Quality of Life Research (2019) 28:1725–1750
https://doi.org/10.1007/s11136-019-02189-7

REVIEW

Do 8- to 18-year-old children/adolescents with chronic physical health conditions have worse health-related quality of life than their healthy peers? a meta-analysis of studies using the KIDSCREEN questionnaires

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Accepted: 22 April 2019 / Published online: 4 May 2019
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Abstract

Purpose This meta-analytic review aimed to estimate the magnitude of health-related quality of life (HrQoL) impairments, as assessed by the KIDSCREEN questionnaires, both self- and parent-reported, in 8- to 18-years-old children/adolescents with chronic health conditions.

Methods To identify studies using the KIDSCREEN questionnaires, three electronic databases (PubMed, PsycINFO, EBSCOhost Psychology & Behavioral Sciences) were searched. The final search (February 14–15, 2018) revealed 528 non-duplicated articles, of which 23 papers (21 studies) directly compared the HrQoL of pediatric patients to community/healthy controls and were included in the meta-analysis. Pooled mean differences (*MD*) with 95% CIs were estimated using the inverse-variance random-effects method.

Results Of the 21 studies, 16 used self-reports, one used parent-reports and four adopted a multi-informant approach. Self-reported data were retrieved from 20 studies (4852 cases/28,578 controls), and parent-reported data were retrieved from four studies (511 cases/433 controls). Pediatric patients presented significant HrQoL impairments in the domains of physical well-being (*MD* = − 4.84, 95% CI − 6.44/− 3.24 for self-reports; *MD* = − 6.86, 95% CI − 10.42/− 3.29 for parent-reports) and peers and social support (*MD* = − 1.29, 95% CI − 2.25/− 0.34 for self-reports; *MD* = − 3.90, 95% CI − 5.28/− 2.52 for parent-reports), compared to community/healthy peers. Between-studies heterogeneity was explained by diagnostic categories, instrument version and informants.

Conclusions The identification of significant HrQoL impairments among pediatric patients, specifically in the physical and social domains, highlights the importance of routine psychosocial assessment and intervention in primary pediatric healthcare services. Specific recommendations include the use of profile measures, both self- and parent-reports, and the prioritization of oncology, endocrinology and neurology services.

Keywords Children and adolescents · Chronic health conditions · Health-related quality of life · KIDSCREEN questionnaires · Meta-analytic review · Patient- and parent-reported outcomes

Introduction

Over the last decades, technological advances in medicine have resulted in increased survival rates and a greater prevalence of chronic physical health conditions in childhood [1, 2]. Additionally, environmental (e.g., air pollution) and behavioral changes (e.g., nutrition and physical activity patterns) have contributed to an increased incidence of conditions such as asthma and obesity [3, 4]. The worldwide prevalence of chronic conditions in childhood is approximately 10%, although accurate rates are difficult to estimate because epidemiological studies often focus on specific

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11136-019-02189-7) contains supplementary material, which is available to authorized users.

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diagnoses [5]. Within a non-categorical approach, chronic conditions in children are mainly characterized by (1) limitations in age-appropriate function, activities or social roles; (2) reliance on compensatory mechanisms such as medication, special diet, equipment or personal assistance; and (3) use/need for medical, psychological or educational services beyond routine care [6]. Emphasizing the similarities in functional limitations and their psychosocial consequences (recurrent hospitalizations, limited participation in school/social activities, etc.) across health conditions, rather than the idiosyncratic characteristics of specific diagnoses, enables inter-diagnostic comparisons and has been highly recommended for psychosocial research [7–9].

Studies comparing the health-related quality of life [HrQoL] of pediatric patients and physically healthy peers have yielded inconsistent findings regarding the magnitude of impairments and the most affected domains in pediatric patients. For instance, Varni et al. [2] reported significantly lower HrQoL across children with several disease clusters in comparison to healthy children for all domains of functioning assessed by the Pediatric Quality of Life Inventory (PedsQL). Specifically, medium to large effect sizes for overall HrQoL, physical health, psychosocial health and school functioning were found. In contrast, Grootenhuis et al. [10] reported only a few diagnosis-specific differences between pediatric patients and controls in motor functioning, autonomy and social functioning, but not in physical functioning and emotions, as assessed by the Dutch TNO-AZL Children's Quality of Life questionnaire (TACQoL). These heterogeneous results might be explained by participants' sociodemographic and clinical characteristics but also by the methodological challenges in pediatric HrQoL assessment, namely the selection of developmentally appropriate questionnaires, the HrQoL dimensions being assessed and the use of child- or parent-reports [11, 12].

To assess HrQoL in children/adolescents, the WHO [13] states that instruments should be child-centered, rely on subjective self-report (supplemented by proxy judgments if the child is too young/disabled to provide a self-report), be age-appropriate and cross-culturally comparable, include generic and specific modules, and emphasize the health-enhancing aspects of HrQoL. These requirements were thoroughly met by the KIDSCREEN project [14], which was simultaneously conducted in 13 European countries and followed the complex methodological approach proposed by the WHOQOL Group for international instrument development [15–18]. This project developed reliable, valid, age-appropriate and cross-culturally comparable measures in long (KIDSCREEN-52) and short forms (KIDSCREEN-27; KIDSCREEN-10 Index) to assess subjective health and well-being in healthy and chronically ill children/adolescents aged 8–18 years [19]. The KIDSCREEN measures have been translated and validated for more than 40 European and non-European countries and have been used in numerous clinical studies and large health surveys (e.g., the European SPARCLE project [20, 21]; the Health Behavior in School-aged Children (HBSC) study [22, 23]).

The main objectives of this meta-analytic review were (1) to estimate the mean differences (*MD*) in HrQoL, as assessed by the KIDSCREEN questionnaires, between 8- to 18-years-old children/adolescents with chronic physical health conditions and community/healthy controls; and (2) to identify possible causes of heterogeneity by examining differences between subgroups of studies according to diagnoses, informants (i.e., patient- vs. parent-reports), instrument versions (long vs. short-forms), and methodological quality ratings (i.e., low vs. average vs. high quality). By summarizing the results of case–control studies, this study might contribute to improving the current understanding of the consequences of pediatric chronic conditions for patients' overall adaptation and identifying specific areas of functioning that should be targeted by medical treatments and/or psychosocial interventions.

Methods

Search strategy

To identify published literature that applied the KIDSCREEN questionnaires, a systematic search was conducted in three electronic databases: PubMed (US National Library of Medicine), PsycINFO, and the EBSCOhost Psychology & Behavioral Sciences Collection. The keyword "kidscreen" was searched in all fields because the instruments used to assess HrQoL are frequently not named in the title/abstract. The final search was conducted on February 14–15, 2018. Additionally, the reference lists of all eligible articles were screened to identify other potentially relevant articles.

Eligibility criteria

Eligibility criteria were defined for types of studies, participants, comparisons and outcome measures according to the PICOS approach [24]. Only empirical quantitative studies that were published in peer-reviewed journals and written in English were considered.

For participants, eligibility criteria included samples of 8- to 18-years-old children/adolescents with a chronic physical health condition. Only children/adolescents between 8 and 18 years of age were included because younger children might be unable to provide reliable and valid answers due to insufficient language/reading proficiency [25]. Moreover, both the child- and parent-report versions of the KIDSCREEN questionnaires were developed for 8- to 18-year-olds, and there is no evidence of their psychometric

performance in younger children. Chronic health conditions in childhood were defined according to the four criteria proposed by Mokkink and colleagues: "A disease or condition is considered to be a chronic condition in childhood if: (1) it occurs in children aged 0 up to 18 years; (2) the diagnosis is based on medical scientific knowledge and can be established using reproducible and valid methods or instruments according to professional standards; (3) it is not (yet) curable or, for mental health conditions, if it is highly resistant to treatment and (4) it has been present for longer than 3 months or it will, very probably, last longer than 3 months, or it has occurred three times or more during the past year and will probably reoccur" [26] (p. 1444). The operationalization of these criteria was based on the ICD-10 classification [27]. Mental and behavior disorders (codes F00-F99) were excluded because of their distinctive etiology and diagnostic and therapeutic procedures and because greater HrQoL impairments have been described for mental health disorders compared to physical conditions [28, 29].

Regarding comparisons/controls, studies were required to report direct comparisons between pediatric patients and community/healthy controls. Community controls were defined as age-matched children/adolescents without a specific diagnosis but whose health status with regard to other physical and/or mental health conditions was unknown; conversely, healthy controls were considered when the study had clearly assessed and excluded children with a history of any chronic health conditions, mental or behavior disorders and/or developmental delays. Comparative studies using population norms as the reference group were also excluded because potential confounders could not be adjusted, while control groups could be specifically selected to differ from the targeted group only by the variables of interest and to prevent unforeseen variability (e.g., variability related to the geographic area or socioeconomic conditions) [30]. Moreover, normative samples may include both healthy children and pediatric patients in a proportion that resembles the prevalence of chronic health conditions in the population, and thus, they may partially overlap with the target group.

Regarding outcome measures, we considered the mean difference between cases and controls on the KIDSCREEN domains completed either by self- or parent-report. The KIDSCREEN-52 measures ten domains: Physical well-being (five items), Psychological well-being (six items), Moods and emotions (seven items), Self-perception (five items), Autonomy (five items), Parent relations and home life (six items), Financial resources (three items), Peers and social support (six items), School environment (six items), and Social acceptance (bullying) (three items). The KIDSCREEN-27 is derived from the 52-item version and assesses five domains: Physical well-being (five items), Psychological well-being (seven items retrieved from the Psychological well-being, Moods and emotions, and Self-perception domains), Autonomy and parent relations (seven items representing the Autonomy, Parent relations and home life, and Financial resources domains), Peers and social support (four items) and School environment (four items). The KIDSCREEN-10 Index is derived from the 27-item version and provides an index HrQoL score. All versions are scored on a five-point Likert scale, with higher scores indicating better HrQoL; the provision of T-scores with $M = 50$ and $SD = 10$ for the reference population enables comparability across instrument versions [19].

