintenance of HRQL has become an important goal in health care and complements established health outcome indicators such as mortality and morbidity (6, 7).

The inclusion of PROs is inconsistent in different areas of the health sector. While PROs are indispensable in health research and required by health authorities, their routine use in clinical practice has not yet been established (1, 8, 9). Currently, there are several issues that prevent the large-scale implementation of PROs in clinical practice. The challenges include practical issues related to infrastructure, processes, and resources (5, 8, 10). In clinical routine, PRO results are most valuable if they are available shortly after completion of the assessment, similar to radiographs or laboratory values (5). Tasks such as data collection, entry, and scoring must be organised to ensure that PRO scores are available for clinical evaluation (5). Barriers regarding social, cultural, and personal attitude towards using PROs in clinical care can also hamper implementation (5, 8, 11). Although, HRQL is often stated as a treatment goal in health care, the treatment typically remains focused on the pathophysiological processes and symptom management, based on the assumption that improvement and maintenance of HRQL can be accomplished simultaneously. Moreover, a lack of knowledge regarding PROs and PROMs and lack of experience in interpreting PRO scores have been reported as obstacles using PROs in clinical practice (5, 11).

The choice of a PROM should be based on various considerations such as psychometric properties and characteristics of an instrument and purpose of use (1). Instruments are usually developed for a defined population and to measure specific aspects that are integrated in a conceptual framework (1). In addition, results of different PROMs, allegedly assessing the same health aspects or domains, are frequently not comparable if not scored on the same metric (12). The respondent burden is another important aspect to consider when selecting a PROM (13).

Precision of measurement can be enhanced by increasing the number of items in a PROM; however, each additional item adds to the burden on the patients because answering a large set of items can be exhausting. Thus, the length of a PROM must be carefully balanced between high precision (i.e., more items) and the respondent burden. Furthermore, the mode of administration (such as paper-and-pencil questionnaires or electronic assessment via personal computers, tablet computers, or smart phones) and the availability of translation and cultural adaptation of a PROM must be taken into account (1).

Although the development and implementation of PROs have predominantly focused on adult PRO measures, the field of paediatrics is catching up (3). Particular considerations are necessary when developing new measures for young patients owing to factors such as age and developmental stage (14). In general, children need sufficient reading skills to answer the items, but more importantly, they need the cognitive abilities to understand the concepts that are being assessed (14). The lack of evidence that children younger than five years can report valid and reliable data on aspects of HRQL has led to the common agreement that proxy reports (mostly parent-reported) should be used to assess HRQL for children under five years (14, 15).

Over the last decade, various self- and proxy-reported instruments to assess HRQL in children and adolescents have been developed and validated (3, 15-17). Although most of these are based on static assessment – that is, the same items are administered to all respondents – a new generation of PROMs have been receiving considerable attention in the field of PROs. These are based on modern test theory methods and allow the application of computer-adaptive testing (CAT) (12, 18, 19). To date, only few PRO-CATs are available in the field of paediatrics. The CAT tests are based on item response theory (IRT) methods, a probabilistic framework that links item responses to the underlying latent variables (20), an approach that offers the potential to measure more precisely while reducing the respondent burden (12, 18). Based on a predefined algorithm patients have to answer only items that add additional information for estimating the latent trait of a specific domain. The CAT accesses adomain-specific item bank that includes a broad range of items all related to the same content area (e.g., physical function, sleep, and fatigue), which represents the different severity levels of the continuum of the specific domain. All items of an item bank are calibrated on one metric; thus, they are set in relation to each other, taking into account the item difficulty of each item. After the respondent answers the first item (predefined start item), the individual location on the latent trait (referred to as the theta score) of the respondent is calculated (12). On the basis of this score, a first crude

estimation of the respondent's theta score on the continuum is made. Based on this initial information, the CAT selects the next item, that is, the item that provides maximum information about the latent trait of the respondent (12, 18). Thus, each respondent answers an individual set of items selected from the item bank. As all items are calibrated on one metric, the estimated theta scores remain comparable between respondents (21). Many IRT-based measures transform theta scores to the widely used T-score metric (linear transformation). Intuitive evaluation of the T-scores (M = 50; SD = 10) is possible as the mean corresponds to mean of the reference population (often the norm population) used for the calibration of the item bank.

Using the modern test theory approach, the Kids-CAT study developed and validated the first German-language CAT to assess the generic HRQL of children and adolescents and to test the newly developed tool in a clinical setting. Item banks for each domain were calibrated using data from German-speaking countries from four large European studies to estimate item parameters (22). Scoring of the Kids-CAT is based on the T-metric, with a mean of 50 (SD = +/- 10), corresponding to the mean of an age- and sex-matched reference population (22). Lower scores on the Kids-CAT indicate worse HRQL. A special feature of the Kids-CAT is the automatically generated feedback report that is available after completion of the CAT, which supports the interpretation of the scores by highlighting scores that divert from the reference population (23, 24). A multidisciplinary team, including interface designers, researchers, and clinicians, designed the Kids-CAT report taking the aspects of user-friendliness and feasibility into consideration. The validation of the Kids-CAT revealed that it is a valid and reliable tool to assess the HRQL of children and adolescents, especially those with lower HRQL (25).

Owing to its good psychometric properties and well-integrated interface, the Kids-CAT has the potential to reduce process-related challenges to using PROs in clinical practice by decreasing the respondent burden and providing results automatically after assessment via a feedback report for paediatricians. However, no data are yet available about the experience of paediatricians and young patients using the Kids-CAT in a clinical setting. Although many studies have investigated HRQL in children and adolescents with chronic conditions, findings vary because only a few studies have assessed the HRQL of young patients over time (26-28). Most importantly, little attention has been devoted to understanding the associations between clinical data and self-reported HRQL.

Overall aim of the thesis

Motivated by the aforementioned research gaps, the present work aimed at investigating the experience of using the Kids-CAT in clinical practice from the perspective of paediatricians as well as the young patients. Moreover, the HRQL of children and adolescents with chronic conditions and the associations between clinical data and HRQL were explored. An investigation of these research questions resulted in the publication of the following three peer-reviewed articles:

Study I: The aim of article I was to investigate whether the Kids-CAT is a user-friendly assessment of HRQL of young patients and to investigate the experience of paediatricians using the Kids-CAT in clinical practice regarding its relevance and usefulness (29).

Study II: The aim of article II was to investigate HRQL of children and adolescents with three different chronic conditions and to explore the association between self-reported HRQL data and the clinical assessment of paediatricians (30).

Study III: The aim of article III was to explore the relationship between glycated haemoglobin (HbA1c) levels and self-reported HRQL measured by the Kids-CAT in a diabetic sub-sample over six months (31).

Methods

Design, setting, and participants of the Kids-CAT study

The Kids-CAT study was a prospective longitudinal observational study (25). Children (age group 7–11 years) and adolescents (age group 12-17 years) with chronic conditions were followed up over one year. Data collection was performed in two specialised outpatient clinics of the University Medical Centre Schleswig Holstein in Kiel and Lübeck, Germany using a convenience sampling strategy. Young patients who attended the clinics for regular check-ups were recruited. Inclusion criteria were age (between 7 and 17 years); a diagnosis of asthma, diabetes mellitus, or juvenile arthritis (according to the German version of the International Classification of Disease, 10th revision (ICD-10-GM) (32)); and sufficient reading skills as well as sufficient knowledge of German. Out of 397 young patients invited for study participation, 312 young patients were included in the Kids-CAT study.

Data for the Kids-CAT study were collected at eight assessment time points over one year, with monthly assessments for the first six months and a follow-up assessment at 12 months. The assessments at baseline (T1) and three-month (T4), six-month (T7), and 12-month (T8) follow-ups were performed in the respective outpatient clinics, whereas the remaining assessments (months 1, 2, 4, and 5) were performed at home. The assessment at the clinic included self-reported HRQL assessments (Kids-CAT and additional validation instruments) and clinical data, which were assessed by the treating paediatricians. At the end of each assessment, the automatically generated Kids-CAT report was provided to the treating paediatricians. In contrast, the home assessments included the Kids-CAT and selected additional health items. For clinical assessments, young patients completed the Kids-CAT during the waiting time using a PC or tablet computer. For the home assessments, young patients received an email with the link to start the assessment usually on a PC, tablet computer, or mobile device.

The design of the Kids-CAT study, including the three studies presented in this thesis, is depicted in Figure 1.

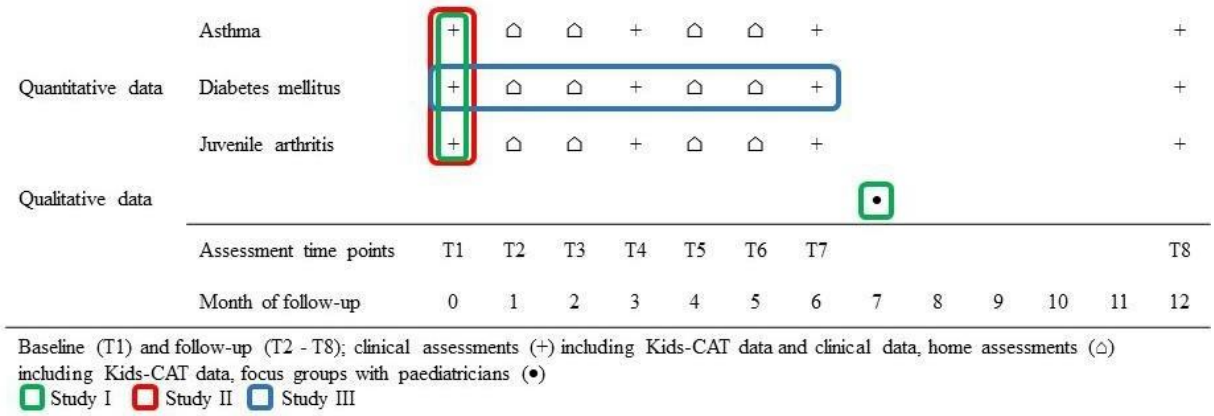

Figure 1: *Kids-CAT study design*

Instruments and variables

Self-reported HRQL

The Kids-CAT used to assess the HRQL of young patients comprised the following five health domains: physical well-being, psychological well-being, parent relations, social support and peers, and school well-being (22, 25). The Kids-CAT contains of 155 items, with each domain item bank containing between 26 and 46 items. The stopping rules of the Kids-CAT were defined as follows, a maximum of seven items per domain or measurement precision of

reliability $r = 0.9$ (a minimum of three items were applied) (22, 25). For each Kids-CAT domain, the T-score and standard error (*SE*) is computed (25). The validation of the Kids-CAT showed good validity and reliability, as well as good measurement precision for children and adolescents with chronic conditions (25).

Clinical data

Clinical data were provided by the treating paediatricians, who completed a form as part of or after the medical encounter, to provide information on the year of diagnosis, co-morbidity, different aspects related to disease control, and paediatricians' assessment of the overall health status of their young patients. Disease duration was calculated based on the year of diagnosis. Additional diagnoses (considering the ICD-10-GM) were recoded into a binary variable representing co-morbidity, with the category 'yes' indicating at least one additional diagnosed chronic health condition.

Three disease-specific sets of items were applied for asthma, diabetes mellitus and juvenile arthritis, respectively. The items 'symptoms during day and night', 'use of emergency medication', 'occurrence of exacerbation', 'information about lung function' and 'restrictions in activities in daily life' were recorded for young patients with asthma. 'HbA1c levels' (further grouped into <7.5%, 7.5 – 9.0% and >9.0% according to medical guidelines (33)), 'vascular complications', 'additional autoimmune diseases', 'episodes of hypo- or hyperglycaemia that required further treatment', and 'occurrence of ketoacidosis over the past four weeks' were collected in children and adolescents with diabetes mellitus. The items set for young patients with juvenile arthritis included 'disease activity level', 'mobility assessment', and 'interference with eyes'. These disease-specific items were used to assess the disease control of young patients. Sum scores for each disease-specific item set were calculated based on medical guidelines and consensus between clinicians and researchers, where higher scores indicate worse disease control (30). The final score for disease control was categorised into good versus poor disease control using disease-specific cut-off points (cut-off points: asthma >0; diabetes >1; juvenile arthritis >4). Overall health status was rated by the paediatricians using a five-point Likert scale.

Sociodemographic data

Data regarding sociodemographic variables including age and sex were obtained from the patients' medical records. At baseline, socioeconomic status (SES; education, occupation and income), was reported by parents using a validated set of questions (34).

Ethical considerations

The study was performed according to the ethical standards of the Helsinki Declaration and its subsequent amendments. The ethics committees of the Chamber of Physicians in Kiel and Lübeck and the Chamber of Psychotherapists in Hamburg, Germany, approved the study. Informed consent was obtained from parents; informed assent was obtained from children and adolescents.

In the following section, the methods of the three studies are described in more detail.

Study I

In study I, a multimethod approach was applied using qualitative data from focus groups and quantitative data from clinical assessments (T1, T4, T7, and T8) of the Kids-CAT study. Further details are provided in publication I (29).

Sample

Study I included eight paediatricians specialised in pulmonology, diabetology, or rheumatology for the qualitative part of the study. For the quantitative part of the study, the full Kids-CAT sample was included, that is, 312 children and adolescents with chronic conditions (i.e. asthma, diabetes mellitus, or juvenile arthritis) who completed the Kids-CAT at least once at a clinical assessment time point.

Procedure

For the qualitative part of the study, the experiences of the paediatricians who used the Kids-CAT, including the Kids-CAT report, were assessed as part of focus group interviews at each of the two outpatient clinics, with four paediatricians from each outpatient clinic participating. The paediatricians who worked with the Kids-CAT in clinical routine were asked to complete a short sociodemographic questionnaire during the group interviews. The focus groups were conducted seven months after the start of the Kids-CAT study, were audio-recorded and lasted approximately 60 minutes.

For the quantitative part of the study, the user-friendliness of the Kids-CAT was evaluated using a short questionnaire administered to the children and adolescents. The perceived feasibility and comprehensibility of the Kids-CAT were assessed using three Likert-scaled items. In addition, time to complete the Kids-CAT was measured using the start and end time of each assessment.

Analysis

Qualitative analysis according to Mayring (35) was used for the data analysis of the focus group interviews. Based on the focus group interview guide, corresponding categories were created using a deductive approach. Coding of the transcripts was conducted by two researchers independently and identified codes assigned to the predefined categories. For codes not fitting one of the predefined categories, new categories or sub-categories were created. Discrepancies between identified codes and assigned categories were discussed until consensus was reached.

Quantitative analyses were performed to assess the feasibility of completing the Kids-CAT as perceived by the young patients. Descriptive analyses of the three feasibility items were performed for each clinical measurement point and stratified by age group (children vs. adolescents). Age group differences were examined using Mann-Whitney *U* tests. Independent *t*-tests were conducted to compare the time taken by children and adolescents to complete the Kids-CAT.

Study II

In study II, cross-sectional data of the Kids-CAT study, including baseline data, were used. Further details are provided in publication II (30).

Sample

The full Kids-CAT sample of children and adolescents with asthma, diabetes mellitus, or juvenile arthritis who completed the Kids-CAT at T1 were included in study II. Out of 312 children and adolescents included in the Kids-CAT study, three participants were excluded from the analysis owing to missing HRQL data at baseline, resulting in 309 patients.