Study selection

Study selection was conducted in two stages. Initially, the first author screened the titles and abstracts of all retrieved records to identify articles with relevant research objectives and methods and to decide whether to obtain the full-text. This first screening was over-inclusive, and only obviously irrelevant and duplicate records were excluded. Subsequently, the full-texts were independently assessed for eligibility by the first and second authors. Inter-rater agreement on study selection was calculated with Cohen's kappa coefficient, considering $k < 0.00$ as poor, $k \leq 0.20$ as slight, $k \leq 0.40$ as fair, $k \leq 0.60$ as moderate, $k \leq 0.80$ as substantial and $k > 0.81$ as almost perfect agreement [31]. Disagreements were resolved by discussion until consensus was reached.

Data extraction

A data collection form was developed for this review based on the Data Extraction Template for Cochrane Reviews [32]. Data were extracted by the first author and verified for accuracy by the second author. For each study, we extracted information on publication (authors, year); methods (study design, procedures, inclusion/exclusion criteria); participants (number of eligible/included participants, non-response rate, country, age, sex, clinical characteristics); outcomes (informants and instrument version used, reliability/validity of the KIDSCREEN questionnaires); and quantitative results for the pediatric and control groups (sample size [*n*], mean [*M*] and standard deviation [*SD*]). When summary data were not available, other descriptive statistics (e.g., medians and interquartile ranges, standard errors [SE], confidence intervals [CIs]) were converted into the desirable format [33, 34]. For studies reporting data separately for subgroups of participants (e.g., children and adolescents; boys and girls), data were gathered into a single sample size that combined *M* and *SD* values [33]. When *MD* could not be computed from the available data, additional information was requested from the corresponding author by email.

Methodological quality assessment

The methodological quality of the studies included in the systematic review was independently assessed by the first and second authors using an adapted version of the Newcastle–Ottawa Quality (NOQ) assessment scale [35]. The NOQ was developed using a Delphi process and subsequently tested on systematic reviews and further refined. Thus, it can be considered a valid, repeatable and simple tool to assess the quality of non-randomized case–control studies included in systematic reviews. Studies were awarded up to 11 points based on the selection of participants (definition and representativeness of cases, selection and definition of controls; maximum of four points), comparability between cases and controls (maximum of two points) and HrQoL assessment (the measures' reliability/validity, informants, procedures, and response rate; maximum of five points). Studies awarded 0–4 points were classified as low quality, those with 5–6 points were average quality, and those with 7–11 points were high quality. Inter-rater agreement was calculated with intraclass correlation coefficients (ICCs) for quality scores and Cohen's kappa coefficient for quality category; disagreements were resolved by discussion until consensus was reached.

Quantitative synthesis of results

Meta-analyses of continuous data were performed with Review Manager Version 5.3 [36] using the inverse-variance random-effects method to incorporate between-studies heterogeneity (i.e., covariates that have been related to HrQoL scores and that are likely to differ across studies). Because this statistical method assumes that the outcomes have a normal distribution, skewness was inspected in each study by checking whether the mean was smaller than 2*SD* for both cases and controls [37]. When *T*-scores were not directly reported in individual studies, $M \pm SD$ scores were transformed to Rasch person parameters according to the KIDSCREEN syntax for each dimension. Although the computation of a total score was not foreseen for the KIDSCREEN long versions, weighted *M*(*SD*) total scores were computed for subgroup analyses after adjusting for Rasch person parameters to enable comparability across instrument versions.

Once the results of all the individual studies were standardized, the *MD* between cases and controls and its 95% CI were computed for each outcome measure as the summary statistic for the estimate of effects. Separate meta-analyses were performed for each domain and for the HrQoL Index. The ten domains of the KIDSCREEN-52 were clustered to match the five-domain structure of the KIDSCREEN-27, although each domain/questionnaire version was treated as a subgroup. Considering the minimally important difference in HrQoL of a half *SD* [38] and as recommended in the KIDSCREEN Manual [19], an $MD \geq 5$ was considered clinically significant.

Additional analyses

The τ^2 statistic (squared estimated *SD* of underlying effects across studies) was used to describe between-studies variance, and the I^2 index described the percent of variability in effect estimates due to heterogeneity [39, 40]. When considerable heterogeneity was observed ($I^2 > 50\%$) [40], differences between subgroups of studies were examined with χ^2-tests (subgroup analyses by diagnostic category to explore the diversity of participants; subgroup analyses comparing instrument versions, informants and quality ratings to investigate methodological diversity).

Results

Study selection

The literature search identified 528 non-duplicated articles, of which 66 were selected for full-text eligibility assessment (Fig. 1). Forty articles were excluded for the following reasons: (1) the sample included children younger than 8 or older than 18 years and no separate data were reported for the 8–18 years age-group ($n = 8$); (2) absence of a sample of children/adolescents with chronic conditions defined according to the criteria proposed by Mokkink and colleagues [7] and operationalized by the ICD-10 classification [33] or the inclusion of patients with mental/behavior disorders classified under codes F00-F99 ($n = 18$); (3) absence of community/healthy controls or use of normative data as a reference group ($n = 8$); (4) no data on pediatric HrQoL as assessed by the KIDSCREEN questionnaires ($n = 1$); (5) no comparative data on HrQoL between pediatric and control groups ($n = 4$); and (6) insufficient/inconsistent data ($n = 1$).

To avoid multiple-publication bias, two papers reporting data from the same sample were also excluded (priority was given to the article that reported data from the largest sample), and three papers reporting data from subsamples of the same study were extracted together. Additional quantitative data were requested from the authors for four studies, and summary statistics were obtained for three studies; the remaining study was excluded due to insufficient quantitative data. Ultimately, 21 different studies reported in 23 papers were included in the meta-analysis. Inter-rater agreement for the selection of papers was moderate ($k = 0.56$, $p < .001$).

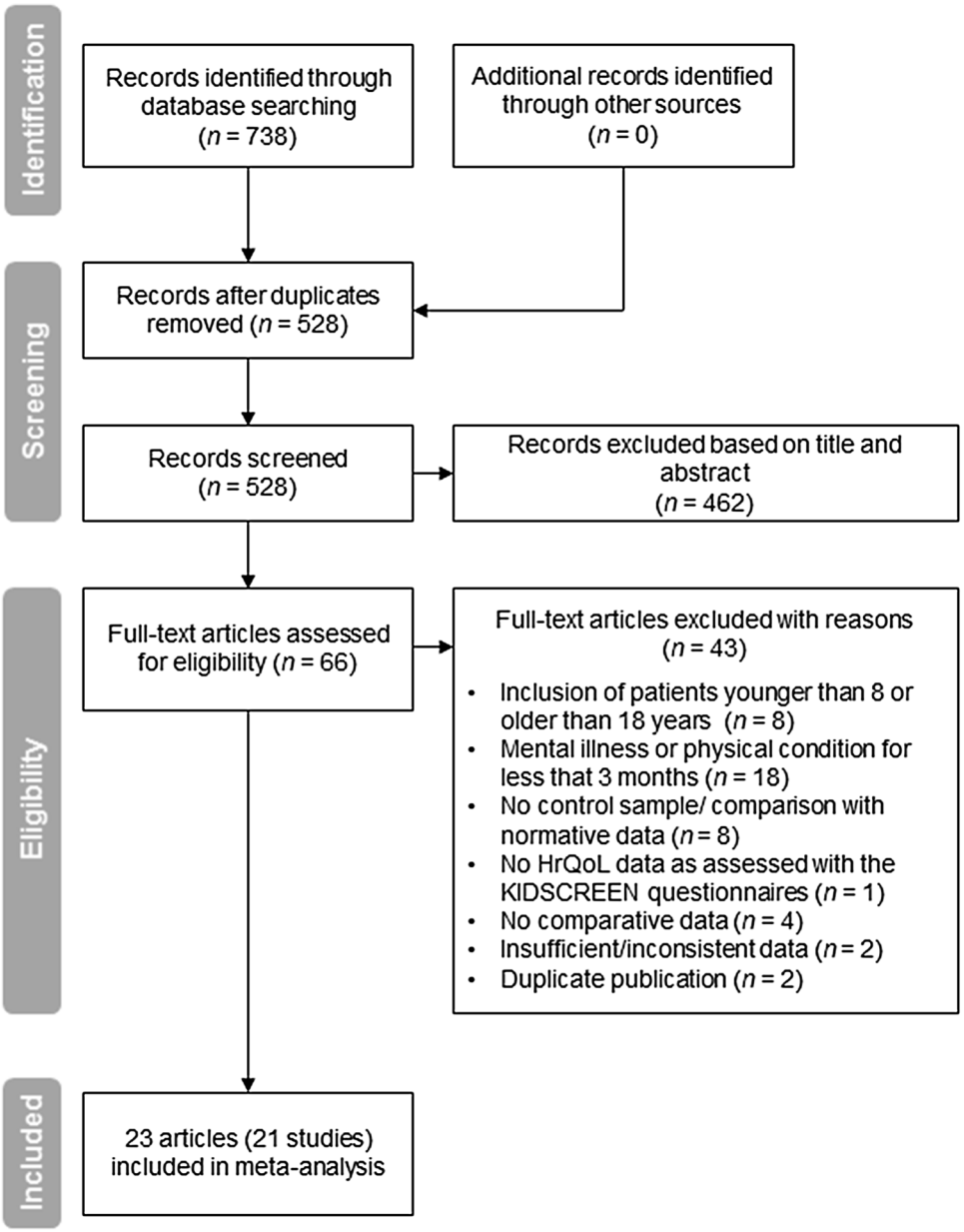

Fig. 1 Flowchart for selection of studies

Study characteristics

The 21 studies examining children/adolescents' HrQoL (Table 1) included a total of 4952 pediatric patients aged 8–18 years ($M = 11.92$, $SD = 2.77$; 52.7% male) and 28,678 controls (mean age = 11.59, $SD = 2.37$; 49.4% male) from 15 European and two non-European countries. According to the ICD-10 [27], chronic conditions were broadly classified into (C00-C97) malignant neoplasms [41]; (D50-D89) diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism [42]; (E00-E90) endocrine, nutritional and metabolic diseases [43–49]; (G00-G99) diseases of the nervous system [44, 50, 51]; (H60-H95) diseases of the ear and mastoid process [52]; (I00-I99) diseases of the circulatory system [53]; (J00-J99) diseases of the respiratory system [44, 54]; (K00-K93) diseases of the digestive system [55–57]; (M00-M99) diseases of the musculoskeletal system and connective tissue [58, 59]; (N00-N99) diseases of the genitourinary system [60]; (Q00-Q99) congenital malformations, deformations and chromosomal abnormalities [61, 62]; and (R00-R99) symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified [63].

Most studies had a cross-sectional design ($n = 18$, 85.7%), and the three studies with longitudinal designs [54, 57, 59] only assessed HrQoL at follow-ups. For HrQoL assessment, 16 studies (76.2%) used patient-reports [41–49, 53–59, 62, 63], one (4.8%) used parent-reports [50], and

Table 1 Study design and sample characteristics reported in the 21 studies included in the systematic review

Study (year); country	Study design; period of data collection	Selection criteria	Sample size	Age in years $M \pm SD$ (range)	Sex (%) male	Measures	Outcomes and results from comparative analyses
(C00-C97) Malignant neoplasms [41]							
van Riel et al. (2014) [41] The Netherlands	Cross-sectional case–control study January 2011–April 2011	Inclusion criteria for cases: adolescents aged 12–18 years with a primary malignant bone tumor, undergoing treatment or up to 3 months after adjuvant treatment Exclusion criteria for cases: presence of metastatic disease Exclusion criteria for controls: presence of a chronic disease	Cases: 10 adolescents with a primary malignant bone tumor Controls: 20 healthy adolescents	Cases: 15 (range: 12–17) Controls: 15 (range: 13–18)	Cases: 20.0% Controls: 20.0%	KIDSCREEN-52 (self-report)	Physical well-being** Psychological well-being Moods and emotions Self-perception Autonomy* Parent relations and home life Financial resources Peers and social support* School environment* Bullying
(D50-D89) Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism [42]							
Hijmans et al. (2010) [42] The Netherlands	Cross-sectional case–control study October 2007–October 2008	Inclusion criteria for cases: children aged 6–18 years receiving treatment for a severe form of sickle cell disease (SCD) (HbSS or HbS-b0-thalassemia) Inclusion criteria for controls: healthy siblings of the group of participants/non-participating children with SCD receiving care at the same hospital	Cases: 40 children/adolescents with sickle cell disease Controls: 36 healthy siblings	Cases: 11.7 ± 3.1 (range: 6–18) Controls: 11.6 ± 3.4 (range: 6–18, but no significant differences in HrQoL between children aged 6–7 [$n = 12$] and 8–18 [$n = 28$])	Cases: 50.0% Controls: 50.0%	KIDSCREEN-52 (self-report)	Physical well-being* Psychological well-being Moods and emotions Self-perception Autonomy* (a) Parent relations and home life Financial resources Peers and social support School environment Bullying

Table 1 (continued)

Study (year); country	Study design; period of data collection	Selection criteria	Sample size	Age in years $M \pm SD$ (range)	Sex (%) male	Measures	Outcomes and results from comparative analyses
(E00-E90) Endocrine, nutritional and metabolic diseases [43–49]							
Morales et al. (2013) [43] Spain	Cross-sectional study 2010–2011	Inclusion criteria: children between 8 and 11 years of age enrolled in the 4th and 5th grades in 20 public primary schools	Cases: 411 children with overweight or obesity Controls: 747 normal weight children	Total sample: 9.5 ± 0.7 (range: 8–11)	Cases: 53.8% Controls: 49.0%	KIDSCREEN-52 (self-report)	Physical well-being** (♂) Psychological well-being Moods and emotions Self-perception** (♀) Autonomy Parent relations and home life Financial resources Peers and social support School environment Bullying
						KIDSCREEN-10 (self-report)	HrQoL Index
Moreira et al. (2013, 2014), Gouveia et al. (2014) [44–46] Portugal	Cross-sectional case–control study 2009–2012	Inclusion criteria for cases: youth aged 8–18 years; clinical diagnosis of asthma, type 1 diabetes, cerebral palsy (IQ ≥ 70), epilepsy or obesity (BMI ≥ 95th percentile); absence of comorbidity with other significant mental or medical condition or developmental delays; ability to understand and answer the questionnaires Inclusion criteria for controls: absence of chronic health conditions, developmental delays, or severe psychiatric disorders and age between 8 and 18 years	Cases: 689 children/adolescents with asthma ($n = 308$), type 1 diabetes ($n = 88$), cerebral palsy ($n = 93$), epilepsy ($n = 68$), and obesity ($n = 132$) Controls: 299 healthy children/adolescents	Cases: 12.4 ± 2.8 (range: 8–18) Controls: 11.8 ± 3.3 (range: 8–18)	Cases: 56.1% Controls: 46.8%	KIDSCREEN-10 (self-report)	HrQoL Index** (significant differences between children with epilepsy, cerebral palsy or obesity and healthy controls, only for the age-group 8–12)

Table 1 (continued)

Study (year); country	Study design; period of data collection	Selection criteria	Sample size	Age in years $M \pm SD$ (range)	Sex (%) male	Measures	Outcomes and results from comparative analyses
Muros et al. (2017) [47] Spain	Cross-sectional study March 2014–May 2014	Inclusion criteria: age between 11 and 14 years; being enrolled in public school from a medium–high socioeconomic area of Granada Exclusion criteria: failing to complete some element of testing, or absence from school on their testing day	Cases: 101 adolescents with overweight or obesity Controls: 345 normal-weight adolescents	Cases: 12.6 ± 1.2 (range: 11–14) Controls: 12.6 ± 1.2 (range: 11–14)	48.5% (total sample)	KIDSCREEN-27 (self-report)	HrQoL total score**
Olaya-Contreras et al. (2015) [48] Colombia	School-based cross-sectional study January 2013–June 2013	Inclusion criteria: children/adolescents from socioeconomically disadvantaged neighborhoods enrolled in the 6th, 7th and 8th grade	Cases: 152 adolescents with overweight (zBMI +1.0 to +2.0; $n = 127$) or obesity (zBMI > +2.0; $n = 25$) Controls: 451 adolescents with normal weight	Cases: 12.8 ± 0.9 (range: 10–14) Controls: 13.1 ± 0.9 (range: 10–14)	Cases: 58.6% Controls: 53.7%	KIDSCREEN-27 (self-report)	Physical well-being** Psychological well-being Autonomy and parents Peers and social support School environment
Ottova et al. (2012) [49] Germany, Spain, Poland, France, Czech Republic, UK, Netherlands, Austria, Switzerland, and Hungary	Multinational health survey April 2003–November 2003	Inclusion criteria: children/adolescents between 8 and 18 years of age Exclusion criteria: NR	Cases: 1849 children/adolescents with overweight or obesity Controls: 11192 children/adolescents with normal weight	Cases: NR (range: 8–18) Controls: NR (range: 8–18)	Cases: 52.5% Controls: 46.5%	KIDSCREEN-52 (self-report)	Physical well-being** Psychological well-being Moods and emotions** Self-perception** Autonomy Parent relations and home life Financial resources Peers and social support** School environment* Bullying**

Table 1 (continued)

Study (year); country	Study design; period of data collection	Selection criteria	Sample size	Age in years $M \pm SD$ (range)	Sex (%) male	Measures	Outcomes and results from comparative analyses
(G00-G99) Diseases of the nervous system [44, 50, 51]							
Bompori et al. (2014) [50] Greece	Observational case–control study January 2012–March 2012	Inclusion criteria: diagnosis of epilepsy made at least 6 months earlier Exclusion criteria: patients who were currently hospitalized for seizure exacerbation, who suffered from progressive neurodegenerative or neurocutaneous disorders	Cases: 100 children/adolescents with epilepsy Controls: 100 healthy children/adolescents	Cases: 11.0 ± 2.6 (range: 8–16) Controls: 11.0 ± 2.5 (range: 8–16)	Cases: 58.0% Controls: 58.0% Parents: Cases: 28.0% Controls: 22.0%	KIDSCREEN-27 (parent-report)	Physical well-being** Psychological well-being Autonomy and parents Peers and social support School environment**
Zamani et al. (2016) [51] Iran	Cross-sectional case–control study	Inclusion criteria: age between 8 and 18 years, clinical picture of disease, high levels of muscle enzymes, and Duchenne muscular dystrophy confirmed via biopsy or genetic testing Exclusion criteria: presence of mental disorders, and a lack of confirmatory biopsy or genetic testing	Cases: 85 male children/adolescents with Duchenne muscular dystrophy Controls: 136 male healthy children/adolescents	Cases:12.6 ± 3.3 (range: 8–18) Controls: 12.1 ± 2.5 (range: 8–18)	Cases: 100% Controls: 100% Parents: NR (preferably mothers)	KIDSCREEN-27 (self-report)	Physical well-being** Psychological well-being Autonomy and parents Peers and social support** School environment
						KIDSCREEN-27 (parent-report)	Physical well-being** Psychological well-being** Autonomy and parents Peers and social support** School environment