Statistical analysis

Descriptive analyses were performed to determine the sociodemographic characteristics and paediatrician-reported clinical data of the sample. Mean T-scores of the five Kids-CAT domains were calculated for the total sample and further stratified by disease and sociodemographic and clinical data. The three disease groups were compared using analyses of variance (ANOVAs) for continuous variables and the χ^2-test for categorical variables (36).

To explain the variation in HRQL on the basis of sociodemographic and clinical data, a linear regression model was used for each of the five domains after applying multiple imputations for replacing missing data (37, 38). Sociodemographic variables (age in years, sex, and SES) and

clinical data (disease group, disease duration, co-morbidity, disease control, and overall health status) were added to the model as independent variables; the respective Kids-CAT domain T-score was entered as a dependent variable in the regression model.

Study III

In study III, longitudinal data of the diabetic sub-sample of the Kids-CAT study were used, including seven measurement points over six months. Further details are provided in publication III (31).

Sample

Out of 312 children and adolescents included in the Kids-CAT study, 203 children and adolescents had a diagnosis of diabetes mellitus type I (T1DM; ICD-10-GM code E10 (32)) and were included in the analyses performed in study III.

Statistical analysis

Descriptive analyses were performed to characterise the study sample and to assess HRQL over six months. Individual changes in HRQL were investigated at the domain level over time by calculating the percentage of young patients who reported improvement or decline at the subsequent measurement points. A T-score of a young patient that was outside the confidence interval of the T-score of the preceding measurement point was defined as indicative of an individual change.

Analysis of missing data were conducted, and multiple imputations performed (37, 38). Subsequently, linear mixed models were fitted to investigate HRQL over time at the domain level. The effect of baseline HbA1c groups (<7.5%, 7.5 – 9.0%, and >9.0%) and time and the interaction between the two variables were entered as a fixed effect while controlling for age and sex. A random intercept for each individual was added to the model (random effect).

Path analyses were performed to investigate the temporal relationship between Kids-CAT domains and HbA1c levels. An exploratory approach was taken to develop and fit path models at the domain level. The effect of HbA1c levels on each Kids-CAT domain and vice versa over six months (baseline, after three months, and after six months) were estimated while controlling for age and sex. Chi-squared (χ^2) value , root means square error of approximation (RMSEA), comparative fit index (CFI), and Tucker Lewis index (TLI) were used to evaluate model fit (39).

Results

Hereinafter, the results of the three studies are reported in detail.

Study I

The Kids-CAT study included 312 children and adolescents with asthma (*n* = 58; 18.5%), diabetes (*n* = 205; 65.9%), and juvenile arthritis (*n* = 49; 15.6%). The mean age of the young patients was 12.5 years, and 47.4% were female. The eight paediatricians who participated in the two focus groups had sub-specialisations in paediatric diabetology, pulmonology, and rheumatology. Their average work experience was 13 years, ranging from 6.5 to 18 years, mean age was 43.4 years, and 50% were female.

Children and adolescents had to answer approximately seven items per domain (range: 5–7), corresponding to a total of 35 items per Kids-CAT. At baseline, young patients needed a mean time of 7:46 minutes (*SD* = 3:41 minutes) for completion with decreasing time to complete with subsequent assessment. Children required statistically significantly longer (by approximately 3 minutes) to complete the Kids-CAT than adolescents ($p < 0.001$), which was true across all assessment time points. The three Kids-CAT feasibility items revealed that 89.4% of young patients experienced the Kids-CAT as easy or very easy to complete. In terms of readability, 88.7% reported that the Kids-CAT was easy to read. Support needs were reported by 20.4%, with children needing significantly more support than adolescents ($p < 0.001$).

The focus groups with paediatricians revealed six categories related to their experience with using the Kids-CAT in clinical practice. These were *comprehensibility*, *comprehensiveness*, *patient–physician communication and relationship*, *time management*, *responsibility*, and *suggested improvements* (29).

Paediatricians reported that the implementation of the Kids-CAT in clinical routine was feasible and that the Kids-CAT report was considered comprehensible. In particular, the graphical display, which uses traffic-light colour coding, facilitated the interpretation of the Kids-CAT results. Participants in focus groups stated that the results of the Kids-CAT facilitated a comprehensive understanding of their patients. The data were valued as meaningful additional information that allowed the identification of important aspects with regard to patients' HRQL. Furthermore, paediatricians commented on the effect of the Kids-CAT on patient–physician communication and relationships. The systematic assessment of HRQL was described as helpful to identify difficulties. However, participants stated that they were hesitant to address

issues not related to their area of expertise, such as psychological wellbeing. Participants suggested that working in interdisciplinary teams (e.g., including psychologists or social workers) would be preferable. In this way, individual cases could be discussed and, if necessary, referred to colleagues.

Finally, focus group participants suggested improvements that would facilitate the implementation of the Kids-CAT in clinical routine. These included the integration of the Kids-CAT report into the medical record system, as this would provide other professionals access to the results as well. As the current Kids-CAT report focuses only on the most recent results, an additional progress report was suggested to monitor the results of young patients over time.

Study II

Out of the 309 young patients included in study II, 18.8% (n = 58) had asthma, 65.4% (n = 202) had diabetes mellitus, and 15.8% (n = 49) had juvenile arthritis. The mean age was 12.5 years and 47.9% were female. The socioeconomic status of families revealed that 97.2% of patients had a medium or high SES. The mean disease duration was 5.44 years (SD = 3.7 years) and 32.5% (n = 100) had at least one additional chronic health condition. The paediatricians assessed the disease control of 70.8% of the sample as good. Overall health status as assessed by paediatricians was rated fair to poor for 19.1% (n = 58) of the patients. Further details are provided in publication II.

Overall, average domain T-scores were within the range of 50 (SD = +/-10), that is, comparable to an age- and sex-matched German-speaking reference population. The mean T-scores were 48.15 (SD = 10.4) for physical well-being, 49.96 (SD = 9.3) for emotional well-being, 53.84 (SD = 8.9) for parent relations, 54.10 (SD = 8.2) for social support and peers, and 52.25 (SD = 9.5) for school well-being. Considerably lower scores (T-score <40) were reported in at least one of the five domains by 35.3% (n = 109) of the young patients.

Comparison between disease groups indicated that young patients with asthma reported significantly lower scores for physical well-being ($p < 0.05$) than patients with diabetes. Lower physical well-being scores were also found for young patients with at least one co-morbidity ($p < 0.05$), poor disease control ($p < 0.05$), and poor overall health status ($p < 0.05$) as rated by paediatricians. Apart from physical well-being, young patients who were rated as having fair to poor overall health also had significantly lower scores in the Kids-CAT domains psychological well-being, parent relations, and school well-being ($p < 0.05$).

The regression analysis showed a low proportion of variance in the five Kids-CAT domains, as explained by the sociodemographic and clinical data. Predictors explained 18.5% of the variance in physical well-being (R^2 = 0.185, adjusted R^2 = 0.160) with the variables age, disease control, and overall health status being statistically significant. For psychological well-being, predictors explained 10.6% of the variance (R^2 = 0.106, adjusted R^2 = 0.079), with sex and overall health status being statistically significant. For parent relations, 4.7% of the variance was explained by the predictor variables (R^2 = 0.047, adjusted R^2 = 0.019), with age and overall health status being statistically significant. For social support and peers, 6.5% of the variance was explained in the model (R^2 = 0.065, adjusted R^2 = 0.036), with age and SES being statistically significant predictors. For school well-being, 6.3% of the variance was explained (R^2 = 0.063, adjusted R^2 = 0.034) by the predictors, with SES being a statistically significant predictor. Further details of the multivariable linear regression models can be found in publication II (30).

Study III

For study III, 203 young patients diagnosed with T1DM were included in the analyses. Further details regarding study participation and loss to follow-up are presented in publication III (31).

The mean age of the respondents was 12.8 years; 44.3% were female. Mean disease duration was 5.4 years, with a mean age of primary T1DM manifestation of 7.3 years. At baseline, the mean HbA1c levels of young patients were 7.97% (*SD* = 1.37, range = 8.90). Grouping based on HbA1c levels showed that 37.8% had a value of <7.5%, 44.9% had a value between 7.5% and 9.0%, and 17.3% had a value of >9.0% (31).

Over six months, mean T-scores of the five Kids-CAT domains of young patients with T1DM were between 40 and 60, which are within one standard deviation of the mean T-scores of the age-matched German-speaking reference population. Approximately 20% of the participants reported significant changes (lower or higher T-scores) in health domains from one assessment time point to the next. At an individual level, the decrease in T-scores (worsening HRQL) from one assessment time point to the next was at least -7.53 for physical well-being, -6.51 for psychological well-being, -6.35 for parent relations, -6.49 for social support and peers, and -6.45 for school well-being.

Minimal changes in Kids-CAT domain scores over time were found within groups of young patients according to their baseline HbA1c levels, with the exception of the third group (1:

<7.5%; 2: 7.5–9.0%; 3: >9.0%). The psychological well-being of the patients declined over time; however, the difference was not statistically significant. Between-group comparisons revealed that young patients with baseline HbA1c levels of >9.0% had significantly lower T-scores for the domains physical well-being (B = -5.60, SE = 2.21; $p < 0.05$) and parent relations (B = -4.32, SE = 1.99; $p < 0.05$) compared to patients with HbA1c levels of <7.5%, but not compared with patients with HbA1c levels between 7.5% and 9.0%.

Associations between HbA1c levels and Kids-CAT domains over time (baseline, after three months, and after six months) were modelled for each domain using path analysis (Figure 2). All five models showed a good to acceptable fit of the data according to the fit indices χ^2, RMSEA, CFI, and TLI (31).

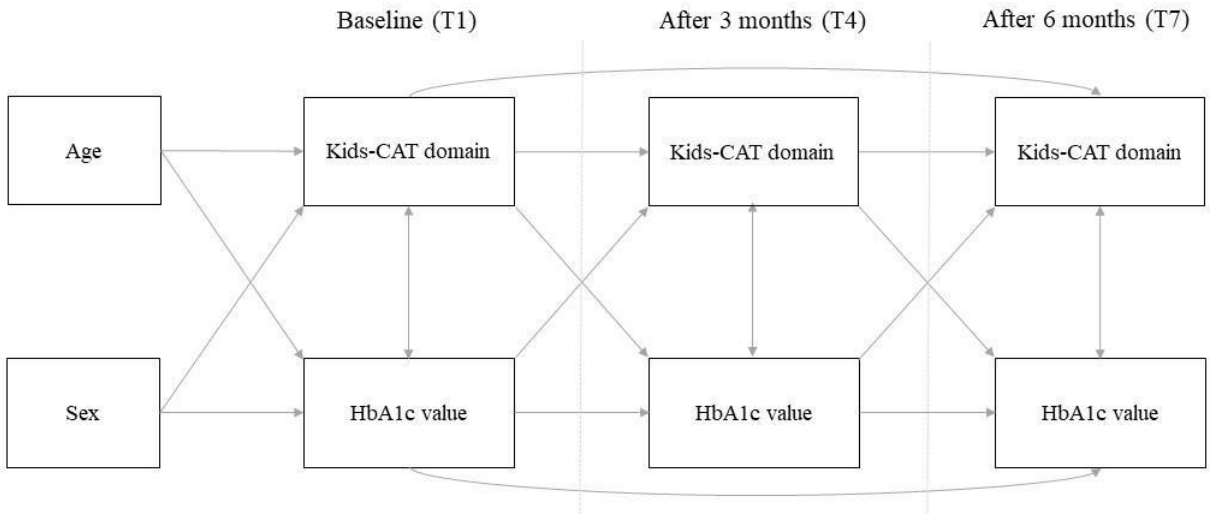

Figure 2: *Example of path models including Kids-CAT domains and HbA1c levels and age and sex as covariates. Single-sided arrows represent direct effect paths, whereas double-sided arrows represent correlations.*

All path estimates of domain T-scores over time and all path estimates of HbA1c levels over time were positively associated (statistically significant), with nearer time points being more strongly related. For all five path models, statistically significant positive associations between age and HbA1c levels were found. For the covariate sex, statistically significant associations were found only for psychological well-being, with young males reporting higher psychological well-being than young females.

For the domain physical well-being, the path model revealed negative correlations between T-scores and HbA1c levels at baseline (B = -2.15, SE = 0.99; $p < 0.05$), indicating that higher

HbA1c were associated with lower physical well-being. The path model showed statistically significant negative temporal associations between HbA1c levels (after three months) and physical well-being (after six months; B = -1.02, SE = 0.49; $p < 0.05$). Moreover, statistically significant negative temporal associations between physical well-being (after three months) and HbA1c levels (after six months) were found for the reverse path (B = -0.01, SE = 0.01; $p < 0.05$). Remaining paths were not statistically significant. For the domain psychological well-being, the path model revealed statistically significant negative associations between baseline HbA1c and psychological well-being after three months (B = -1.46, SE = 0.49; $p < 0.05$). The remaining paths were not statistically significant. For the domain parent relations, the path model showed statistically significant negative correlations between baseline HbA1c levels and baseline domain T-scores (B = -2.15, SE = 0.97; $p < 0.05$). Statistically significant negative temporal relationships were found between HbA1c levels at baseline and parent relations after three months (B = -1.12, SE = 0.41; $p < 0.05$), as well as between HbA1c levels after three months and parent relations after six months (B = -0.80, SE = 0.40; $p < 0.05$). The remaining paths were not statistically significant. For the domains social support and peers and school well-being, the path models showed no statistically significant associations between domain T-scores and HbA1c levels.

Discussion

This thesis investigated the application of the Kids-CAT in clinical practice, particularly regarding the tool's user-friendliness and practicability. Moreover, cross-sectional and longitudinal associations between clinical data and self-reported HRQL of young patients were examined.

Findings of study I revealed that the Kids-CAT is a user-friendly tool and easy to complete for young patients. As children and adolescents were involved in the development phase of the Kids-CAT, it was expected that the content and the functionality of the developed electronic assessment would be adequate for the target group (5). These findings are consistent with other studies reporting that electronic assessment tools are easy to fill out for children and adolescents and even preferred over paper-and-pencil questionnaires (40, 41).

Paediatricians using the Kids-CAT in clinical practice appreciated the tool and the additional information about the HRQL of their patients. This additional information appears to have a positive impact on communication between paediatricians and young patients, as previously

described by others (42). The assessment of HRQL assists young patients in indicating their perceived health status to their paediatrician. This can facilitate patient-centred communication by addressing the revealed health problems during the medical encounter (43, 44).

Results of study II showed good HRQL domain scores of children and adolescents with asthma, diabetes mellitus, and juvenile arthritis that were comparable to those of the age- and sex-matched German-speaking reference population, with slightly lower mean scores for physical well-being (30, 31). Results of study III, obtained longitudinal data of a sub-sample of young patients with T1DM, confirmed the results of study II, suggesting good HRQL and only minimal change in domain scores over six months. Previous studies have reported contradictory results, with young patients diagnosed with chronic conditions reporting lower HRQL in all domains (26, 28, 45). The results have to be discussed in light of the study design. Participants of the Kids-CAT study were recruited in outpatient clinics during regular check-ups. Thus, the included patients presumably did not have acute health problems, which could explain their good scores across the Kids-CAT domains. In addition, coping strategies and adaptation to illness could further explain these findings (46, 47). The mean disease duration of the diabetic sub-sample was 5.4 years, suggesting well-adjusted diabetes management and a stable health condition (48, 49).