Table 1 (continued)

Study (year); country	Study design; period of data collection	Selection criteria	Sample size	Age in years $M \pm SD$ (range)	Sex (%) male	Measures	Outcomes and results from comparative analyses
(H60-H95) Diseases of the ear and mastoid process [52]							
Duarte et al. (2014) [52] Portugal	Cross-sectional case–control study September 2010–June 2011	Inclusion criteria: prelingual deaf children/adolescents with and without cochlear implants, aged between 8 and 18 years Exclusion criteria: children with other disabilities, such as cerebral palsy, auditory neuropathy, syndromes, hypoplasia of the auditory nerve and bilateral implant	Cases: 44 prelingual deaf children/adolescents with and without cochlear implants Controls: 17 normal-hearing children/adolescents	Cases: 12.1 ± 4.2 (range: 8–18) Controls: 10.0 ± 3.0 (range: 8–18)	Cases: 45.5% Controls: 35.3% Parents: 15% (total sample)	KIDSCREEN-52 (self-report)	Physical well-being* Psychological well-being** Moods and emotions Self-perception** Autonomy* Parent relations and home life* Financial resources Peers and social support School environment Bullying*
						KIDSCREEN-52 (parent-report)	Physical well-being Psychological well-being# Moods and emotions Self-perception Autonomy Parent relations and home life Financial resources Peers and social support School environment Bullying
(I00-I99) Diseases of the circulatory system [53]							
Janiec et al. (2011) [53] Poland	Prospective study	Inclusion criteria: patients aged 8–18 years with mitral valve prolapse (MVP) in NYHA class I	Cases: 67 children/adolescents with MVP Controls: 31 healthy volunteers	Cases: 13.9 ± 2.6 (range: 8–18) Controls: NR	Cases: 29.9% Controls: NR	KIDSCREEN-27 (self-report)	Physical well-being** Psychological well-being Autonomy and parents Peers and social support School environment
(J00-J99) Diseases of the respiratory system [44, 54]							
Hedman et al. (2017) [54] Sweden	Population-based cohort (comparative data on HrQoL from the 14–15-year follow-up)	Inclusion criteria: children aged 7–8 years enrolled in the 1st and 2nd grades	Cases: 245 adolescents with current asthma Controls: 1972 adolescents without current asthma	Cases: NR (range: 14–15) Controls: NR (range: 14-15)	Cases: 49.8% Controls: 51.5%	KIDSCREEN-10 (self-report)	HrQoL Index** (♀)

Table 1 (continued)

Study (year); country	Study design; period of data collection	Selection criteria	Sample size	Age in years $M \pm SD$ (range)	Sex (%) male	Measures	Outcomes and results from comparative analyses
(K00-K93) Diseases of the digestive system [55–57]							
Jelenova et al. (2015) [55] Czech Republic	Cross-sectional case–control study 2013–2015	Inclusion criteria: patients between 13 and 16 years of age, diagnosed with inflammatory bowel disease (IBD) (Crohn disease or ulcerative colitis) for at least six months	Cases: 29 adolescents with IBD Controls: 40 healthy controls	Cases: 15.0 ± 1.3 (range: 13–16) Controls: 14.9 ± 0.4 (range: 13–16)	Cases: 51.7% Controls: 75.0%	KIDSCREEN-10 (self-report)	HrQoL Index
Myléus et al. (2014) [56] Sweden	School-based cross-sectional multi-center screening study 2005, 2009	Inclusion criteria: school children in the 6th grade Celiac disease criteria: marked enteropathy (Marsh III), or the combination of milder enteropathy (Marsh I-II), HLADQ2 and/or DQ8 haplotype (genetic predisposition), symptoms/signs compatible with celiac disease, and clinical response to a gluten-free diet	Cases: 328 children with celiac disease (diagnosed, $n = 90$; undetected, $n = 238$) Controls: 12037 children with normal serological markers	Total sample: NR (range: ≈ 12)	Cases: 39.3% Controls: 51.0%	KIDSCREEN-52 (self-report)	Physical well-being Psychological well-being Moods and emotions Self-perception Autonomy Parent relations and home life Financial resources Peers and social support School environment Bullying HrQoL total score
Strinnholm et al. (2017) [57] Sweden	Population-based cohort of school-children (current study based on follow-up) October 2010–November 2010	Inclusion criteria: adolescents between 12 and 13 years of age who reported complete elimination of milk, egg, fish or wheat due to food hyper-sensitivity (FHS) and completed clinical examination at the time of 2010 follow-up Exclusion criteria: NR	Cases: 75 adolescents with FHS (food allergy, $n = 23$; outgrown food allergy, $n = 16$; lactose intolerance, $n = 33$; non-categorized, $n = 3$) Controls: 209 adolescents with unrestricted diets	Total sample: NR (range: 12–13)	Cases: 41.3% Controls: 51.7%	KIDSCREEN-52 (self-report)	Physical well-being Psychological well-being Moods and emotions Self-perception Autonomy Parent relations and home life Financial resources Peers and social support School environment Bullying* (♀)

Table 1 (continued)

Study (year); country	Study design; period of data collection	Selection criteria	Sample size	Age in years $M \pm SD$ (range)	Sex (%) male	Measures	Outcomes and results from comparative analyses
(M00-M99) Diseases of the musculoskeletal system and connective tissue [58, 59]							
Fontecha et al. (2011) [58] Spain and Switzerland	Cross-sectional case–control study January 2006–October 2007	Inclusion criteria: age between 12 and 16 years and self-reported pain below the line of the 12th rib and above the inferior gluteal folds lasting 1 day or longer during the preceding month Exclusion criteria: signs of nerve compression, scoliosis more than 15º, lumbar kyphosis, high-degree spondylolisthesis, recent trauma, tumor, infection, inflammatory disease, and metabolic disease	Cases: 76 adolescents with low back pain (LBP) referred to the hospital Controls: 152 school adolescents without LBP	Cases: 14.5 ± 1.5 (range: 12–16) Controls: 14.5 ± 1.2 (range: 12–16)	Cases: 40.8% Controls: 40.8%	KIDSCREEN-52 (self-report)	Physical well-being Psychological well-being[##] Moods and emotions[##] Self-perception Autonomy Parent relations and home life Financial resources Peers and social support[##] School environment Bullying
Palmen et al. (2014) [59] Germany	Longitudinal study (HrQoL data was collected at the time of the follow-up examination at least 2 years postoperatively) 2002–2008	Inclusion criteria: unilateral hip involvement, a severe course of the disease with Caterall type 3 or 4, Herring B or C and a loss of containment demanding a pelvic/femoral osteotomy; age between 5 and 11 years at the time of surgery; attendance of a physiotherapy program over at least 1 year postoperatively Exclusion criteria: additional disease that might affect HrQoL	Cases: 17 children/adolescent with Legg-Calvé-Perthes disease Controls: 63 healthy children/adolescents	Cases: 12.1 ± 2.1 (range: 8–15) Controls: 12.1 ± 2.0 (range: 8–15)	Cases: 94.1% Controls: 61.9%	KIDSCREEN-10 (self-report)	HrQoL Index[##]

Table 1 (continued)

Study (year); country	Study design; period of data collection	Selection criteria	Sample size	Age in years $M \pm SD$ (range)	Sex (%) male	Measures	Outcomes and results from comparative analyses
(N00-N99) Diseases of the genitourinary system [60]							
Dotis et al. (2016) [60] Greece	Cross-sectional case–control study December 2013–March 2014	Inclusion criteria: children/adolescents between 8 and 18 years with chronic kidney disease who had not sustained a change in their method of treatment over the last 3 months, patients with end-stage renal disease on peritoneal dialysis who had not sustained a change in their method of treatment during the last 2 months, or patients who had undergone renal transplantation and had a functioning graft for at least 1 year	Cases: 55 children/adolescents with chronic kidney disease, renal transplantation or end-stage renal disease Controls: 55 healthy children/adolescents	Cases: 13.1 ± 4.0 (range 8–18) Controls: NR (range 8–18)	Cases: 49.1% Controls: same proportion of males as the patient group Parents: Cases: 16.4% Controls: NR	KIDSCREEN-52 (self-report)	Physical well-being** Psychological well-being Moods and emotions Self-perception Autonomy Parent relations and home life Financial resources Peers and social support School environment Bullying
						KIDSCREEN-52 (parent-report)	No comparative analysis between cases and controls were performed for parent-reported HrQoL
(Q00-Q99) Congenital malformations, deformations and chromosomal abnormalities [61, 62]							
Amedro et al. (2015) [61] France and Belgium	Cross-sectional case–control study April 2009–October 2011	Inclusion criteria: congenital heart diseases (CHD) (cardiac exploration for syncope/faint, thoracic pain, palpitations, dyspnea, etc.) Exclusion criteria: comorbid severe chronic disease, recent surgical or catheter cardiac intervention and hospitalized children	Cases: 282 children/adolescents with CHD Controls: 180 healthy children/adolescents	Cases: 12.3 ± 3.0 (range: 8–18) Controls: 12.4 ± 2.7 (range: 8–18)	Cases: 65.6% Controls: 52.2% Parents: NR	KIDSCREEN-52 (self-report)	Physical well-being** Psychological well-being Moods and emotions Self-perception Autonomy Parent relations and home life Financial resources** Peers and social support** School environment Bullying
						KIDSCREEN-27 (parent-report)	Physical well-being** Psychological well-being* Autonomy and parents Peers and social support** School environment**

Table 1 (continued)

Study (year); country	Study design; period of data collection	Selection criteria	Sample size	Age in years $M \pm SD$ (range)	Sex (%) male	Measures	Outcomes and results from comparative analyses
Sundell et al. (2017) [62] Sweden	Two-center, cross-sectional, case–control study May 2012–January 2014	Inclusion criteria: 5- and 10-year-old children with cleft lip and/or palate (CL/P), with different types of syndromes Exclusion criteria: NR	Cases: 59 children with CL/P Controls: 168 healthy non-cleft children	Cases: 10.3 ± 0.9 (range: 9–10) Controls: 10.0 ± 0.7 (range: 9–11)	Cases: 36.0% Controls: 64.0%	KIDSCREEN-52 (self-report)	Physical well-being Psychological well-being Moods and emotions Self-perception Autonomy Parent relations and home life Financial resources Peers and social support School environment Bullying
(R00-R99) Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified [63]							
Haraldstad et al. (2011) [63] Norway	Cross-sectional study	Inclusion criteria: school children/adolescents enrolled in classes that covered grades 3, 5, 7 and 9 in elementary schools and grades 1 and 3 in secondary schools	Cases: 238 children/adolescents with chronic pain (> 3 months) Controls: 428 children/adolescents without pain in the last 3 months	Cases: NR (range: 8–18) Controls: NR (range: 8–18)	46.0% (total sample)	KIDSCREEN-10 (self-report)	HrQoL Index**

(♀) Significant differences only for the subgroup of girls; (♂) Significant differences only for the subgroup of boys; (a) Significant differences only for the age-group of adolescents aged 12-18 years

BMI body mass index, *CHD* congenital heart disease, *CL/P* cleft lip and/or palate, *FHS* food hypersensitivity, *HrQoL* health-related quality of life, *IBD* inflammatory bowel disease, *IQ* intelligence quotient, *LBP* low back pain, *MVP* mitral valve prolapse, *NR* not reported, *SCD* sickle cell disease

*HrQoL for cases < HrQoL for controls, $p \leq .05$, two tailed

**HrQoL for cases < HrQoL for controls, $p \leq .01$, two tailed

#HrQoL for cases > HrQoL for controls, $p \leq .05$, two tailed;

##HrQoL for cases > HrQoL for controls, $p \leq .01$, two tailed

four (19.0%) adopted a multi-informant approach [51, 52, 60, 61]. Thus, self-reported data were retrieved from 20 studies and included 4852 pediatric patients and 28,578 controls; parent-reported data were retrieved from four studies and included 511 parents of pediatric patients and 433 parents of community/healthy children (parent data from one study [59] was excluded due to missing summary statistics for controls). The proxy-reports were mainly completed by the mothers (78.5%). For the patient-reports, the KIDSCREEN-52 was most commonly used ($n = 11$, 55%) [41–43, 49, 52, 56–58, 60–62], while four studies (19.0%) used the KIDSCREEN-27 [47, 48, 51, 53] and five (23.8%) used the KIDSCREEN-10 Index [44–46, 54, 55, 59, 63]. Regarding parent-reports, two studies (40.0%) used the KIDSCREEN-52 [52, 60], and three studies (60.0%) used the KIDSCREEN-27 [50, 51, 61].

Methodological quality

The percentage of studies awarded 0, 1 or 2 points according to the adapted NOQ assessment scale [35] is summarized in Fig. 2, and a detailed description of quality assessment is provided in Online Resource 1. Most studies ($n = 15$, 71.4%) were assessed as average quality; only two studies were assessed as low quality [53, 55], and four studies were assessed as high quality [50, 56, 57, 61]. The main reasons for lower quality scores were as follows: no description of controls' health state (81.0%); no examination of the reliability/validity of the KIDSCREEN questionnaires in the study sample (81.0%); and response rates that were below 80%, not reported or differed significantly between respondents and non-respondents (76.2%). Inter-rater agreement was excellent for quality scores (ICC = .92, 95% CI .81/.97) and substantial for quality categories ($k = 0.79$, $p < .001$).

Quantitative synthesis of results

Pooled estimates for HrQoL domains confirmed lower HrQoL in pediatric patients compared to healthy/community peers for Physical well-being ($MD = -4.84$, 95% CI −6.44/−3.24 for self-reports, and $MD = -6.86$, 95% CI −10.42/−3.29 for parent-reports; Fig. 3); self-reported Psychological well-being ($MD = -0.61$, 95% CI −1.16/−0.06; Fig. 4); and Peers and social support ($MD = -1.29$, 95% CI −2.25/−0.34 for self-reports, and $MD = -3.90$, 95% CI −5.28/−2.52 for parent-reports; Fig. 5). Considering the threshold of a half *SD* [19, 38], the *MD* for parent-reported Physical well-being can be considered clinically significant, while the *MD* for self-reported Physical well-being, self-reported Psychological well-being and self- and parent-reported Peers and social support were statistically, but not clinically, significant. No significant differences were observed for parent-reported Psychological well-being,

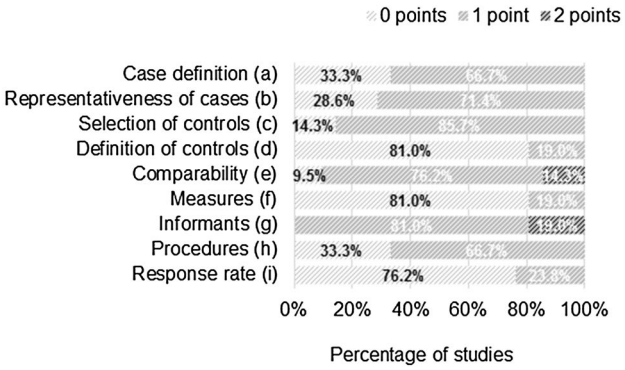

Fig. 2 Quality assessment of the 21 studies included in the systematic review. **a** Case definition: 1 point for diagnosis of a chronic health condition established by a physician, based on medical records or on physiological indicators; **b** representativeness of cases:1 point for selection of a random sample of patients, all eligible patients in a defined healthcare/educational institution or consecutive series of patients over a defined period of time; **c** selection of controls: 1 point for selection of controls within the same community/geographic area as cases; **d** definition of controls: 1 point for selection of healthy controls with no history of chronic conditions; **e** comparability: 1 point if the study controlled for disease severity/clinical characteristics, and 1 additional point if the study controlled for sociodemographic confounders; **f** measures: 1 point for the ascertainment of good reliability/validity of the measures in the study's sample; **g** informants: 1 point for the use of patient- or parent-reported measures or 2 points for inclusion of both informants; **h** procedures: 1 point for the use of the same procedures for assessing cases and controls; **i** Response rate: 1 point for response rate that was similar for cases and controls, higher than 80%, or non-significant differences between respondents and non-respondents

Autonomy and parent relation (Fig. 6), School environment (Fig. 7) and Social acceptance/bullying (Fig. 8), or for the HrQoL Index provided by the KIDSCREEN-10 (Fig. 9). Significant between-studies heterogeneity ($I^2 \geq 50\%$) was found for all HrQoL domains, except self- and parent-reported Autonomy and parent relation.

Additional analyses

The high heterogeneity across studies can be explained by the patients' diagnostic category, the KIDSCREEN version used and the informants (Table 2). Specifically, children/adolescents with malignant neoplasms; endocrine, nutritional or metabolic diseases; diseases of the nervous system; congenital anomalies; or chronic pain had significant HrQoL impairments, while patients with diseases of the respiratory, digestive, genitourinary, musculoskeletal or circulatory systems presented HrQoL similar to that of healthy peers. Further, studies that relied on the long versions of the KIDSCREEN were more likely to detect significant differences between pediatric patients and controls (with larger effect sizes and lower heterogeneity for studies using the KIDSCREEN-27) compared to studies using