For certain Kids-CAT domains, significant differences in T-scores were found according to clinical data. An unexpected result of study II was the small positive association between having at least one co-morbidity and the domains psychological well-being, parent relations, social support and peers, and school well-being. Receiving additional support, care, and attention from the social environment (family, friends, and school) could explain the higher scores in selected domains despite the potential higher burden of having a co-morbidity. The negative relationship between HbA1c levels and the health domains physical well-being and parent relations (study III) are consistent with the findings of previous studies (50, 51). As high HbA1c levels increase the risk of diabetes-related complications, it can be hypothesised that young patients with consistently high HbA1c levels will report decreasing physical well-being scores over time. Due to the short follow-up period of six months, this assumption could not be confirmed by study III. However, previous studies have revealed that increasing symptoms and complications of T1DM patients have a negative effect on self-reported HRQL (52, 53).

Self-reported HRQL and sociodemographic characteristics and clinical data are linked, but associations are minimal, indicating that it is difficult to draw inferences about the HRQL of

young patients from clinical data, and vice versa (54, 55). In light of the fact that children and adolescents with chronic conditions have an increased risk of developing emotional, developmental, or behavioural problems, self-reported HRQL reveals additional important information (7, 56). Thus, clinical data should be complemented by HRQL data to identify undetected health care needs (3, 44). Moreover, the small directional association of HbA1c levels and the Kids-CAT domains physical well-being, psychological well-being, and parent relations indicates that an improvement in HbA1c levels does not lead to an improvement in the HRQL of young patients, or vice versa (57). HRQL is an important and distinct treatment goal in young patients with chronic conditions; therefore, regular assessment is necessary to reliably monitor HRQL (7, 58).

The minimal associations between clinical data and HRQL presented in this thesis can be explained by a conceptual framework. The complex associations between biological and physiological processes, symptoms, functionality, health perceptions, and HRQL are outlined in the conceptual model of patient outcomes as introduced by Wilson and Cleary (59, 60). Chronic conditions, such as asthma, juvenile arthritis, or T1DM, are determined by biological and physiological dysfunctions, which are assessed in routine clinical care using tests, laboratory values, or physical examination (59). Those assessments give information about specific organs or cell functions (59). Dysfunction of biological and physiological processes leads to symptoms experienced by patients (59, 60). However, the relationship between physical and biological processes and experienced symptoms is complex (59). High blood glucose levels do not necessarily lead to acute symptoms. Similarly, medical treatment, such as insulin therapy aimed at normalising blood sugar levels, does not necessarily reduce all symptoms experienced by a patient. In addition to biological processes, individual and environmental factors influence patients' perceptions of symptoms and limitations in functionality (59, 60). Outcomes such as patient health perception and HRQL are associated and influenced not only by dysfunction of biological and physiological processes, symptoms and functional aspects but also by individual-specific and environmental factors (59, 60). This conceptual framework of patient outcomes supports the assessment of HRQL as associations between physiological and biological processes and HRQL are not causally determined.

The present thesis has certain limitations. First, the generalisability of the results is limited because the sampling strategy included convenience sampling of study participants (patients and paediatricians) in two selected outpatient clinics in Germany. For instance, the sample of

young patients did not include sufficient young patients with a migrant background or with low SES, factors that have an impact on HRQL (61). Second, the conceptualisation of the variable 'disease control' presents a simplification of a complex construct that was harmonised for each chronic condition for the purpose of the analyses. The conceptualisation of this variable, based on a qualitative approach adopted by the Kids-CAT research group, might be evaluated differently by other groups. Third, instead of extracting clinical data from patients' records, the study asked paediatricians to report the data using a standardised form, which may have led to differences in reporting, such as underreporting of co-morbidities. Finally, the sample size for path models corresponded only to minimal sample size requirements (62, 63). Therefore, the explorative analyses need to be interpreted cautiously.

Further research based on the findings is needed to investigate the impact of implementing PROs on treatment decisions in clinical practice. Moreover, to better understand and interpret Kids-CAT scores, it is also important to determine clinically meaningful differences for the Kids-CAT. Finally, the question of whether PRO scores systematically differ when PRO assessments are completed at home or at the clinic should be investigated, especially given the emerging field of web-based applications to assess PROs.

Conclusion

This thesis showed that the Kids-CAT is a user-friendly and practicable tool to assess the HRQL of children and adolescents in clinical practice. Self-reported HRQL data provide valuable information to paediatricians that cannot be derived reliably from sociodemographic and clinical data. Although children and adolescents with selected chronic conditions report good HRQL at the group level, one-third of young patients reported significantly lower scores in certain Kids-CAT domains. Therefore, HRQL assessment facilitates the identification of health care needs that may otherwise be overlooked. The minimal association between HRQL data and clinical data supports the notion that HRQL is a distinct treatment goal, which must be monitored and addressed in clinical practice.

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Affidavit (Eidesstattliche Versicherung)

Ich, Kathrin Irmgard Fischer, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: *Health-related Quality of Life of Children and Adolescents with Chronic Conditions: Evaluation and Application of the Kids-CAT in Clinical Practice* (Die gesundheitsbezogene Lebensqualität von Kindern und Jugendlichen mit chronischen Erkrankungen: Evaluierung und Anwedung des Kids-CATs in der klinischen Praxis) selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum

_____
Unterschrift

Declaration of contribution (Anteilserklärung an den erfolgten Publikationen)

Kathrin Irmgard Fischer hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1:

Barthel D*, Fischer KI*, Nolte S, Otto C, Meyrose AK, Reisinger S, Fas M, Thyen U, Klein M, Muehlan H, Ankermann T, Walter O, Rose M, & Ravens-Sieberer U (shared first authorship). Implementation of the Kids-CAT in clinical settings: a newly developed computer-adaptive test to facilitate the assessment of patient-reported outcomes of children and adolescents in clinical practice in Germany. Quality of Life Research, 2016.

Beitrag im Einzelnen:

- Entwicklung des Forschungsziels und der Forschungsfragen gemeinsam mit Dana Barthel
- Aufbereitung, Analyse und Interpretation der Ergebnisse gemeinsam mit Dana Barthel (zu gleichen Teilen)
- Verfassung des ersten Publikationsentwurfs gemeinsam mit Dana Barthel (zu gleichen Teilen)
- Einarbeitung der intern und externen Reviews und Überarbeitung des Manuskripts gemeinsam mit Dana Barthel

Publikation 2:

Fischer KI, Barthel D, Otto C, Ravens-Sieberer U, Thyen U, Klein M, Walter O, Rose M, & Nolte S. Minimal Associations between Clinical Data and Children's Self-reported Health-related Quality of Life in Children with Chronic Conditions – a Cross-sectional Study. Frontiers in Pediatrics, 2019.

Beitrag im Einzelnen:

- Idee zur Studie und Entwicklung des Forschungsziels gemeinsam mit Co-Autoren
- Aufbereitung und Bereinigung des Datensatzes auf dem die Publikation basiert
- Auswertung der Daten und Erstellen der Tabellen und Grafiken
- Interpretation der Ergebnisse in Zusammenarbeit mit den Co-Autoren
- Verfassung des ersten Publikationsentwurfs
- Koordination und Einarbeitung der internen und externen Reviews und Überarbeitung des Manuskripts

Publikation 3:

Fischer KI, Fischer FH, Barthel D, Otto C, Thyen U, Klein M, Walter O, Ravens-Sieberer U, Rose M, Nolte S. Trajectories of Health-Related Quality of Life and HbA1c Values of Children and Adolescents With Diabetes Mellitus Type 1 Over 6 Months: A Longitudinal Observational Study. Frontiers in Pediatrics, 2020.

Beitrag im Einzelnen:

- Idee zur Studie und Entwicklung des Forschungsziels gemeinsam mit Co-Autoren
- Aufbereitung und Bereinigung des Datensatzes auf dem die Publikation basiert
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Minimal Associations Between Clinical Data and Children's Self-Reported Health-Related Quality of Life in Children With Chronic Conditions—A Cross-Sectional Study

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Introduction: The improvement—or at least maintenance—of health-related quality of life (HRQoL) in children and adolescents is one of the main aims of chronic disease care. This study examines HRQoL of children and adolescents with three different chronic conditions (i.e., diabetes mellitus, asthma, juvenile arthritis) using the computer-adaptive test Kids-CAT, comprising five HRQoL domains: physical well-being, psychological well-being, parent relations, social support and peers, and school well-being. Further, associations between HRQoL and distinct clinical data and medical assessments are investigated to explore how much variability of the five domains can be explained by these variables.

Methods: Cross-sectional data of the Kids-CAT study was analyzed. The Kids-CAT was used in two outpatient clinics in northern Germany gathering data on self-reported HRQoL in $n = 309$ children and adolescents aged 7–17 years. Additionally, general patient information, clinical data, and pediatrician-reported medical assessments were measured. Multiple regression analyses were conducted to explore associations between HRQoL and selected variables (i.e., disease duration, co-morbidity, disease control, overall health status).

Results: Overall, self-reported HRQoL in all five domains were comparable to data of an age- and sex-matched reference population. Results of regression analyses indicated that the investigated variables only minimally explain variance in the five Kids-CAT domains. Sociodemographic, clinical data, and medical assessments explained 18.4% of the variance in physical well-being, 10.7% in psychological well-being, and <10% of the variance in parent relations, social support and peers, and school well-being.

Conclusion: Sociodemographic data, disease duration, co-morbidity, and medical assessments, such as disease control or pediatrician-assessed overall health status show low association with HRQoL of children and adolescents with chronic conditions. Data on self-reported HRQoL delivers valuable information on children's well-being and can improve healthcare professionals' understanding of the subjective well-being of their young patients. The implementation of tools like the Kids-CAT can facilitate the identification of potential problem areas, which should enable healthcare professionals to better address specific healthcare needs.

Clinical Trial Registration: identifier: DRKS00006326 (retrospectively registered); Date of registry: August 1st, 2014.

Keywords: health-related quality of life, pediatrics, self-report, patient outcome assessments, chronic disease, computer-adaptive testing

INTRODUCTION

An increasing number of children and adolescents live with chronic conditions, such as asthma, diabetes mellitus or juvenile arthritis (1, 2). The aim of healthcare is to improve clinical outcomes of these young patients. Over the past few decades, advancements in healthcare have resulted in new and advanced treatment modalities that led to a reduction of symptoms, improved survival, and increased life expectancy among children and adolescents with chronic disease (1, 3). As such improvements lead to an overall increase in years lived with disease, health-related quality of life (HRQoL) is an increasingly important outcome in healthcare (2, 4).

The concept of HRQoL, as defined by the World Health Organization, is "a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, and their relationships to salient features of their environment" (5). In medical research, HRQoL has become an important outcome measure over the last decades, while it is also increasingly recognized in clinical practice as a valuable and important source of information, especially regarding patient-centered care (6–8).

The assessment of HRQoL in clinical practice has the potential to support healthcare in various ways. Patient-reported outcome (PRO) measures can be applied and used in various ways, e.g., as screening or monitoring tools, to promote patient-centered care or to facilitate communication on an individual patient level (9). The implementation of PRO measures can enable clinicians to identify problems in specific HRQoL domains and additional healthcare needs, which might not be detected otherwise (10, 11). Overall, the assessment of HRQoL supports healthcare professionals to get a more comprehensive idea of patient's health status (8, 10, 11).

While various generic and disease-specific HRQoL instruments are available for use in pediatrics (12), widespread implementation of HRQoL instruments in clinical practice has not yet been accomplished (13). Previous research identified various obstacles of implementing HRQoL measures in clinical practice, such as the additional effort in proportion needed (8, 14, 15). In recent years, technical and methodological advancements have led to a new generation of HRQoL instruments, i.e., computer-adaptive tests (CAT). CATs are developed based on modern test theory methods and their dynamic nature have the potential to increase measurement precision while reducing respondent burden (16). The electronic assessment also reduces staff burden compared to paper-pencil assessment of HRQoL. Through electronic assessment data is automatically stored in a data base and immediately scored, so that results are available in real-time (15, 16). These features of CATs might reduce logistical barriers. To our knowledge, only few CATs are available in the field of pediatrics. Besides the PEDI-CAT, a revised version of the Pediatric Evaluation of Disability Inventory (PEDI) (17), the CP-CAT, used to measure physical functioning in children with cerebral palsy (18), and the Kids-CAT, a generic instrument to assess HRQoL in children (19, 20), have been developed in pediatric care. Further, the PROMIS initiative developed a number of pediatric item banks available for CATs (21).

Despite recent advancements in the field of patient- reported outcomes with the development of increasingly sophisticated assessment instruments, many clinicians still assume that additional information regarding relevant problems of their patients are not needed, as these issues would be discovered during the consultation (8). Generally, outcome measures predominantly focus on clinical parameters, such as symptoms and laboratory diagnostics to monitor and evaluate healthcare. Combined with patients' medical history and medical assessments during the consultation, these parameters help treating pediatricians to gain a picture of the patients' health status and are the basis for treatment decisions. Most commonly, if assessed at all, HRQoL is assessed in a rather unstandardized way during or after the consultation, e.g., pediatricians' proxy estimation of overall health of the young patient (11).

Abbreviations: CAT, computer-adaptive test; HRQoL, health-related quality of life; SES, socioeconomic status.

This raises the question whether the available information is sufficient for pediatricians to get a precise picture of patients' health status or whether the compilation of information that is usually available to pediatricians bears the risk of misjudgment of their patients' HRQoL if HRQoL outcomes are not routinely assessed. We hypothesized that there is only little relation between HRQoL outcomes, and factors routinely assessed in pediatric care.

The aim of this study was (1) to estimate HRQoL of children and adolescents with chronic conditions in relation to a reference population and (2) to explore how much variability of HRQoL domains could be explained by sociodemographic factors, selected pediatrician-reported clinical data, and pediatricians' medical assessments of their young patients.

MATERIALS AND METHODS

The STROBE guideline was used for reporting study results (22). The STROBE statement checklist can be found in the Supplementary Material (**Supplement Table 2**).

Study Design, Setting, and Participants

Cross-sectional data (baseline assessment) of the Kids-CAT study, a prospective longitudinal observational study, is used (20). Data was collected at two specialist outpatient clinics at the University Medical Center Schleswig Holstein in Kiel and Lübeck, Germany, between June 2013 and April 2014. Study nurses recruited children and adolescents, attending the clinics for regular check-ups (convenience sample). Eligibility criteria were age (7–17 years), clinical diagnosis of asthma, diabetes mellitus, or juvenile arthritis [according to International Classification of Disease, 10th version, German modification (23)], sufficient reading skills, and sufficient knowledge of German, (assessed through parents). Out of 397 patients approached by the study nurses, 312 children and adolescents participated in the study (24). Three cases were excluded from the presented analyses due to missing HRQoL data; hence, $n = 309$ children and adolescents were included in this study. The overall study design and process of recruitment is described elsewhere (20).