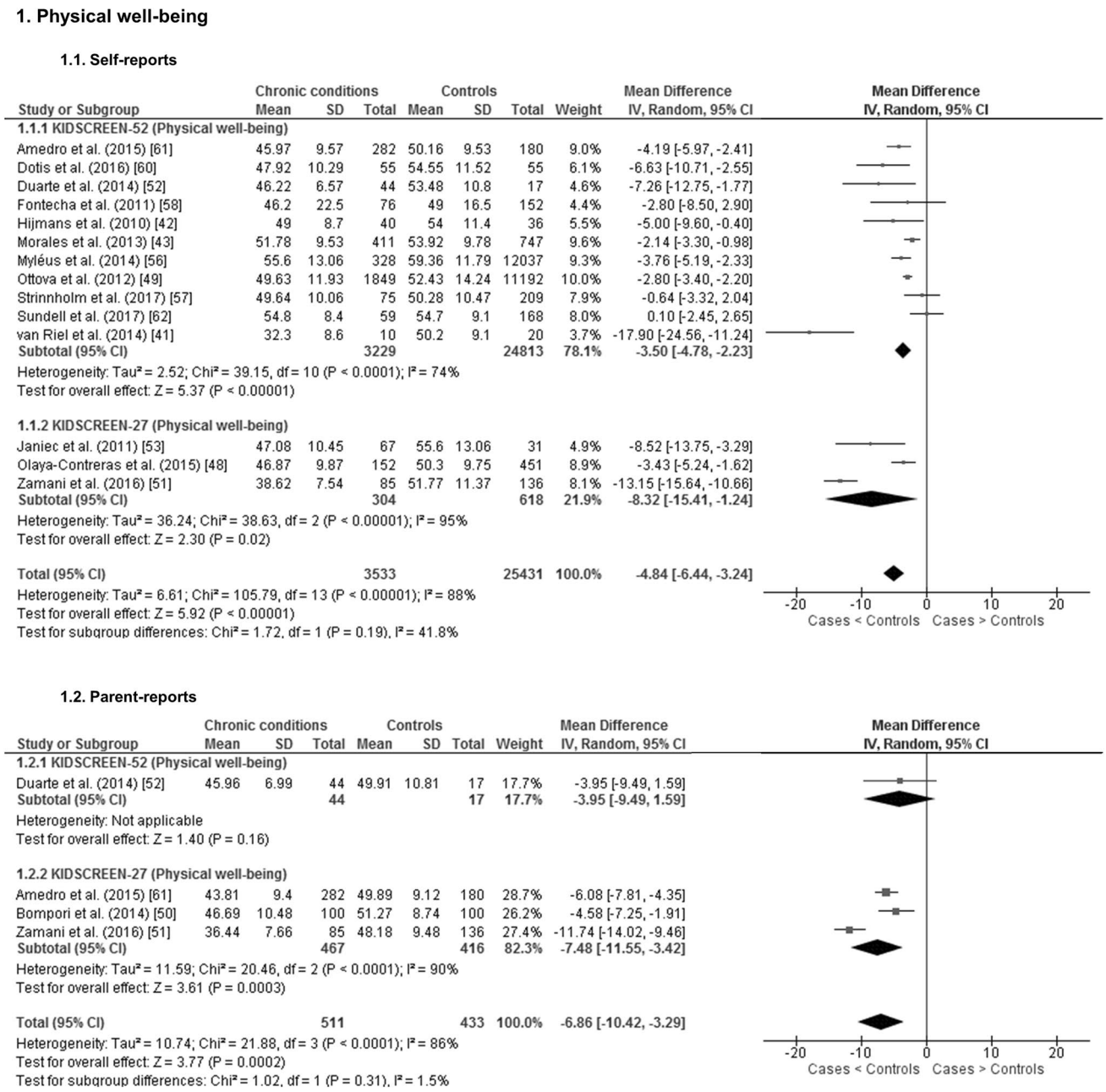

Fig. 3 Forest plots for meta-analysis of differences for (1) Physical well-being, (1.1) self-reported and (1.2) parent-reported, between pediatric patients and community/healthy controls

the KIDSCREEN-10 Index. Moreover, greater differences between cases and controls and lower heterogeneity were found for studies using parent-reports compared to those using patient-reported HrQoL. No significant differences were observed between subgroups of studies according to methodological quality ratings. The forest plots for subgroup analyses of HrQoL total scores by ICD-10 classification, instrument version, informants and methodological quality ratings are presented in Online Resources 2–5.

Discussion

This is the first meta-analytic review to gather comparative studies of HrQoL in children/adolescents with physical chronic conditions and community/healthy controls. Our main contribution was the ascertainment of the magnitude of HrQoL impairments and the identification of physical and social domains as the most affected in pediatric patients.

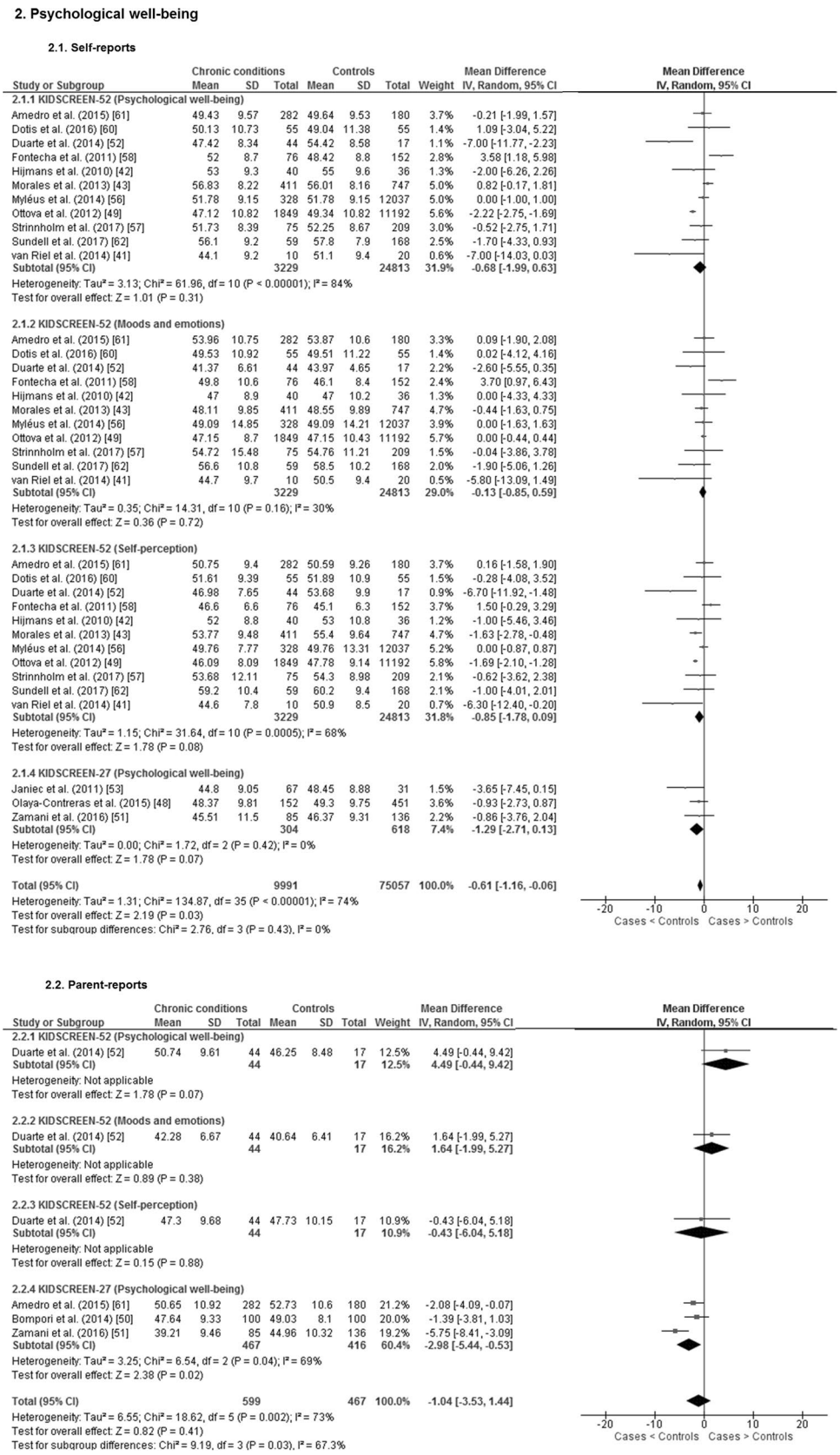

Fig. 4 Forest plots for meta-analysis of differences for (2) Psychological well-being, (2.1) self-reported and (2.2) parent-reported, between pediatric patients and community/healthy controls