Outcome Variables—Self-Reported Health-Related Quality of Life

Self-reported HRQoL was assessed using the Kids-CAT, one of the first CATs in the field of pediatrics (19). It is based on the domain structure of the KIDSCREEN-27 (25) and covers the five domains physical well-being, psychological well-being, parent relations, social support and peers, and school well-being. The Kids-CAT is constructed on the basis of item response theory (26, 27). Each domain consists of an underlying item bank, including various items to measures a wide range of the respective domain. The Kids-CAT comprises in total 155 items. The item bank physical well-being consists of 26 items, 46 items are included in the psychological well-being item bank, the item banks parent relations and social support and peers comprises 26 items, and 31 items are included in the item bank to assess school well-being of children and adolescents. Due to the adaptive nature of CATs, children have to answer a maximum of 35 items, as specified in the stopping rules (maximum seven items per domain to be answered, or measurement precision of 0.95 is reached). Computerized adaptive testing works based on a CAT algorithm administering individual item sets to each child/adolescent. Once all items are filled out by the child, the respondent's latent trait scores (theta scores) are computed for each domain providing an estimation of the value of the assumed latent construct, i.e., physical well-being, psychological well-being, parent relation, social support and peers, and school well-being. Data from four large norm studies, including ∼10,500 children and adolescents of German-speaking countries (Austria, Germany, Switzerland) was merged and used to calibrate the five item banks applying the KIDSCREEN items as anchors (19). Theta scores were transformed to a T-scores metric (mean $M = 50$ and standard deviation, $SD = 10$), with a score of 50 representing the mean score of a sex-and age-matched reference population (28). In this way, Kids-CAT scores are set in relation to the reference population and can be interpreted accordingly. The mean age of the reference population was between 12.8 and 13.3 years depending on the domain and ∼ 6% had a chronic disease or disability (19). The development process of the Kids-CAT is reported elsewhere (19). Results from validation study suggest satisfactory psychometric properties of the Kids-CAT (20). Further, the Kids-CAT appears to be feasible and acceptable in clinical practice as reported by physicians, children, and adolescents (24).

Predictor Variables—Pediatrician-Reported Clinical Data and Medical Assessments

Pediatricians were asked to complete a form for all participating children and adolescents within or after patient consultation, including the following items: year of diagnosis, co-morbidity, disease control, and pediatricians' assessment of patients' overall health status.

We estimated disease duration based on the year of diagnosis. For additional analysis purposes, we transformed the continuous variable disease duration into a dichotomous variable based on a median split with the categories "less than or equal to 5 years" and "more than 5 years." Co-morbidity was assessed using an open-ended question to be completed by the treating pediatrician considering additional diagnoses (according to International Classification of Disease, 10th version, German modification (ICD-10-GM) (23). We created a binary variable indicating whether at least one additional chronic health condition was diagnosed.

Disease control was assessed using a set of disease-specific items for the three chronic conditions. For asthma, items regarding symptoms during day and night, restrictions in daily life activities, use of emergency medication, information on lung function, and occurrence of exacerbation were assessed (29). For diabetes, information on HbA1c-level, existence of vascular complications, existence of further autoimmune diseases, occurrence of ketoacidosis over the past 4 weeks, and hypo- or hyperglycemic episodes requiring further treatment were assessed (30). For juvenile arthritis, items were based on the

International League of Associations for Rheumatology (ILAR) classification and included assessment of current disease activity level, questions about mobility, and interference with eyes (31). Based on medical guidelines and consensus between clinicians and researchers, disease-specific sum scores were computed and then classified into good vs. poor disease control. For asthma the score ranged from zero to seven (cut off score: >0), for diabetes from 0 to 12 points (cut off score: >1) and for juvenile arthritis from three to eight (cut off score: >4). For all disease –specific sum scores a higher score indicated worse disease control. For more details, see **Supplement Table 1**.

Further, we asked pediatricians to rate the overall health status of their patients by use of a 5-point Likert scale ranging from very good to very poor. For further analyses, we created a dichotomous variable by collapsing the categories very good and good and the categories fair, poor, and very poor. However, the latter category was not chosen by any of the treating pediatricians.

Predictor Variables—Sociodemographic Characteristics

Age and sex of participants were extracted from medical records. For sub-analysis, age was grouped into the two categories children (7–11 years) and adolescents (12–17 years).

Following the approach by Lampert et al. information on socioeconomic status (SES) for both parents were assessed using eight validated questions on education, occupation, and income (32). Weighted sum scores (3–21 points) of these items were computed and further categorized into low (3–7.9 points), medium (8–13.8 points), and high SES (13.9–21 points) (32, 33).

Data Analyses

Descriptive analyses for sociodemographic characteristics, pediatrician-reported clinical data and medical assessments were conducted including bivariate analyses to compare the three disease-specific groups of our sample. Analyses of variance (ANOVA) were performed with robust option Brown-Forsythe (34) for continuous variables (i.e., age, disease duration) and χ^2-tests for categorical variables (i.e., sex, age group, SES, co-morbidity, disease control, overall health status).

To explore self-reported HRQoL, mean T-scores for the five Kids-CAT domains were calculated for the total sample as well as stratified by sociodemographic characteristics, disease group, pediatrician-reported clinical data and medical assessments. Analyses included independent *t*-tests, ANOVA, and χ^2-tests.

Finally, five linear regression models were calculated. For these analyses, we aimed to use complete datasets. Out of 309 cases 73 cases (23.6%) presented incomplete data in six variables out of 13 variables included in our analyses. The variable SES (20.1%) presented a considerably higher percentage of missing values in our sample compared with other variables. For disease control, 3.6% of the values were missing. For all other variables the percentage of missing was <2%. As data is assumingly missing completely at random (MCAR), following Little's test (35) that resulted in a $\chi^2 = 37.756$ (df = 37; $p < 0.435$), we applied multiple imputations (MI) for missing data replacement using the fully conditional specification method to create $m = 20$ datasets (35, 36). For the linear regression models, socio-demographic variables, pediatrician-reported clinical data, and medical assessments were entered as independent variables, while the Kids-CAT domains were defined as outcomes, i.e., dependent variables. Each model was used to determine how much variation in the corresponding HRQoL domain could be explained by independent variables and if individual independent variables significantly predicted the dependent variable. The models included the following independent variables: age (in years), sex, disease group, and SES (sum score), disease duration, co-morbidity, disease control and overall health status rated by pediatricians. For disease group, dummy-coded variables were created with "juvenile arthritis" as reference group. To check the validity of the results, sensitivity analysis were conducted comparing the linear regression models using the pooled results of the imputed data sets to the results of the original data using complete case analyses.

Statistical analyses were performed using R Studio Version 1.0.136 with package mice (37) and IBM SPSS Statistics for Windows Version 22.0.

Ethics Approval and Consent to Participate

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval was obtained from the Chambers of Physicians Kiel and Lübeck, and Chamber of Psychotherapists Hamburg, Germany. Informed consent was obtained from all participants included in the study (informed consent of parents or legal guardians, informed assent of children and adolescents).

RESULTS

Sample Characteristics

Cross-sectional data was available from 309 children and adolescents (**Table 1**). Of these, 18.8% ($n = 58$) were diagnosed with asthma, 65.4% ($n = 202$) with diabetes mellitus (type 1), and 15.9% ($n = 49$) with juvenile arthritis. Mean disease duration was $M = 5.44$ ($SD = 3.73$) years. At least one additional diagnosed health condition was reported for 32.5% ($n = 100$) of the participants. Based on pediatricians' assessments, disease control was rated as poor for 29.2% ($n = 87$) of the participants; overall health status was assessed by pediatricians as fair or poor for 19.1% ($n = 58$) of the children and adolescents.

Self-Reported Health-Related Quality of Life

Mean T-scores for all Kids-CAT domains (**Table 2**) as well as associated 95% confidence intervals for the clinical sample were within the normal range of 40–60 as determined based on data of the reference population (with mean = 50).

Mean T-scores of the physical well-being domain were slightly lower for study participants compared to children/adolescents of the reference population. In contrast, T-scores reported for parent relations, social support and peers, and school well- being were slightly higher than mean scores of the reference population. However, our sample showed a wide distribution

TABLE 1 | Sociodemographic variables, pediatrician-reported clinical data, and medical assessments of chronically ill children and adolescents.

	N	Total sample (n = 309) Mean (SD) or %	Asthma (n = 58) Mean (SD) or %	Diabetes (n = 202) Mean (SD) or %	Juvenile arthritis (n = 49) Mean (SD) or %
SOCIODEMOGRAPHIC CHARACTERISTIC					
Age in years, *mean (SD)*	309	12.49 (2.79)	11.76 (2.45)	12.74 (2.79)	12.29 (3.01)
Age group, %	309				
Children (7–11 years)	118	38.2	46.6	36.1	36.7
Adolescents (12–17 years)	191	61.8	53.4	63.9	63.3
Sex (female), *%*	148	47.9	37.9	45.0	71.4
Socioeconomic status of the family, *%*	247				
High	66	26.7	27.3	26.8	25.6
Medium	174	70.4	70.5	70.1	71.8
Low	7	2.8	2.3	3.0	2.6
PEDIATRICIAN-REPORTED CLINICAL DATA AND MEDICAL ASSESSMENTS					
Disease duration in years, *mean (SD)*	307	5.43 (3.72)	6.48 (3.10)	5.43 (3.74)	4.24 (3.99)
Co-morbidity (yes), *%*	308	32.5	86.0	19.8	22.4
Disease control, *%*	298				
Good	211	70.8	53.6	74.1	77.8
Overall health status (pediatrician assessment), *%*	304				
Very good / Good	246	80.9	59.6	87.4	79.2

within domain scores with a range of 54.6 for physical well-being (M = 48.15; SD = 10.39), 44.2 for emotional well-being (M = 49.96; SD = 9.30), 41.49 for parent relations (M = 53.84; SD = 8.93), 36.86 for social support and peers (M = 54.10; SD = 8.22), and 46.09 for school well-being (M = 52.25; SD = 9.54) (**Figure 1**). Further analyses showed that 35.3% (n = 109) of children and adolescents indicated considerably lower HRQoL levels compared to the reference population in at least one of the five Kids-CAT domains, with respective T- score of <40. Children and adolescents most frequently reported considerably lower physical well-being (21.4% (n = 66) of children and adolescents reported a T-score <40).

Bivariate analyses (**Table 2**) revealed that differences in sociodemographic characteristics (i.e., sex, age group, SES, and disease group) were associated with significantly different scores in single Kids-CAT domains. Considering pediatrician-reported clinical data and medical assessments, statistically significant differences in physical well-being scores according to co-morbidity ($p < 0.05$), disease control ($p \leq 0.001$), and overall health status ($p \leq 0.001$) were found. Patients, whose overall health status had been rated as fair to poor by pediatricians, reported statistically lower physical well-being, psychological well-being, parent relations and school well-being compared to those who had been rated with very good to good overall health status.

Associations Between Kids-CAT Domains and Clinical Data and Medical Assessment

The pooled results of 20 datasets following multiple imputation revealed that the proportions of variance in the five Kids-CAT domains that could be explained by sociodemographic variables, clinical data, and medical assessments was low (**Table 3**). For physical well-being, predictors explained 18.5% of the variance in the analyzed sample (R^2 = 0.185, *adjusted* R^2 = 0.160), whereas age, disease control, and fair to poor overall health status were statistically significant. For psychological well-being, 10.6% of the variance could be explained by the predictor variables (R^2 = 0.106, *adjusted* R^2 = 0.079), with sex and fair to poor overall health status being statistically significant. For parent relations, 4.7% of the variance could be explained (R^2 = 0.047, *adjusted* R^2 = 0.019) by the model, with age and fair to poor overall health status being statistically significant predictors of the model. For social support and peers, 6.5% of the variance could be explained (R^2 = 0.065, *adjusted* R^2 = 0.036), with age and SES being a statistically significant predictor. Finally, for school well-being, 6.3% of the variance could be explained (R^2 = 0.063, *adjusted* R^2 = 0.034), with SES as statistically significant predictor. Regarding the medical assessments of pediatricians, poor disease control correlated negatively with physical well-being. For overall health status, T-scores in the domains physical well-being, psychological well-being and parent relations were lower for patients with a fair to poor overall health status.

DISCUSSION

We found that children and adolescents with chronic conditions reported HRQoL scores that were on average comparable to an age- and sex-matched German-speaking reference population. That is, children and adolescents included in our sample assessed their HRQoL similarly to peers, even though they have a chronic condition and are undergoing routine medical treatment. While 21.4% of our sample indicated a considerably low physical well-being (i.e., T-score <40), high scores were

TABLE 2 | Self-reported HRQoL in groups according to sociodemographic and pediatrician-reported clinical data and medical assessments among chronically ill children and adolescents.

				Physical well-being	Psychological well-being	Parent relations	Social support and peers	School well-being
			N	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*
Socio-demographic characteristics	Sex	Male	161	48.78 (9.72)	52.15 (8.57)*	53.73 (9.13)	53.77 (8.27)	52.44 (9.41)
		Female	148	47.48 (11.07)	47.57 (9.51)*	53.97 (8.74)	54.46 (8.19)	52.04 (9.70)
	Age group	Children	118	49.10 (9.47)	49.79 (9.08)	52.61 (8.75)	52.58 (8.57)*	51.94 (10.06)
		Adolescents	191	47.57 (10.90)	50.06 (9.46)	54.61 (8.98)	55.04 (7.88)*	52.45 (9.22)
	Disease group	Asthma	58	45.19 (11.66)*	48.91 (9.73)	52.72 (8.48)	54.95 (8.12)	52.13 (8.55)
		Diabetes	202	49.54 (9.54)*	50.23 (9.20)	53.91 (9.13)	54.33 (8.36)	52.03 (9.93)
		Juvenile Arthritis	49	45.96 (11.25)	50.08 (9.30)	54.90 (8.61)	52.16 (7.64)	53.32 (9.10)
	Socioeconomic status	High	66	48.56 (10.52)	50.93 (7.22)	54.98 (7.86)	54.47 (7.02)	55.36 (8.68)*
		Medium	147	48.81 (10.29)	49.85 (10.28)	53.71 (9.17)	53.79 (8.84)	50.88 (9.67)*
		Low	7	40.37 (14.11)	50.28 (9.69)	55.22 (6.38)	51.20 (7.62)	50.08 (9.74)
Pediatrician-reported clinical data and medical assessments	Disease duration	≤5 years	159	48.46 (9.83)	50.56 (9.25)	54.76 (8.71)	53.89 (8.79)	52.47 (9.75)
		>5 years	148	47.99 (10.83)	49.29 (9.40)	52.88 (9.08)	54.32 (7.61)	52.01 (9.39)
	Co-morbidity	Yes	100	46.09 (10.94)*	49.35 (9.73)	53.52 (8.82)	55.35 (7.91)	52.08 (9.08)
		No	208	49.27 (9.83)*	50.26 (9.12)	53.96 (9.00)	53.46 (8.32)	52.32 (9.79)
	Disease Control	Good	211	50.13 (9.52)*	50.89 (9.12)*	54.56 (9.08)	53.66 (8.26)	52.83 (9.76)
		Poor	87	44.40 (10.79)*	47.88 (9.13)*	52.50 (8.41)	55.26 (8.11)	50.93 (8.95)
	Overall health status	Very good / Good	246	50.02 (9.39)*	50.81 (8.80)*	54.55 (8.70)*	54.02 (8.04)	52.80 (9.50)*
		Fair / Poor	58	40.73 (10.85)*	46.38 (10.38)*	50.90 (9.29)*	54.10 (9.13)	49.86 (9.57)*
Total				48.15 (10.39)	49.96 (9.30)	53.84 (8.93)	54.10 (8.22)	52.25 (9.54)

$p < 0.05$, based on t-tests or analyses of variance (ANOVAs) with Hochberg's GT2 Post hoc test.

reported for parent relations and social support and peers. However, it should be noted that we did not compare HRQoL of chronically ill children to HRQoL of healthy peers, but made use of T-scores, which are centered to the scores of a relevant reference population. Previous studies that compared self-reports of chronically ill children to their peers without chronic conditions reported similar results for physical well- being, but they found lower scores for social domains, such as parent relations, social support and peers, and school well-being (25, 38). Similar to our findings, the difference in HRQoL scores between children with and without chronic conditions were also small for all measured health domains (25, 38). Considering that our data collection took place in an outpatient setting where children and adolescents attended the clinic for a regular check-up rather than attending because of acute symptoms, it is not surprising. Coping strategies and adaptation to illness could provide an explanation for our findings (1, 3). It should be further kept in mind that self-reported HRQoL measures how the young patients perceive their health status considering the individual limitations and opportunities (39, 40).

The comparison of T-scores according to sociodemographic and pediatrician-reported clinical data and medical assessment revealed statistically significant differences in specific domains. However, is should be noted that statically significant differences do not necessarily indicate clinically important differences (41). An interesting finding was the small positive effect of having at least one comorbid disease on the domains psychological well-being, parent relations, social support and peers, and school well-being. One reason for this finding could be additional support, care and attention from family and friends given the higher burden of having a comorbid disease.

When comparing HRQoL of children and adolescents with different health conditions, the characteristics of the underlying medical condition seems to influence the impact of the condition as also shown by others (3). Our data suggests that children and adolescents with diabetes mellitus reported the highest HRQoL scores followed by those with juvenile arthritis. Lowest scores, especially in the domain physical well-being, were reported by children and adolescents with asthma. Similar results were reported by Varni et al. (38) comparing HRQoL of children with different chronic conditions; however, in the Varni et al. study children and adolescents with juvenile arthritis reported worse HRQoL scores compared to those with asthma or diabetes mellitus (38). A viable explanation for the differences between our study and the Varni et al. (38) study may be explained by the high percentage of children and adolescents with asthma who have co-morbidities and poor disease control in our sample. Further, it might be related to the fact that, due to German national guidelines and the local conditions, children and adolescents with asthma are treated by their primary care pediatricians who only refer patients to specialized tertiary care clinics, if they do not achieve adequate disease control (42). Hence, it can be assumed that our asthma sample consisted only of those patients with the worst disease parameters. In contrast, patients with diabetes mellitus and juvenile arthritis are generally seen in specialized clinics; hence, our sample would

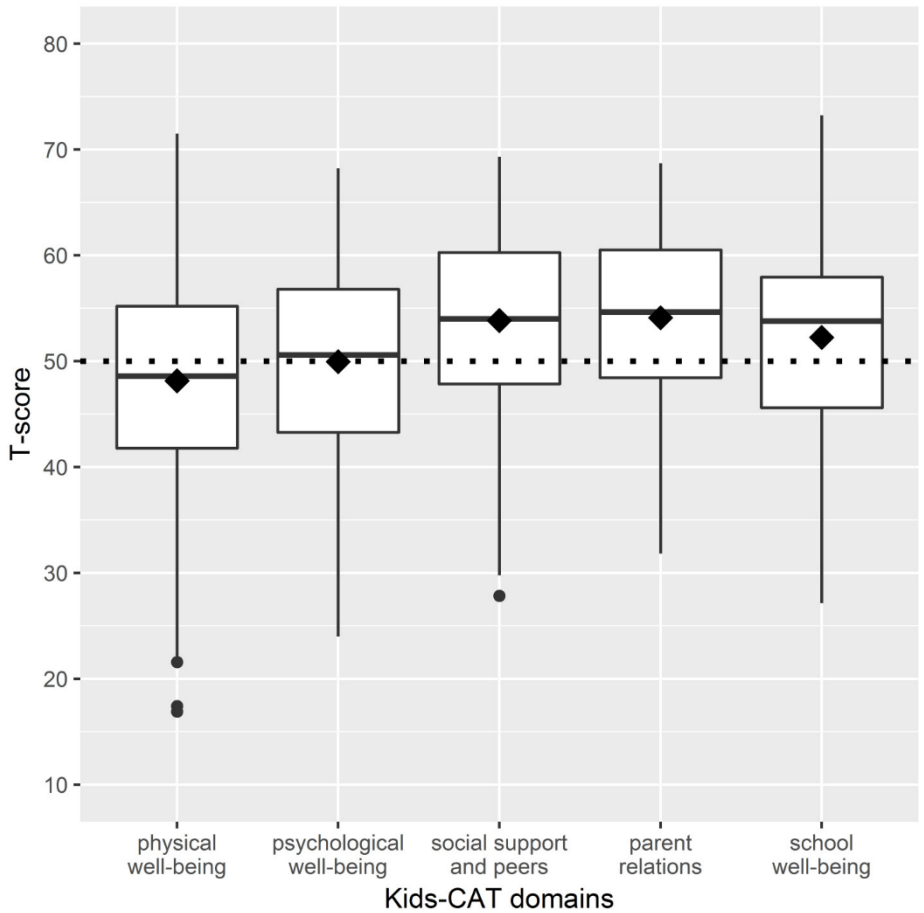

FIGURE 1 | Boxplots of HRQoL dimensions - distribution of T-scores of the five Kids-CAT domains. The boxes represent the interquartile range between the first and the third quartile, the horizontal bold line in each box shows the median T-score of each Kids-CAT domain. The diamond shows the mean score of the respective domain. The small black dots beyond the end of the whiskers are outliers. The dotted line represents the mean T-score of the reference population (T-score of 50 with a SD of +/− 10).

have included the milder spectrum of patients of these two disease groups. This notion is reflected by the distribution of factor disease control. While half of the children and adolescents with asthma were allocated to the group "poor disease control", less than one third were classified as poorly controlled for the diabetes mellitus and juvenile arthritis subsamples, respectively.

We found that selected predictor variables explained only little variability of the Kids-CAT domains. In particular, the proportions of variance explained by the investigated clinical data and medical assessments in the Kids-CAT domains were low ranging from 1.1% to 11.6%. Our findings can be explained by the model of patient outcomes by Wilson and Cleary (43). It conceptualizes the relationship of different outcomes in consideration of the somatic paradigm of health, reflecting that symptoms, functional status, and health perception are influenced by individual and environmental characteristics (43). While clinical data focuses on the underlying conditions and complaints of patients, the Kids-CAT domains refer to the functional status and health perception of young patients (43). The minimal association found in our study shows that both measures are linked but are clearly distinguishable from each other in terms of what they measure (44). Thus, it is hardly possible to draw inferences from clinical data and medical assessments to generic HRQoL of children and adolescents with chronic conditions and vice versa (45, 46). In particular, the only marginally explained variance for domain psychological well-being is an important result given the increased risk of children and adolescents with chronic conditions to develop emotional, developmental, and behavioral problems (11, 47). The implementation of a self-report instrument such as the Kids-CAT, with its feedback report on a domain level, enables pediatricians to gain crucial information about their young patients' HRQoL (24, 48, 49). It can be a useful adjunct to traditional clinical data to facilitate shared decision-making and support a patient-centered care approach (50).

Despite a comprehensive study design and thorough data collection, this study has potential limitations. First, data collection took place at two selected outpatient clinics and comprised participants recruited during regular check-ups.

TABLE 3 | Multivariable linear regression models of the relationship of sociodemographic variables and clinical data with the five Kids-CAT domains.

Variable	Physical well-being		Psychological well-being		Parent relations		Social support and peers		School well-being	
	B (SE)	95%CI	B (SE)	95%CI	B (SE)	95%CI	B (SE)	95%CI	B (SE)	95%CI
Constant	53.37		56.84		50.79		41.61		46.58	
Sex (female)	−0.60 (1.12)	[−2.80, 1.60]	−4.74* (1.05)	[−6.81, −2.67]	−0.14 (1.03)	[−2.19, 1.91]	0.71 (0.95)	[−1.17, 2.58]	−0.64 (1.11)	[−2.82, 1.54]
Age	−0.52* (0.21)	[−0.93, 0.10]	−0.07 (0.20)	[−0.46, 0.32]	0.41* (0.20)	[0.02, 0.80]	0.36* (0.18)	[0.01, 0.72]	−0.07 (0.211)	[−0.48, 0.35]
Asthma[a]	1.28 (2.16)	[−2.97, 5.53]	−1.67 (2.03)	[−5.66, 2.31]	−0.92 (2.01)	[−4.87, 3.03]	1.78 (1.84)	[−1.83.5.40]	−0.97 (2.14)	[−5.18, 3.23]
Diabetes[a]	2.79 (1.57)	[−0.30, 5.87]	−1.31 (1.47)	[−4.19, 1.58]	−1.19 (1.46)	[−4.05, 1.68]	2.24 (1.33)	[−0.58, 4.86]	−1.42 (1.55)	[−4.46, 1.62]
SES[b]	0.08 (0.20)	[−0.32, 0.47]	−0.09 (0.19)	[−0.45, 0.28]	0.070 (0.21)	[−0.34, 0.47]	0.37* (0.17)	[0.02, 0.71]	0.64* (0.20)	[0.24, 1.04]
Disease duration	0.24 (0.16)	[−0.07, 0.56]	−0.07 (0.15)	[−0.36, 0.23]	−0.23 (0.15)	[−0.52, 0.07]	−0.02 (0.14)	[−0.29, 0.24]	−0.04 (0.16)	[−0.34, 0.27]
Co–morbidity	−1.40 (1.40)	[−4.17, 1.36]	0.10 (1.32)	[−2.48, 2.68]	0.29 (1.30)	[−2.27, 2.86]	1.85 (1.19)	[−0.49, 4.20]	0.19 (1.39)	[−2.55, 2.92]
Disease control (Poor)	−3.28* (1.36)	[−5.99, −0.61]	1.28 (1.28)	[−3.80, 1.24]	−0.70 (1.25)	[−3.16, 1.76]	2.00 (1.16)	[−0.28, 4.29]	−0.47 (1.33)	[−3.08, 2.14]
Overall health status (Fair / Poor)	−7.15* (1.57)	[−10.24, −4.06]	−3.68* (1.50)	[−6.63, 0.73]	−3.15* (1.46)	[−6.03, −0.28]	−0.99 (1.14)	[−3.63, 1.65]	−2.31 (1.55)	[−5.37, 0.75]
R^2 (adj. R^2)	0.19 (0.16)		0.11 (0.08)		0.05 (0.02)		0.07 (0.04)		0.06 (0.03)	
R^2 (adj. R^2)	0.12 (0.11)		0.03 (0.02)		0.03 (0.02)		0.02 (0.01)		0.01 (0.00)	

n = 309 pooled data according to 20 imputed data sets.

[a]variables were entered as dummy variables with disease group juvenile arthritis used as a reference group.

*[b]Socioeconomic status (SES) was entered as continuous variable (sum score); B: unstandardized regression beta coefficient * p < 0.05; R^2: difference in R^2 between basic model (sex, age, disease group, SES) and full model (sex, age, disease group, SES, disease duration, comorbidity, disease control, overall health status).*

It turned out that the sample did not sufficiently cover children and adolescents with low socioeconomic status and immigrant background. Thus, findings based on our convenience sample are not generalizable. Second, both the selection and conceptualization of some of the variables may not have been optimal. Data on co-morbidity was reported by pediatrician and not directly obtained from the medical records. This might have resulted in a slight underreporting of additional medical conditions in the present study. Further, harmonizing the concept of disease control across three disease groups is a challenge and has been accomplished by a qualitative approach, which might be interpreted differently by other research groups. The selection, classification, and assessment of all clinical data was discussed thoroughly within the research group, including stakeholders with different research and clinical expertise. Finally, it should be noted that using the dichotomized variable for disease control represents a simplification of a complex construct, which has various characteristics in clinical practice.

FURTHER RESEARCH

Further research is needed to validate our results. On the one hand, further research is needed to test whether the additional information is beneficial for medical treatment. On the other hand, further research is needed to explore intra-individual variations of self-reported HRQoL as a measure of longitudinal adaptation and how this information can be incorporated into the treatment regimen over time. Moreover, it is important to define when a score is of clinical relevance and further action should be taken. Studies to determine minimal important difference using the Kids-CAT are needed for clinical guidance.

Given the advancements and increasing use of mobile applications to collect PRO data, it is possible to complete assessments almost everywhere. The impact of the setting should be addressed in further studies. In particular, it should be investigated how the setting (e.g., home assessments vs. assessment at the clinic) might influence the response behavior and thus the results for self-reported HRQoL in of children and adolescents.

CONCLUSION

The variability of the HRQoL domains is only minimally explained by selected clinical data and medical assessments, indicating that children's HRQoL can hardly be inferred from these data alone. Especially, the minimal association between psychological well-being, and social health domains, such as parent relations, social support and peers, and school well- being and the selected clinical data shows that the assessment of HRQoL could be a valuable source of information in healthcare. Combining self-reported HRQoL with clinical parameters and traditional medical tests should enhance getting a more comprehensive picture of young patients' health status. In this way, pediatricians might identify additional healthcare needs, which would not be detected otherwise.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher on request.

AUTHOR CONTRIBUTIONS

UR-S, MR, CO, UT, and MK contributed to study concept/design. OW, SN, CO, MR, and UR-S developed the Kids-CAT tool. DB, SN, UT, and MK supervised and managed data collection. OW, CO, and DB were responsible for data surveillance/quality and managed the data preparation. SN was involved in the data interpretation and conceptualization of the paper. KF performed statistical analyses and wrote the first draft of the manuscript. All authors critically revised the manuscript and approved the final manuscript as submitted.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2019.00017/full#supplementary-material

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Trajectories of Health-Related Quality of Life and HbA1c Values of Children and Adolescents With Diabetes Mellitus Type 1 Over 6 Months: A Longitudinal Observational Study

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Introduction: To achieve optimized blood glucose concentrations (assessed by HbA1c) and high health-related quality of life (HRQL), children and adolescents with diabetes mellitus type 1 (T1DM) must follow strict disease management strategies. This study aims to investigate HRQL of children and adolescents with T1DM and its association with HbA1c values over the course of 6 months.

Methods: Patients aged 7–17 years ($n = 203$) with T1DM provided HRQL data on a monthly basis. HRQL was measured using the Kids-CAT, a computer-adaptive test (CAT) comprising five generic HRQL domains. HbA1c concentrations were assessed at baseline, at 3 and 6 months. We explored the trajectory of HRQL at the domain level using linear mixed effects models. Further, we investigated the association between HRQL and HbA1c concentrations over time using path analysis models.

Results: Children and adolescents with T1DM reported high scores across all HRQL domains over time. However, those with an HbA1c concentrations of >9.0% reported significantly lower scores in physical well-being and parent relations compared with those with an HbA1c concentration of <7.5%. Path analysis models revealed a minimal temporal relationship between HbA1c and HRQL, with a small negative impact of HbA1c on physical well-being, psychological well-being and parent relations.