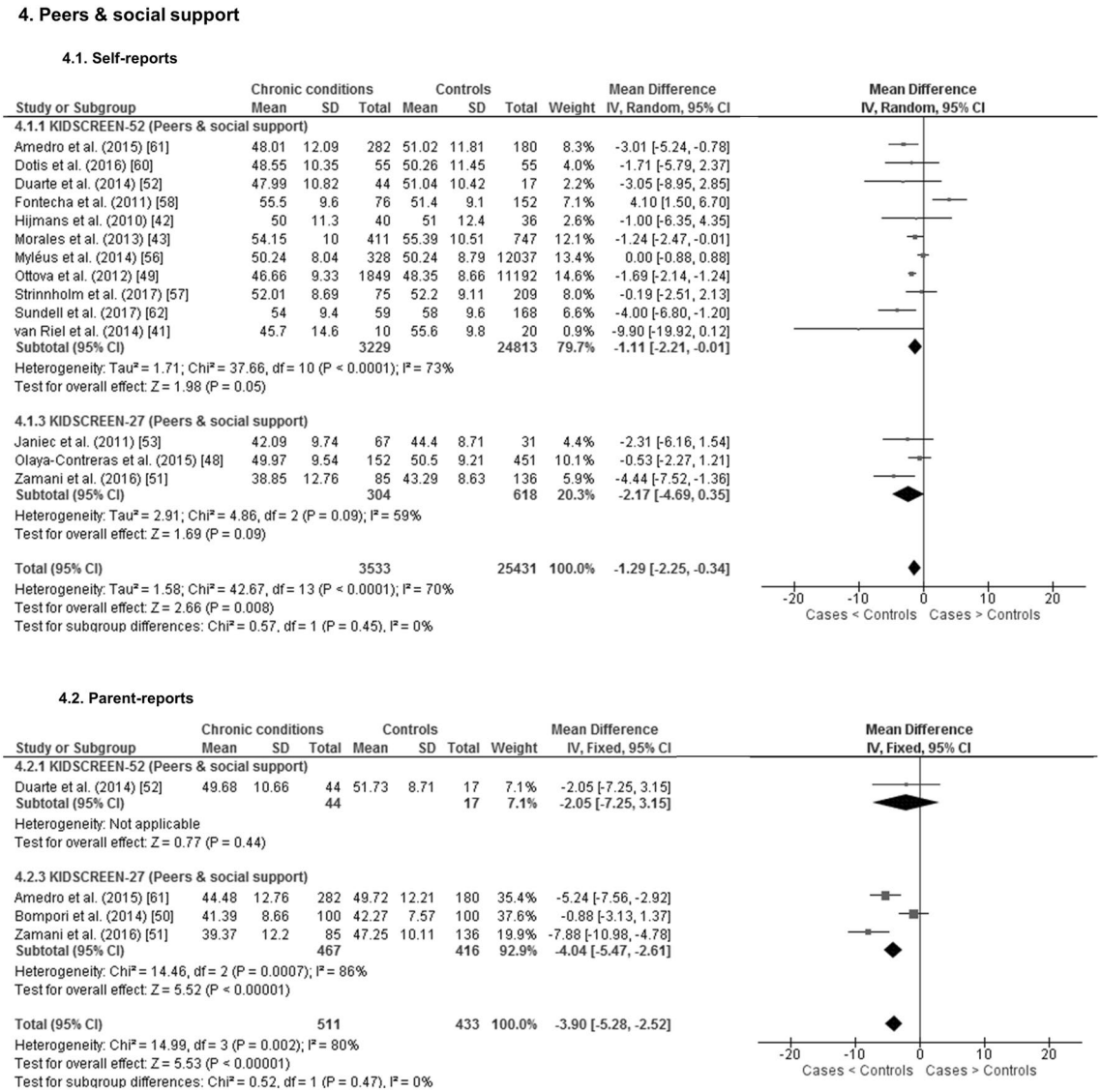

Fig. 5 Forest plots for meta-analysis of differences for (4) Peers & social support, (4.1) self-reported and (4.2) parent-reported, between pediatric patients and community/healthy controls

Regarding Physical well-being, a statistical, but not clinically, significant difference was found for self-reports, while for parent-reports, the *MD* between cases and controls reached clinical significance. A previous meta-analysis of HrQoL differences between healthy controls and children with specific diagnoses, such as central nervous system tumor survivors [64] and those with psoriasis [65], obesity [66], or asthma [67], reported significant HrQoL impairments, but most of these studies only considered global HrQoL or broad dimensions of physical and psychosocial functioning. The mean differences in the Peers and social support domain were also statistically significant for both self- and parent-reports. This result may reflect the inclusion of several studies with children/adolescents with obesity, which has been associated with great HrQoL impairments due to victimization by peers, weight-related teasing and social marginalization [68].

In addition, a statistically (but not clinically) significant difference was found in self-reported Psychological well-being. A previous overview of evidence-based research showed that children/adolescents with chronic conditions have a greater risk of psychosocial impairments, but few present clinically significant psychological symptoms [69]. A statistically significant difference was also found in the meta-analysis of studies using the parent-reported KIDSCREEN-27, which may reflect the inclusion of two of the three studies that included patients diagnosed with diseases of the nervous system [50, 51], which have been

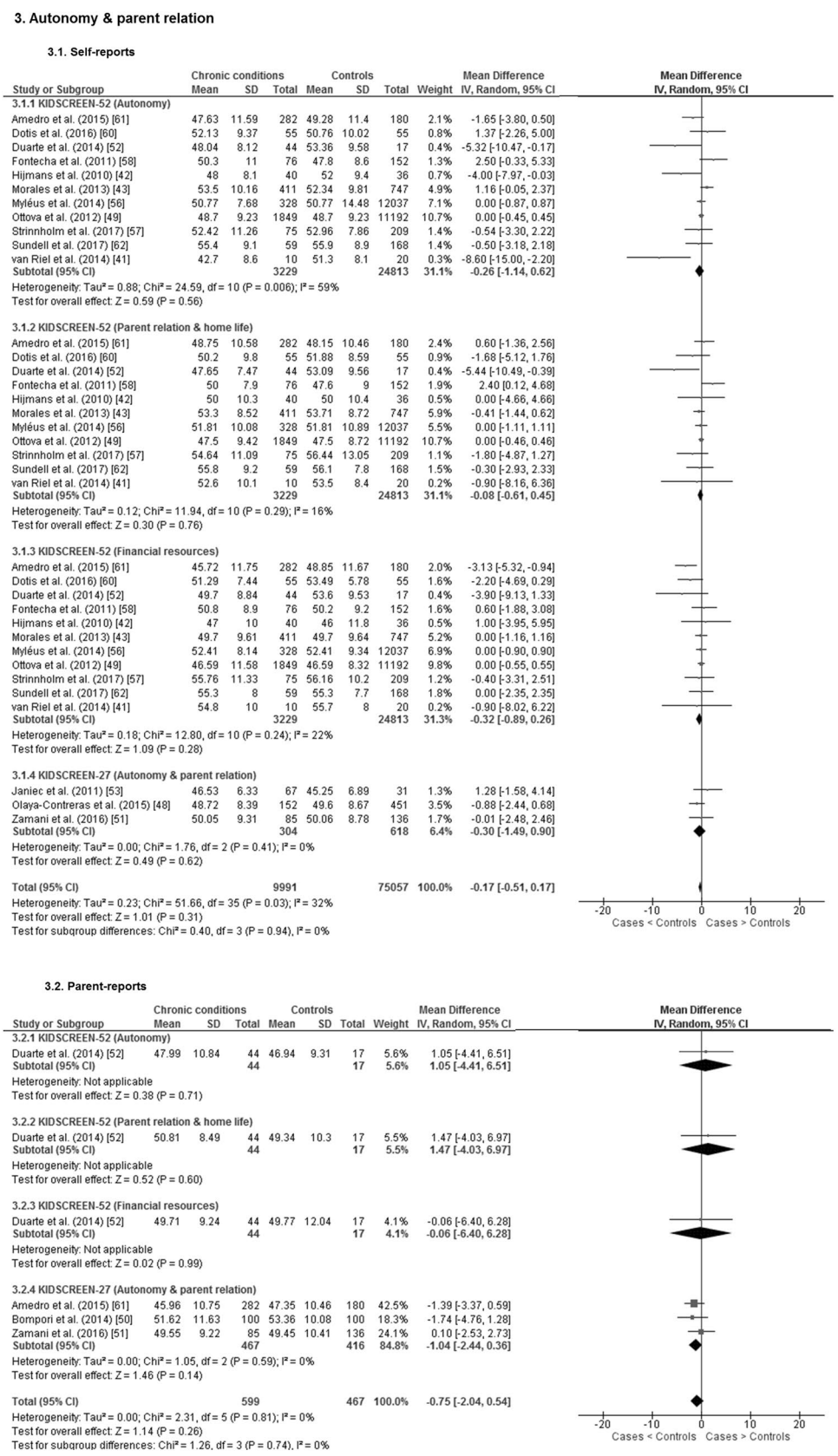

Fig. 6 Forest plots for meta-analysis of differences for (3) Autonomy & parent relation, (3.1) self-reported and (3.2) parent-reported, between pediatric patients and community/healthy controls

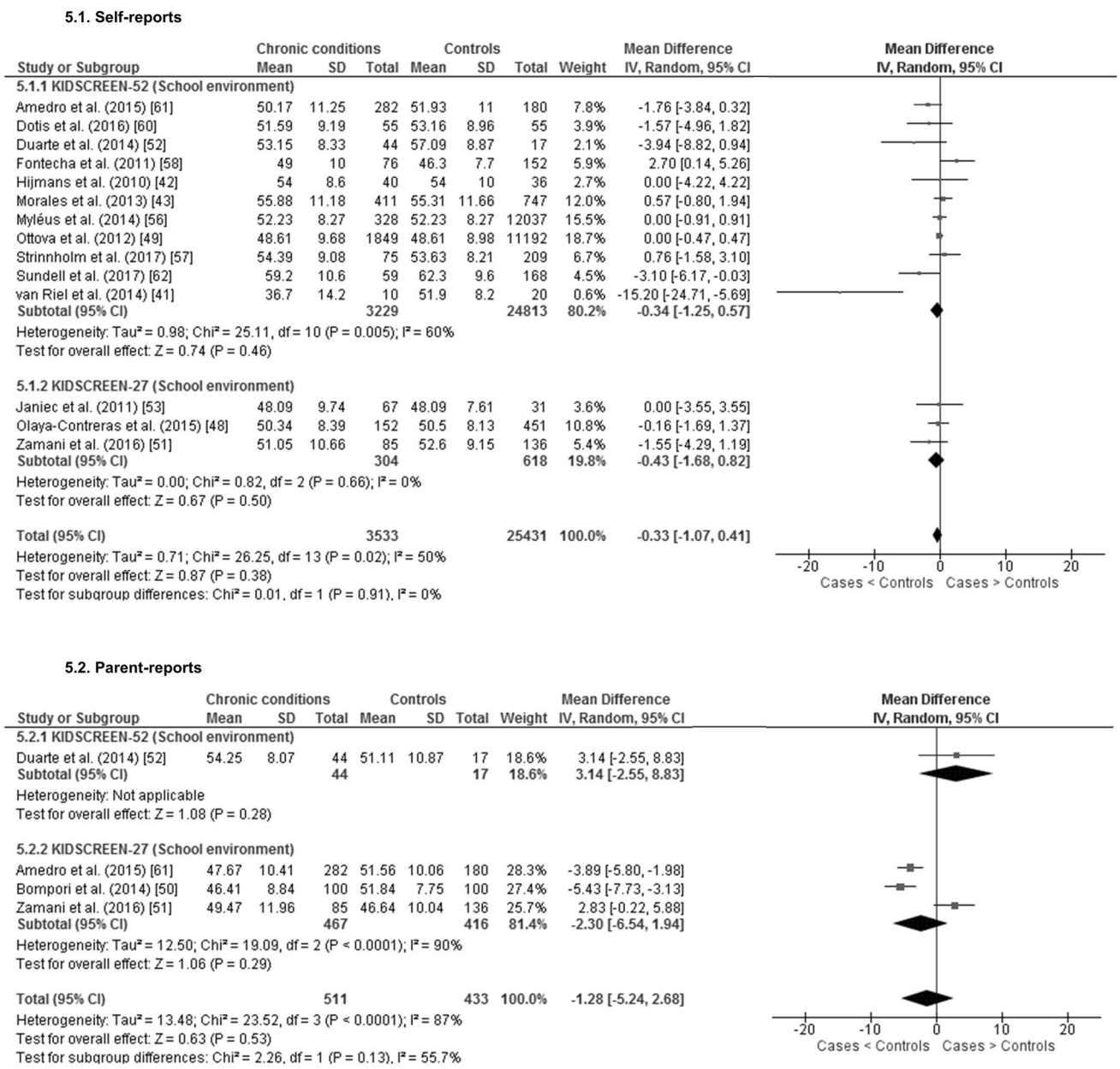

Fig. 7 Forest plots for meta-analysis of differences for (5) School environment, (5.1) self-reported and (5.2) parent-reported, between pediatric patients and community/healthy controls