Conclusion: Although observed HRQL of young patients with T1DM was comparable to age-related German-speaking reference population over the course of 6 months, those with an HbA1c concentration >9.0% reported lower scores in selected HRQL domains.

Thus, special attention should be drawn to HRQL of children and adolescents with higher HbA1c concentrations. The minimal relationship between HbA1c and HRQL indicates that the two therapy goals, i.e., achievement and maintenance of glycemic targets and high HRQL, should be considered and evaluated independently in clinical routine.

Trial Registration: DRKS00006326 (German Clinical Trial Register), date of registration: August 1st, 2014.

Keywords: health-related quality of life, pediatrics, self-report, patient outcome assessments, diabetes mellitus type 1, computer-adaptive testing

INTRODUCTION

Continuous development of treatment opportunities for diabetes mellitus Type 1 (T1DM) allows children and adolescents with T1DM to live a relatively normal life despite their chronic condition. However, the number of children and adolescents diagnosed with T1DM is increasing and all patients affected have to comply with lifelong treatment and care (1, 2). The main T1DM treatment aim is to achieve or maintain glycemic targets to avoid acute and long-term complications (3, 4). Hence, observation of HbA1c concentrations is a crucial indicator to monitor this primary treatment goal (5, 6). Besides the glycemic target, an overarching treatment goal in diabetes care is achieving and maintaining high quality of life, and in particular health-related quality of life (HRQL), of young patients (4, 5).

In terms of glycemic target, the American Diabetes Association recommends age-independent HbA1c concentrations of <7.5% in children and adolescents (5, 7). However, studies have shown that most children and adolescents with T1DM do not meet these recommendations despite comprehensive treatment methods and technological advancements (1, 4, 8, 9). Non-achievement of the glycemic target are due to multiple factors, such as age, sex and quality of life, especially emotional and psychosocial aspects (10–14).

While a precise glycemic target has been defined for children and adolescents with T1DM, it is not the case for the overarching treatment goal HRQL, a multidimensional construct containing physical, mental and social aspects of health (15). Various measures to assess generic as well as diabetes-specific HRQL are available (16, 17). Diabetes-specific HRQL measures assess disease-specific health problems and symptoms. The measurement of generic HRQL allows the comparison of results to healthy peers and the identification of potential problems, which go beyond diabetes-specific symptoms or treatment issues, but are related to metabolic control and diabetes management (16, 18). As outlined by Hilliard et al. (18), HRQL does not only function as a classical outcome parameter but might also serve as measure to identify problems in physical, emotional or social well-being, i.e., aspects that are related to diabetes management and consequently to the glycemic target (18).

So far, HRQL is usually not routinely assessed in clinical practice, but various studies investigated HRQL in children and adolescents with T1DM in comparison with healthy peers and also its association with other clinical parameters. Cross-sectional studies reported varying results when comparing HRQL of children with T1DM with healthy peers. While Varni et al. (19) found significantly lower scores in the domains emotional, psychosocial, and school functioning, Murillo et al. (14) found only slightly lower scores in the domain physical well-being, when comparing children with T1DM with healthy peers (14, 19). In contrast, Wagner et al. (20) reported no differences between children with T1DM with healthy peers, but higher psychological and school well-being scores in sub-groups of children with T1DM (20).

The relationship between the clinical outcome parameter HbA1c concentration, as an indicator for the glycemic target, and HRQL has also been investigated in young patients with diabetes mellitus. While some studies, found no associations between HRQL and glycemic target (21–23), others were able to detect a relationship between both the two outcome parameters (24–27). For example, it was found that higher scores in HRQL were associated with better metabolic control (25), while poor metabolic control was related to psychosocial problems in children and adolescents with T1DM (12, 27).

While most studies were based on cross-sectional data, less is known about the association of HRQL and HbA1c over time. To fill an important gap in the literature, this study aims to investigate the disease trajectory of children and adolescents with T1DM and in what way their self-reported HRQL is associated with HbA1c concentrations. Based on previous research, we hypothesized that high HbA1c concentrations are associated with lower HRQL over time.

MATERIALS AND METHODS

We followed the STROBE Statement und used the STROBE checklist for reporting results of this study (28, 29). The completed STROBE checklist can be found in **Table S1**.

Study Design and Setting of the Study

The present study includes a subsample of children and adolescents with T1DM of the Kids-CAT project. The Kids-CAT project aimed to develop, validate and implement the first German-speaking computer-adaptive test (CAT) to measure HRQL in children and adolescents with chronic conditions (30–32). The prospective longitudinal observational study took place at two pediatric outpatient clinics (Kiel and Lübeck) at the

Abbreviations: CAT, computer-adaptive test; IRT, Item response theory; T1DM, Diabetes mellitus type 1; HRQL, health-related quality of life.

University Medical Center Schleswig Holstein, Germany from June 2013 to October 2014. We applied a convenience sampling strategy, where study nurses at both clinics recruited children and adolescents with chronic conditions (asthma, juvenile arthritis, and diabetes mellitus) who attended the clinic for regular examination. Inclusion criteria were age between 7 and 17 years, clinical diagnosis of diabetes mellitus, asthma or juvenile arthritis and sufficient knowledge of German (spoken and written). The sample size of the study was determined according to the primary objective of the Kids-CAT project. For validation purposes, a sample size of 300 participants were required. A total of 312 children and adolescents participated in the Kids-CAT project, including 205 children and adolescents with diabetes mellitus.

The study was conducted adhering to the Declaration of Helsinki. Ethical approval was granted by Chambers of Physicians Kiel and Lübeck and the Chamber of Psychotherapists Hamburg, Germany. Written informed consent was obtained from parents/legal guardians, informed assent was obtained from children and adolescents.

Participants and Procedure

This study reports data of a subsample including all children and adolescents diagnosed with diabetes mellitus [based on the International Statistical Classification of Disease and Related Health Problems, 10th revision, German Modification (ICD-10-GM) code E 10: Diabetes mellitus Type 1 (33)].

Assessment of HbA1c and HRQL took place at the respective outpatient department or at home. For the HRQL questionnaire, children and adolescents completed these electronically on a laptop, PC, tablet, or smartphone at the outpatient department during the waiting time (clinical assessment) or at home (home assessment). The clinical assessment was embedded in the routine medical encounter of the young patients (approximately once every 3 months). In addition to patient assessments, pediatricians provided further clinical information. For home assessments, study nurses sent a link via email to participants 1–2 days before the predetermined measurement point. Participants were reminded to complete the survey up to three times. For this study, data of seven measurement points over the course of 6 months with monthly intervals between measurements (M = 33.04 days; SD = 11.362) were analyzed.

Measures and Instruments

We measured self-reported HRQL by use of the Kids-CAT. This generic HRQL instrument comprises the domains physical well-being, psychological well-being, parent relations, social support and peers, and school well-being akin to the KIDSCREEN domain structure with a recall period of 1 week (31, 34). The Kids-CAT was developed based on classical test theory and item response theory (IRT) (30, 35). For each of the five health domains an item bank was developed and calibrated including between 26 and 46 items. Thus, a latent trait level (T-score), including the standard error, can be estimated based on a single item. By applying additional items of the same the item bank, the latent trait level of the domain is re-estimated and the measurement precision increases. The Kids-CAT adapts to the individual, meaning that a patient has to answer only a subset of items of a domain, which are selected based on the patient's responses to the first item(s) (altogether three to seven items per domain). Although participants answer different subsets of questions, their estimated latent trait levels (T-scores) are comparable across individuals as well as within individuals over time. The estimated trait levels (higher score indicating better HRQL) for each domain are anchored to a German speaking reference sample (n = 10,577–19,580), meaning that a T-score of 50 with a SD ± 10 corresponds the average HRQL of children and adolescents in the German general population. Measurement properties of the Kids-CAT have been shown to be valid and reliable (31). Further information on the development process can be found elsewhere (30).

We assessed clinical data during the clinical measurement points (at three time points) based on both medical records and forms filled out by pediatricians. HbA1c concentrations for each clinical measurement point were grouped into <7.5, 7.5–9.0, and >9.0% (5, 36). In addition, we calculated the average HbA1c concentration over 6 month for each participant with at least two data points and grouped the average HbA1c concentration as described above. Further, we collected data on the type of therapy (categorical variable) with the options pump therapy, injection therapy, or switching therapy (from injection to pump therapy or vice versa within the period under review), age at the time of diagnosis (discrete variable), duration of the disease in years (discrete variable), as well additional chronic condition(s) (dichotomous variable). Socioeconomic status of the family was assessed based on nine validated questions on education (two items), income (three items), and occupation (four items) of the parents developed by the Robert Koch-Institute and used in German population-based studies (37, 38). We asked parents to complete these questions at baseline. Due to the responses, an SES index (3–21 points) was computed and categorized into high (13.9–21.0 points), middle (8.0–13.8 points), and low (3.0–7.9 points) social status.

Statistical Analyses

First, we performed descriptive analyses at the group level to characterize the study sample and evaluate self-reported HRQL data according to the five Kids-CAT domains over the course of 6 months. Further, we investigated the change in HRQL domains over time on an individual patient level by calculating the percentages of children and adolescents whose T-scores improved and declined from one to the next measurement point. We defined change (improvement or decline) as a T- score of the individual lying outside of the confidence interval of the T-score of the preceding measurement point. For that reason, we calculated for each participant the respective confidence interval on a domain level for each time point, using point estimate and respective standard error provided by the Kids-CAT.

Following these descriptive analyses, we conducted missing data analysis. We checked, if data was missing completely at random (MCAR) using Little's MCAR test and checked patterns of missing data (39). We performed multiple imputation analysis creating m = 20 datasets, using the predictive mean matching method for numeric data, logistic regressions for binary data and

proportional odds models for ordinal data (39–41) for further analysis. Sensitivity analysis were run to compare the original data set and the pooled results of the imputed data sets.

In a third step, we investigated the associations between baseline HbA1c concentration and Kids-CAT domains over time. We grouped participants based on their baseline HbA1c

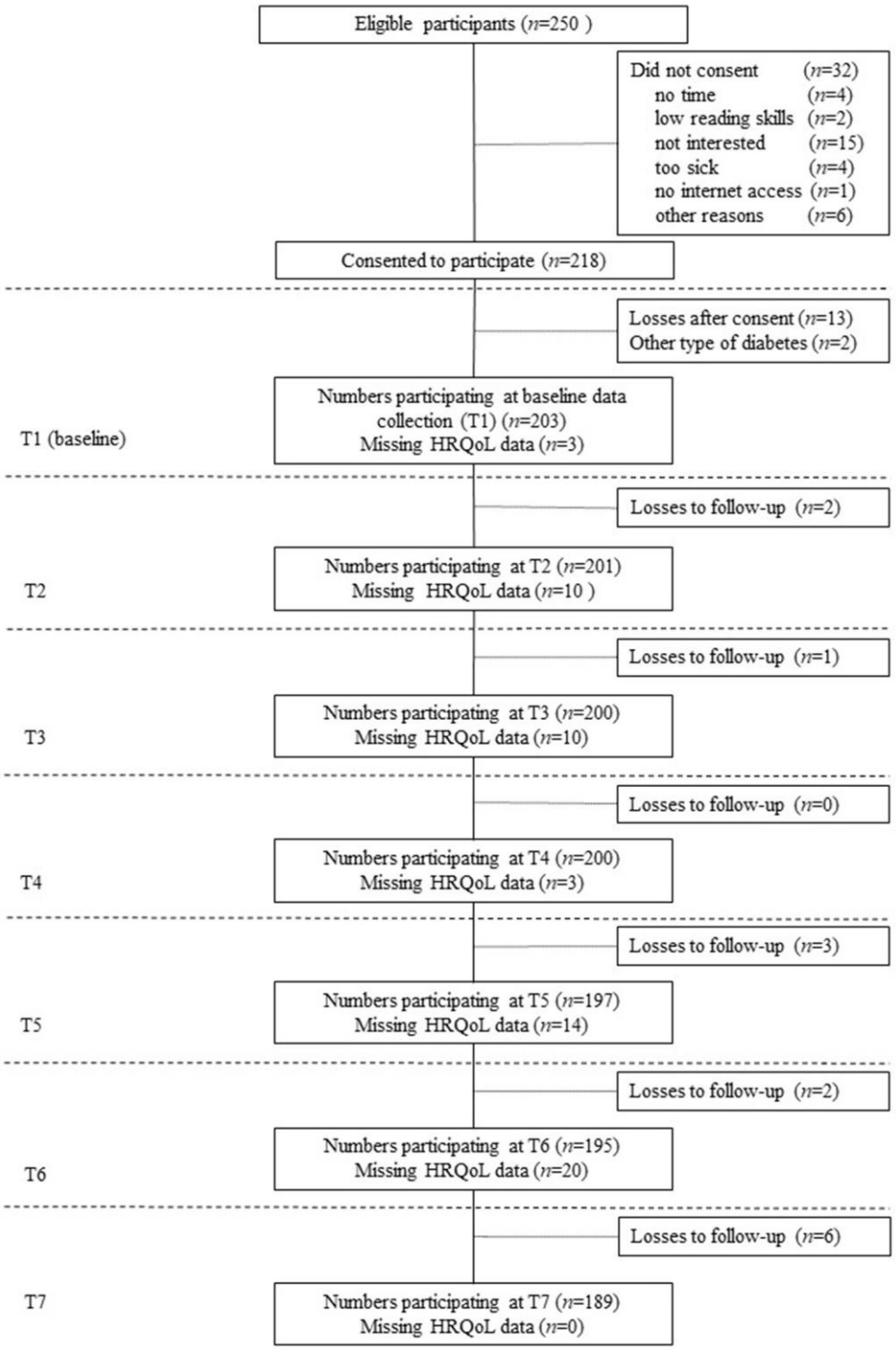


FIGURE 1 | Flow diagram—study participation over time. Loss to follow-up was defined, as missing health-related quality of life (HRQL) data for all subsequent measurement points. Otherwise, missing HRQL data was considered as missing for the respective measurement point.

concentration according to the American Diabetes Association (5) into three groups (1:<7.5%; 2:7.5–9.0%, 3:>9.0%) (5, 6). We investigated the change in HRQL on the domain level over time using linear mixed-effect models fitted by restricted maximum likelihood (REML) estimation. We modeled the effect of the HbA1c group and time as well as an interaction term of both variables (as fixed effects) for each Kids-CAT domain controlling for age and sex; we further included a random intercept for each individual (as random effect).

Finally, we investigated the temporal relationship between the HbA1c concentration and the five Kids-CAT domains over time. We applied an exploratory approach to develop and fit a path model for each Kids-CAT domain including the HbA1c concentration and the respective Kids-CAT domain score (at baseline, after 3 months, after 6 months). We estimated the effect of the HbA1c concentration on the domain T-score and vice versa over time, while controlling for age and sex. Model fit was evaluated by χ^2 value and its associated p-value, Tucker Lewis Index (TLI), comparative fit index (CFI), and root means square error of approximation (RMSEA). We applied the cut of values ≥ 0.95 for TLI and CFI and <0.10 for RMSEA, and evaluated the significance level of χ^2 (42).

Statistical analyses were performed using IBM SPSS Statistics for Windows Version 22 (descriptive analyses) and R Statistics version 3.3.2 using the packages mice for multiple imputation (41) and nlme (43), lme4 (44), lmerTest (45), and MuMIn (46) for mixed model analyses. For path analysis we used the package lavaan and semTools (47, 48). A p-value of $<.05$ was considered as statistically significant.

TABLE 1 | Sociodemographic and clinical characteristics of the investigated children and adolescents with T1DM [baseline assessment (T1)].

	N	Mean (SD)	%
Sociodemographic characteristic			
Age (in years)	203	12.77 (2.78)	
Age group			
Children (7–11 years)	73		36.0
Adolescents (12–17 years)	130		64.0
Sex (female)	90		44.3
Socioeconomic status of the family	166	13.44 (3.06)	
Low	5		3.0
Middle	115		69.3
High	46		27.7
Clinical characteristics (physician r eported)			
Disease duration in years	203	5.36 (3.69)	
Age at disease onset	203	7.41 (3.82)	
Treatment	202		
Pen	60		29.7
Pump	119		58.9
Change of treatment	23		11.4
Co-morbidity (yes)	40		19.7
NGSP HbA1c concentration in %	196	7.97 (1.37)	
<7.5%	74		37.8
7.5–9.0%	88		44.9
>9.0%	34		17.3

RESULTS

Sample Description and Descriptive Analyses

In total, 250 children and adolescents were eligible for study participation according to inclusion criteria. Of these, 218 consented for study participation, however 13 participants where lost after consensus and two participants were excluded from the analyses due to other type of diabetes mellitus. According to this, 203 children and adolescents were included in following analyses (**Figure 1**). There were no statistically significant differences in age ($M_{responder}$ = 12.77, SD = 2.78; $M_{non-responder}$ = 13.24, SD = 3.12; p = 0.295) and sex ($female_{responder}$ = 44.3%; $female_{non\_responder}$ = 57.8%; p = 0.103) between young patients who participated in the study (responders) and those who did not participate (non-responders). Across the seven measurement points, 14 participants were lost to follow-up, which corresponds to 6.9% of the total sample. Participants were considered loss of follow-up, if no HRQL data was available for all subsequent measurement points, otherwise it was considered as missing data for the respective measurement point.

Mean age of the investigated children and adolescents was 12.77 years and 44.3% were female. Children and adolescents, who participated in our study had a mean disease duration of 5.36 years, and the mean age of primary manifestation of T1DM was 7.31 years. Further, co-morbidities were reported for 19.7% of children and adolescents. During the study, 29.7% of the children and adolescents were under insulin pen therapy, 58.9% used an insulin pump and 11.4% switched the type of therapy during the study. The mean NGSP HbA1c concentration at baseline was 7.97% (SD = 1.37, Range = 8.90) and slightly decreased after 6 months to 7.89% (SD = 1.38, Range = 9.40). Further information on sociodemographic and clinical characteristics are presented in **Table 1**.

Overall, T-scores for children and adolescents were comparable to the sex and age-matched German norm population for all five HRQL domains over the course of 6 month, meaning that mean T-scores were between 40 and 60 (**Figure 2**, detailed information on Kids-CAT T-scores on domain level over the course of 6 months are provided in **Table S2**). The range of T-scores was large in all five Kids-CAT domains, which was consistent over time. In addition, outliers were predominately found at the lower end of the range.

On an individual level, around 20% of the participants had significantly higher/lower T-scores from one to the following measurement point, which was consistent across all domains (average change by domain: physical well-being = 21.4%, psychological well-being = 22.9%, parent relations = 19.7%, social support & peers = 19.5%, school well-being = 19.7%) (detailed information are provided in **Table S3**).

In subgroup analyses, we investigated the change in HRQL (improvement or decline) from one to the following measurement point. If HRQL declined in children and

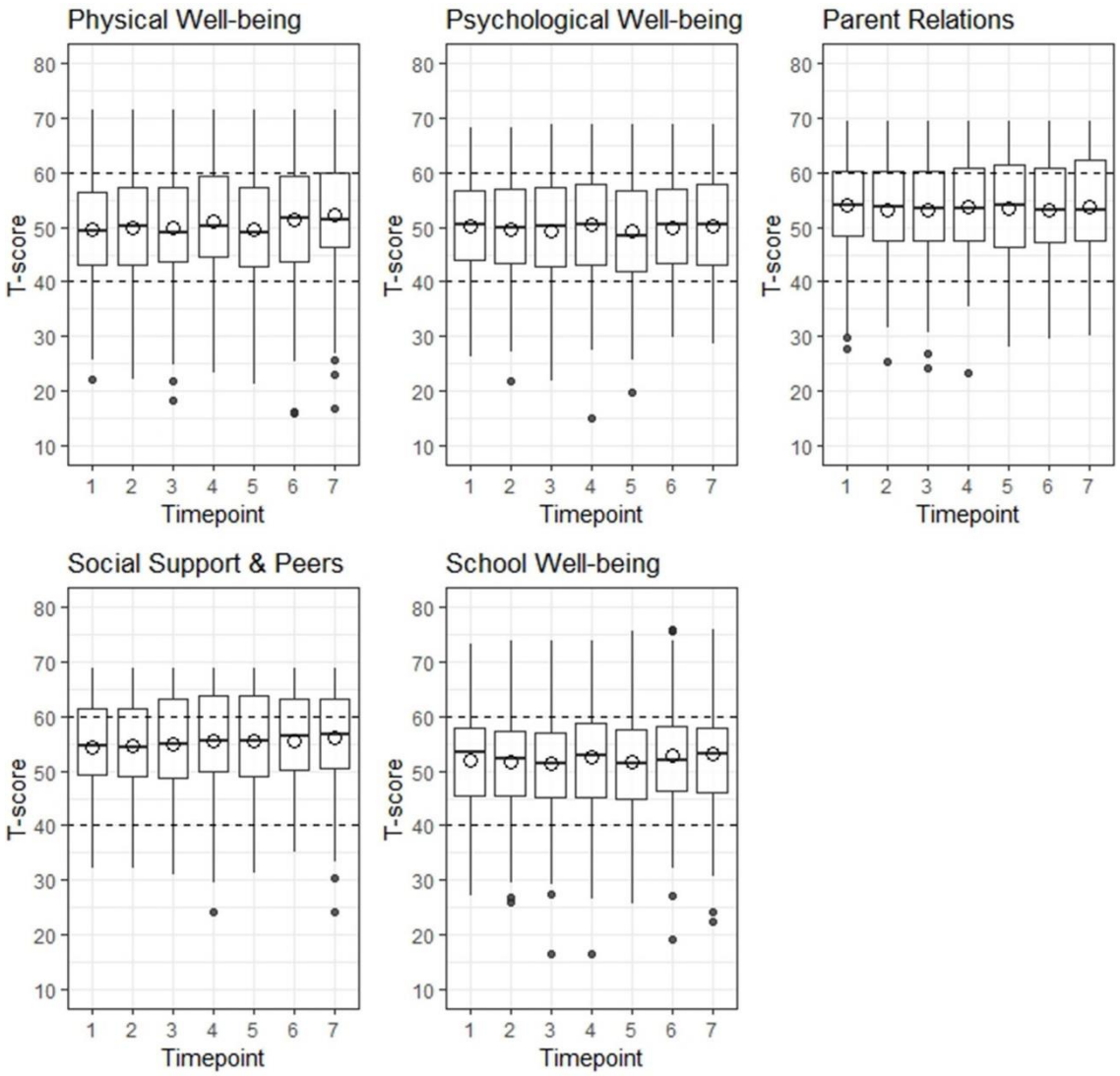


FIGURE 2 | Distribution of health-related quality of life by Kids-CAT domain over 6 months. The area between the horizontal dashed lines indicate the normal range of a German age- and sex-matched norm population. The hollow circles depict the mean T-score. The black dots at the upper and lower end of the whisker indicate outliers.

adolescents from one measurement point to the following one, differences in T-scores were at least −7.53 in physical well-being (−6.51 for psychological well-being, −6.35 for parent relation, −6.49 for social support & peers, −6.45 for school well-being). Similar levels of difference scores were detected in those, who reported improvement in HRQL from one to the next measurement point (at least 7.15 for physical well-being, 6.73 for psychological well-being, 6.16 for parent relations, 6.26 for social support & peers, and 5.91 for school well-being were found; for detailed information see **TableS4**).

Missing Data and Multiple Imputation

Analysis of missing data revealed that 10.3% of data was missing within our data set, varying by variable between 0 and 18.2%. Results of Little's MCAR test revealed that data are not completely missing at random ($p < 0.01$). Thus, we investigated patterns of missing data by visualization. We came to the conclusion that our data is at least missing at random, as no pattern of missing data could be found. Thus, we were able to use multiple imputation techniques to handle missing data. We created 20 datasets, and used these for the subsequent analysis (pooled data analyses).

Trajectory of HRQL Over Time by HbA1c Categories

In a next step, we were interested in the relationship between the three groups based on baseline HbA1c concentrations and HRQL measured by the Kids-CAT over time (**Figure 3**). Model estimates revealed that the group of children and adolescents with HbA1c concentrations >9.0% reported significant lower scores for the domains physical well-being ($B = -5.60$, $SE = 2.21$; $p < 0.05$) and parent relations ($B = -4.32$, $SE = 1.99$; $p < 0.05$) compared

to the reference group (children and adolescents with a HbA1c concentration <7.5%). Nearly all models revealed only minimal change over time, only in the domains physical well-being, social support and school well-being statistically significant changes for a few selected time points were found. However, the change was less than ±4 points compared to the baseline value of these domains. For the domain psychological well-being, change over time based on the HbA1c groups indicated that those children with a baseline HbA1c concentration over 9.0% got worse over time, however, these findings were not statistical significant (results not shown).

Association Between HbA1c Value and HRQL Over Time

In the path analyses, we modeled the effects of Kids-CAT domains (individual path model for each domain) and HbA1c over time [baseline (T1), after three (T4), and after 6 months (T7)] controlling for age and sex. In the first path, we estimated the direct effect of the respective domain over time (T1, T4, T7). The second path estimated the association of HbA1c concentrations over time (T1, T4, T7). Further, we modeled the effect of the baseline T-scores on the HbA1c concentration after 3 months, as well as the effect of the baseline HbA1c concentration on the T-scores after 3 months. Corresponding paths were specified from the respective scores measured at baseline as well as from those assessed after 3 months on scores after 6 months. In addition, correlations between HbA1c concentration and domain-specific T-scores (same measurement point) were estimated. Finally, we added the covariates age and sex to estimate the direct effect on baseline values. The final models with unstandardized parameter estimates for physical well-being, psychological well-being and parent relations are displayed in **Figure 4** (path models for social support & peers and school well-being can be found in **Figure S1**). Fit indices of all five models showed good fit of the data according to TLI, CFI, and RMSEA, while χ^2 was acceptable.

Estimates of all path analysis models showed statistically significant associations between the domain scores over time as well as between the HbA1c concentrations over time with nearer time points more strongly correlated. Further, we found statically significant positive associations between age and HbA1c concentration for the five models, but no statistically significant association between age and the five Kids-CAT domains. Statistical significant associations between sex and HRQL was only found for the domain psychological well-being.

The path analysis model for physical well-being and HbA1c concentrations showed negative correlations at baseline ($B = -2.15$, $SE = 0.99$, $p < 0.05$) that indicated that a higher HbA1c concentration was associated with lower physical well-being. For the temporal correlation, the model revealed statistically significant negative association between HbA1c concentration after 3 months and physical well-being after 6 months ($B = -1.02$, $SE = 0.49$, $p < 0.05$). Further, the model showed statistically significant negative associations between the path physical well-being after 3 months and HbA1c concentration after 6 months ($B = -0.012$, $SE = 0.01$, $p < 0.05$) (**Figure 4**). Remaining paths of the model were not statistically significant.

The path analysis model for psychological well-being and HbA1c concentrations revealed a statistically significant negative association between HbA1c concentration at baseline and psychological well-being after 3 months ($B = -1.46$, $SE = 0.49$, $p < 0.05$), which was not replicable for the path HbA1c concentration after 3 months and psychological well-being after 6 months ($B = -0.80$, $SE = 0.47$, $p < 0.09$). Other paths with regard to the association between HbA1c concentration and psychological well-being were not statistically significant.

The path analysis model for parent relations and HbA1c concentration showed statistically significant negative correlation between baseline HbA1c concentration and parent relations at baseline ($B = -2.15$, $SE = 0.97$, $p < 0.05$). Further, the model revealed a temporal relationship between HbA1c concentration and parent relations. Statistically significant negative associations between baseline HbA1c concentration and parent relations after 3 months ($B = -1.12$, $SE = 0.41$, $p < 0.05$), and HbA1c concentration after 3 months and parent relations after 6 months ($B = -0.80$, $SE = 0.40$, $p < 0.05$) were found. All remaining paths of the model were not statistically significant.

The path analysis models for social support & peers and school well-being revealed no statistical significant associations between the domain scores and HbA1c concentration (see **Figure S1**).

DISCUSSION

In the context of the Kids-CAT study, we explored associations between HbA1c concentrations and HRQL in children and adolescents with T1DM in continuous outpatient treatment over the course of 6 months. Overall, young patients reported average HRQL scores over a 6 months period. Further, for four out of five Kids-CAT domains we found statistically significant higher scores in young patients with a baseline HbA1c concentration <7.5% compared to those with a baseline concentration of >9.0%. At the group level, no significant change over time was detected. However, at the individual patient level, 20% of young patients reported change from one to the following measurement point in at least one HRQL domain. Exploring the temporal relationship between HbA1c concentration and the five Kids-CAT domains, only small associations were detected for the Kids-CAT domains physical and psychological well-being as well as parent relations.

The health-related quality of life scores of the investigated young patients with T1DM corresponded to an age and sex-matched German reference population ($M = 50$; $SD = 10$) (30). Similar findings were reported by previous studies for children and adolescents with T1DM who reported HRQL scores similar to their healthy peers (14, 19, 20). This finding was not surprising, considering the setting and the sample of our study. Assessments were completed during regular check-ups or at home by young patients living with T1DM on average for more than 5 years (range between 0 and 14 years). Thus, it can be assumed that diabetes management was well-adjusted and most participants were in stable health situations, where disease-related symptoms

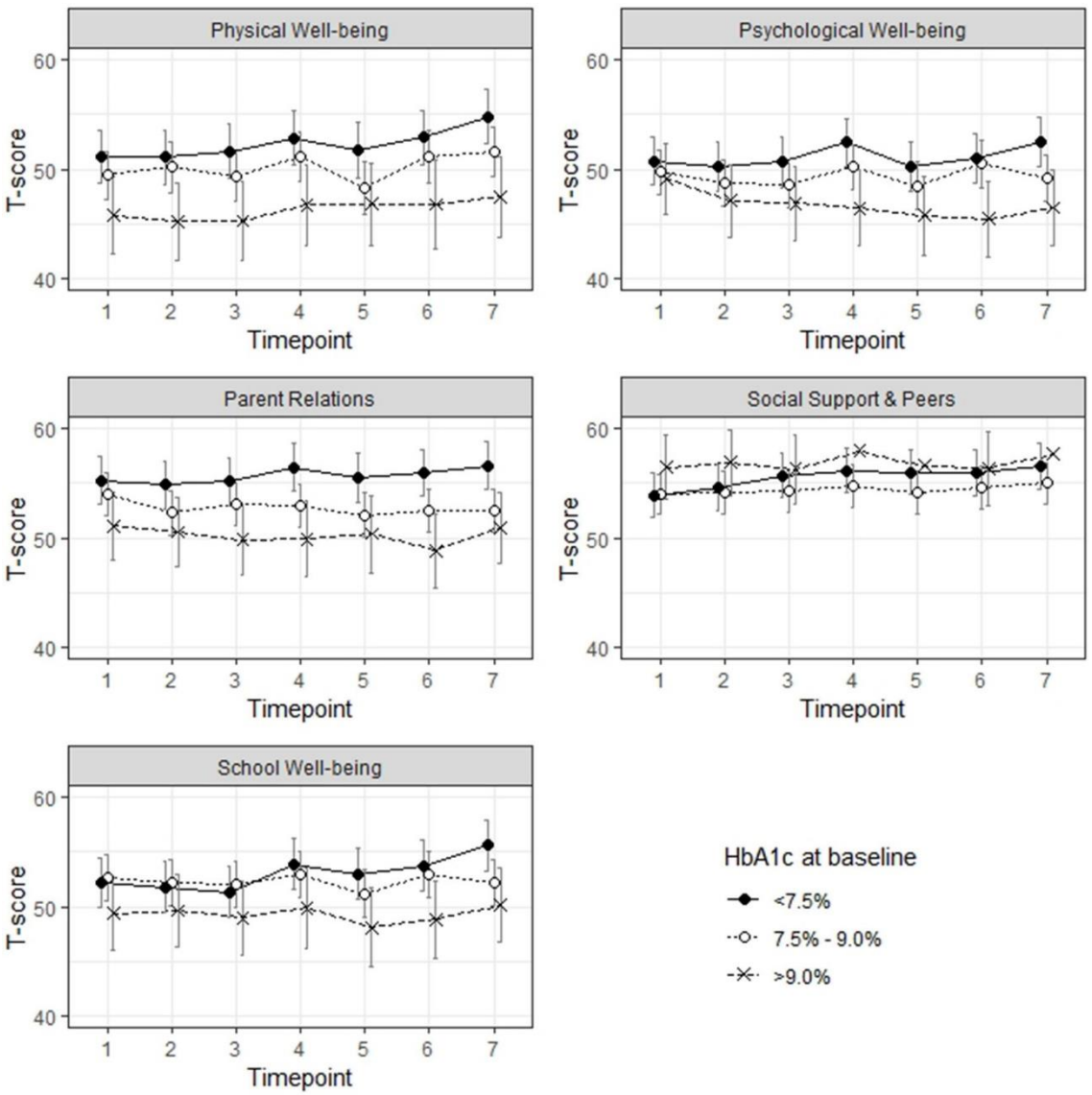
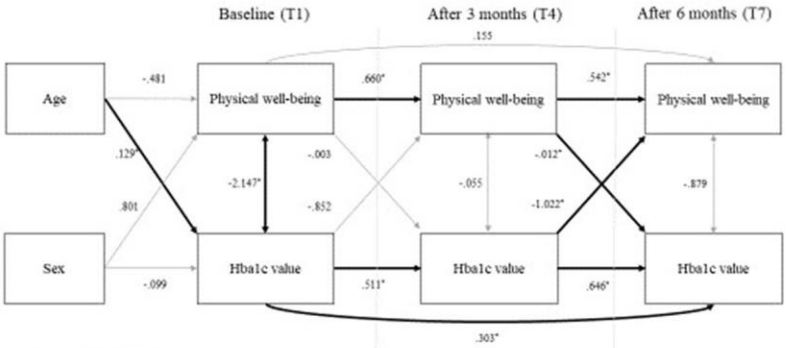


FIGURE 3 | Health-related quality of life over the course of 6 months, group allocation according to respective HbA1c concentration at baseline.

and the management of T1DM was only minimally affecting their generic HRQL (49, 50). However, further studies are needed to investigate the effect of the prolonged T1DM remission phase on HRQL.

At a group level, the changes in the five Kids-CAT domains over time were only minimal, which was expected given the observational study design. However, looking at an individual level, scores varied over time. One fifth of the young patients reported relevant change in at least one HRQL domain. Out of those, approximately 10% reported worse scores and 10% reported better scores from one to the following measurement point. The difference from one to the following measurement point was at minimum six points on the T-metric, which is statistically significant, and can be considered clinically meaningful (51). These findings indicate that regular monitoring of HRQL in clinical practice is useful to detect change early. Further exploration of predictors related to improvement of individuals over time could help to improve resilience and could facilitate to develop measures to improve HRQL of children with T1DM. Previous research found that unhealthy lifestyle habits, such as diet and low physical activity, are associated with lower HRQL (52). Promoting healthy life style habits in children with T1DM could be an important aspect to improve HRQL over time.

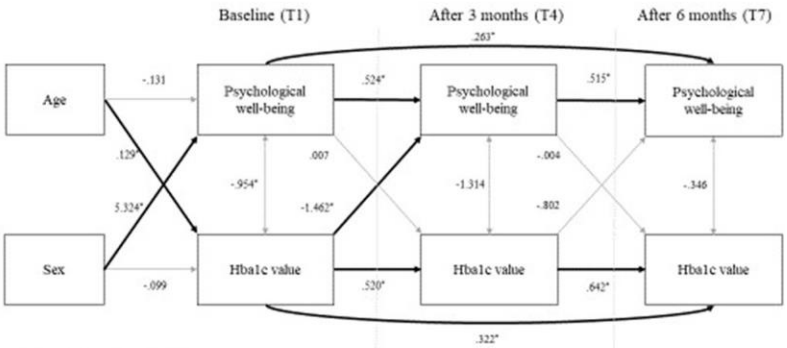
Only minimal changes within the tree groups (baseline HbA1c concentration <7.5%, 7.5–9.0%, >9.0%) were found in each of the five HRQL domains over time. However, statistical significant differences were found between those children with a baseline HbA1c concentration <7.5% and those children with a baseline concentration >9.0% in the domains physical well-being and parent relations, which corresponds to the findings of previous studies (26, 53). Given the increasing risk of diabetes-related late complications due to continuously high HbA1c concentration,



Model estimates / fit indices

χ^2, p-value	TLI	CFI	RMSEA, (90% CI), p_{close}
9.724 , 0.465	1.00	1.00	0.00 (0.00, 0.07), 0.794

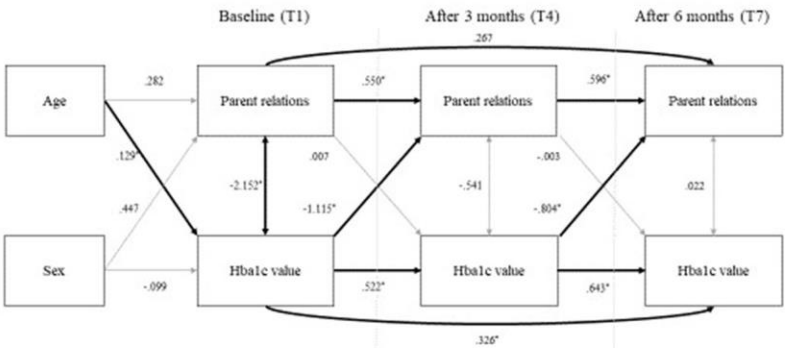
χ^2: Model Chi-Square, TLI: Tucker Lewis Index, CFI: comparative fit index, RMSEA: root means square error of approximation,



Model estimates / fit indices

χ^2, p-value	TLI	CFI	RMSEA, (90% CI), p_{close}
7.343 , 0.693	1.02	1.00	0.00 (0.00, 0.06), 0.913

χ^2: Model Chi-Square, TLI: Tucker Lewis Index, CFI: comparative fit index, RMSEA: root means square error of approximation,



Model estimates / fit indices

χ^2, p-value	TLI	CFI	RMSEA, (90% CI), p_{close}
6.586 , 0.764	1.02	1.00	0.00 (0.00, 0.05), 0.940

χ^2: Model Chi-Square, TLI: Tucker Lewis Index, CFI: comparative fit index, RMSEA: root means square error of approximation,

FIGURE 4 | Path analysis—physical well-being, psychological well-being and parent relations with standardized parameter estimates and model fit indices; bold arrows show statistical significant paths ($p < 0.05$); sex as dichotomous variable (male).

the difference in HRQL between those young patients with a high and a low HbA1c concentration might increase over future years. Considering that we used a more liberal HbA1c target of 7.5% for this study (5), and not the lower HbA1c target of 7.0% recommended by the International Society for Pediatric and Adolescent Diabetes (ISPAD) or even the HbA1c target of 6.5% recommended by the National Institute for Health and Care Excellence (NICE), the differences between groups might be larger (6).

Previous studies showed that HRQL in patients with T1DM decreased with increasing symptoms and complications (54– 56). Further, our results showed that psychological well-being of young patients with a baseline HbA1c concentration >9.0% decreased minimally over the course of 6 months. Given the enhanced risk of young patients with T1DM for developing depressive symptoms, special attention should be paid to the HRQL of children with high HbA1c concentrations (57, 58). We explored the association between HRQL and HbA1c concentration over time in terms of a temporal relationship controlling for age and sex. In contrast to Naughton et al. (59), we were not able to show a statically significant associations between age and HRQL and only statically significant associations between sex and psychological well-being. (59).

The pathway models revealed some statistically significant pathways between HRQL domains and HbA1c concentrations. However, we were not able to determine the direction of associations over time. Whereas, Naughton et.al. (59) reported negative associations between HbA1c and HRQL over time (59), we only found small associations and a tendency that higher HbA1c concentrations may lead to lower scores in the domains physical and psychological well-being as well as parent relations. Hesketh et al. (60) reported similar results for psychological well-being that they could not predict follow- up HbA1c concentrations based on domain scores. However, changes in HbA1c concentrations could be predicted by self-reported physical functioning (60). Our findings can be discussed with regard to the conceptual model by Wilson and Cleary (61) explaining the relationship between clinical variables and HRQL (61). A high HbA1c concentration, as a measure of the average blood sugar levels over time, does only minimally impact the symptom and functional status of the young patient. Further, similar associations between metabolic control, including aspects of diabetes treatment and medical adherence, and quality of life have been described (13, 14). These associations point out the complexity of diabetes management, with different factors being mutually dependent (3, 5). Thus, both treatment goals, low HbA1c concentrations and high HRQL have to be monitored and addressed individually in medical care.

Limitations

This study has some limitations, which have to be discussed in relation to the findings. Not uncommon for a longitudinal study including several time points, we were facing over 10% of missing data. As missing data could affect the results and hence the interpretation of the results, we used state-of-the-art imputation techniques to handle the missing data in our data set. We conducted sensitivity analysis comparing results of the original data set and the pooled results of the imputed data sets.

Further, sample size calculation was based on validation purposes of the Kids-CAT and thus not powered for the analysis presented in the paper. We examined *post hoc* power to detect group differences between young patients with an HbA1c concentration of <7.5% and those with an HbA1c concentration of >9.0%. Considering a difference of five points as clinical relevant, the power of the study is slightly underpowered. For path analysis, our sample size complies only with the minimal requirements. Our ratio of 14.5 participants to one parameter estimated, corresponds to the general consensus of 10:1 ratio in structure equation modeling (62, 63). Thus, our sample size was sufficient for the explorative type of our analyses, but results should be interpreted correspondingly cautious. Owing to our sample size, setting and explorative nature of this study, generalizability of our results is limited. Replication of our results is needed including a bigger sample. In addition, the follow-up of only 6 months is a rather short period to evaluate HRQL considering the lifelong chronic disease.

Finally, due to the study design, we were not able to control for differences between home and clinical assessments. Considering the use of mHealth technology, allowing to complete HRQL assessments everywhere, future studies are needed to determine the potential effect of the setting on HRQL scores.

CONCLUSION

Overall, children and adolescents with T1DM reported high scores in all five Kids-CAT domains over the course of 6 months referring to good HRQL. From one assessment to the next, 20% of the young patients reported clinically meaningful changes in their HRQL as measured with the Kids-CAT despite the observational study design. Young patients with high HbA1c concentrations reported significantly lower scores in the HRQL domains physical well-being and parent relations over the course of 6 months. Moreover, psychological well-being of young patients with high HbA1c concentrations deteriorated over time. Finally, only minimal associations between HbA1c concentrations and HRQL domains were found over the course of 6 month.

Finding of this study indicate that regular monitoring is not only needed for HbA1c concentrations, but also for HRQL in clinical practice. Both outcomes have to be measured in order to address and achieve the treatment goals of health care of young T1DM patients that are achieving the glycemic target as well as high HRQL. Hence, the implementation of measures to assess HRQL facilitates patient-centered care by providing important information to health care professionals.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the corresponding author to any qualified researcher on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Chamber of Physicians Kiel, Germany, Chamber of

Physicians Lübeck, Germany, and Chamber of Psychotherapists Hamburg, Germany. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

UR-S, MR, CO, UT, and MK designed the study concept and design. OW, SN, CO, MR, and UR-S developed the Kids- CAT tool. DB, SN, UT, and MK supervised and managed the data collection. OW, CO, and DB were responsible for data surveillance and data quality and managed the data preparation. KF, FF, and SN conceptualized the paper and interpreted the data. FF supervised the statistical analysis performed by KF. KF wrote the first draft of the manuscript. All authors critically revised the manuscript, gave final approval for submitting the manuscript for review, and agreed to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2019.00566/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Curriculum Vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

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Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

List of Peer-Reviewed Publications

Fischer KI, De Faoite D, Rose M (2020). Patient-Reported Outcomes feedback report for knee arthroplasty patients should present selective information in a simple design – findings of a qualitative study. *Journal of Patient-Reported Outcomes*, DOI: 10.1186/s41687-020-0173-7. Impact factor: n.a.

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Fischer KI, Fischer HF, Barthel D, Otto C, Thyen U, Klein M, Walter O, Ravens-Sieberer U, Rose M, Nolte S (2020). Trajectories of Health-related Quality of Life and HbA1c of children and adolescents with Diabetes mellitus type 1 over six months: A longitudinal observational study. *Frontiers in Pediatrics*, DOI: 10.3389/fped.2019.00566. Impact factor: 2.634

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Barthel D, Otto C, Nolte S, Meyrose AK, Fischer F, Devine J, Walter O, Mierke A, **Fischer KI**, Thyen U, Klein M, Ankermann T, Rose M, Ravens-Sieberer U (2017). The validation of a computer-adaptive test (CAT) for assessing health-related quality of life in children and adolescents in a clinical sample: study design, methods and first results of the Kids-CAT study. *Quality of Life Research*, 26(5), 1105-17. Impact factor: 2.496

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Barthel D*, **Fischer KI*,** Nolte S, Otto C, Meyrose AK, Reisinger S, Dabs M, Thyen U, Klein M, Muehlan H, Ankermann T, Walter O, Rose M, Ravens-Sieberer U (2016). Implementation of the Kids-CAT in clinical settings: a newly developed computer-adaptive test to facilitate the assessment of patient-reported outcomes of children and adolescents in clinical practice in Germany. *Quality of Life Research*, 25(3), 585-94. (*shared first authorship) Impact factor: 2.496

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