associated with decreased HrQoL and more psychological problems [70, 71]. The absence of significant differences between cases and controls in the Autonomy and parent relation, School environment and Social acceptance/bullying domains, together with considerable within-studies variability (i.e., a broad CI in most individual studies), suggest that other intrapersonal characteristics (e.g., age, sex, adherence to treatments) among patients may be associated with different levels of HrQoL impairments.

The subgroup analyses showed that diagnostic category, informants and instrument versions are clinical/methodological features that might contribute to explaining heterogeneity across studies. Regarding diagnostic categories, HrQoL impairments were greater for children with malignant neoplasms; endocrine, nutritional and metabolic diseases (e.g., obesity); diseases of the nervous system (epilepsy, cerebral palsy or muscular dystrophy); congenital malformations (congenital heart diseases or cleft lip/palate); and chronic pain. Analogous results have been found in previous studies

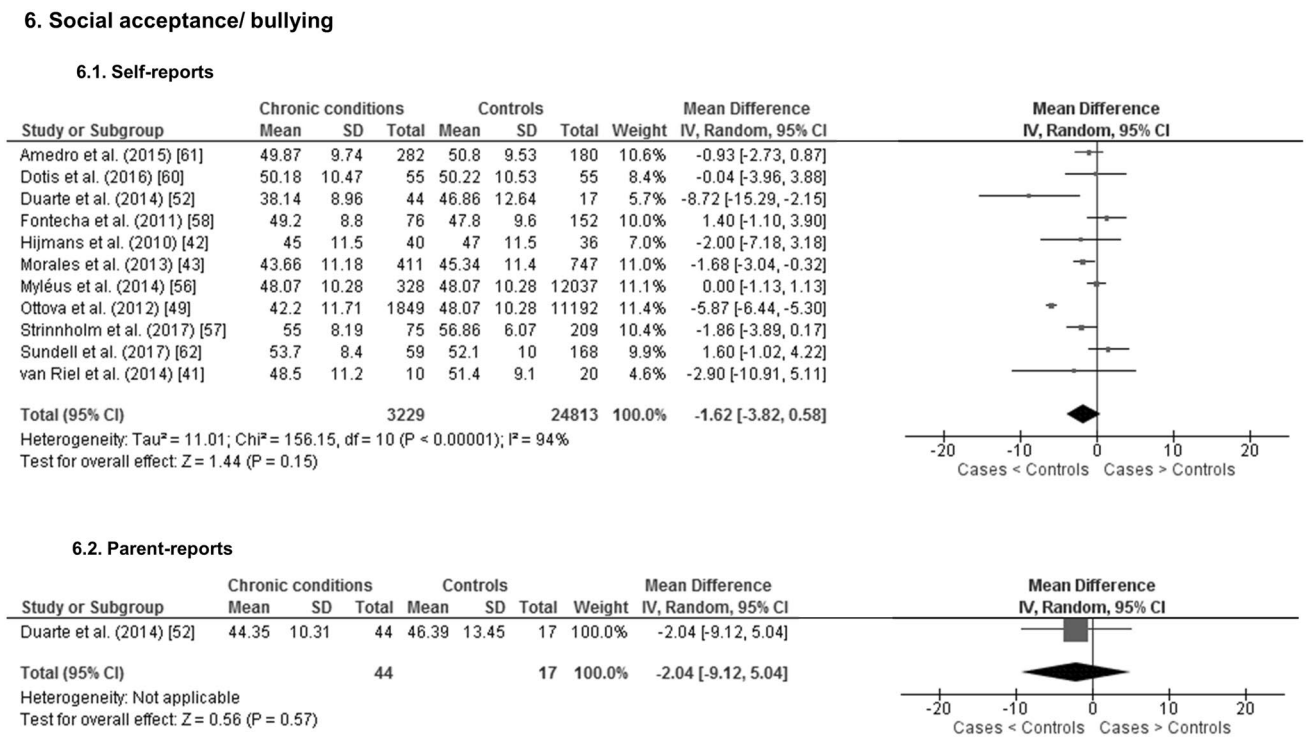

Fig. 8 Forest plots for meta-analysis of differences for (6) Social acceptance/bullying, (6.1) self-reported and (6.2) parent-reported, between pediatric patients and community/healthy controls

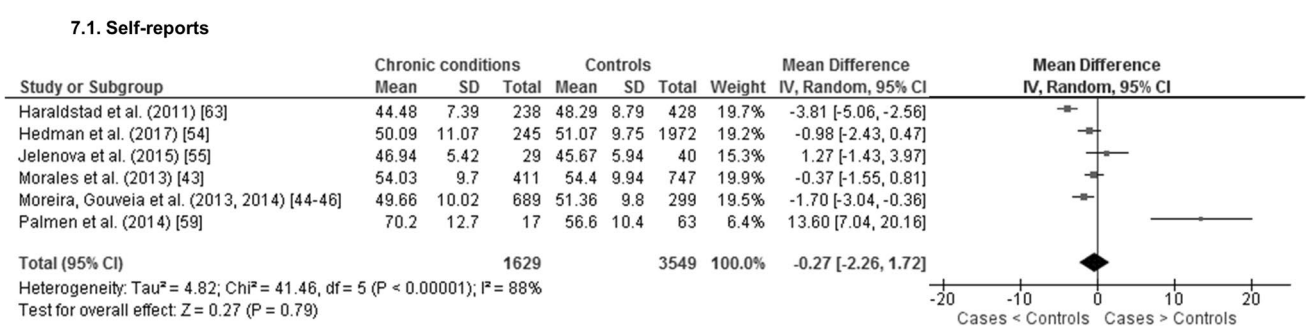

Fig. 9 Forest plots for meta-analysis of differences for (7) HrQoL Index, (7.1) self-reported, between pediatric patients and community/healthy controls

comparing different chronic conditions [2, 44]. From a non-categorical perspective, impairments involving the nervous central system, the external visibility of the condition and the pain/discomfort inherent to the condition and/or treatments can be identified as potential risk factors with a detrimental impact on patients' HrQoL and psychological adaptation. However, disease severity and treatment were not considered in our analyses; for instance, one study [59] only included children who had undergone surgery and attended a physiotherapy program more than 1 year postoperatively, which may explain why they reported enhanced HrQoL, even when their Legg-Calvé-Perthes disease had a severe impact on physical functioning.

Moreover, studies using the longer versions of KIDSCREEN were more likely to detect significant differences between cases and controls (with greater effect sizes for the KIDSCREEN-27), while the meta-analysis of studies using the KIDSCREEN-10 Index showed no significant differences (although the pooled pediatric sample included children/adolescents diagnosed with endocrine, nutritional

Table 2 Subgroup analysis for children/adolescents' HrQoL total scores

	No. of studies	*MD* [95% CI]	χ^2
ICD-10 classification			40.82***
(C00-C97) Malignant neoplasms	1	−7.96 [−15.96/0.04]*	
(D50-D89) Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	1	−1.36 [−5.69/2.97]	
(E00-E90) Endocrine, nutritional and metabolic diseases	6	−1.65 [−2.72/-0.58]**	
(G00-G99) Diseases of the nervous system	5	−3.52 [−4.66/−2.38]***	
(H60-H95) Diseases of the ear and mastoid process	2	−2.36 [−8.00/3.28]	
(I00-I99) Diseases of the circulatory system	1	−2.53 [−6.36/1.30]	
(J00-J99) Diseases of the respiratory system	2	−0.56 [−1.65/0.54]	
(K00-K93) Diseases of the digestive system	3	−0.20 [−1.11/0.71]	
(M00-M99) Diseases of the musculoskeletal system and connective tissue	2	7.51 [−3.60/18.62]	
(N00-N99) Diseases of the genitourinary system	1	−1.10 [−4.60/2.40]	
(Q00-Q99) Congenital malformations, deformations and chromosomal abnormalities	3	−2.09 [−3.52/−0.65]**	
(R00-R99) Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	1	−3.81 [−5.06/−2.56]***	
Instrument version			13.30***
KIDSCREEN-52	12	−0.83 [−1.44/−0.22]**	
KIDSCREEN-27	7	−2.65 [−3.49/−1.82]***	
KIDSCREEN-10 Index	6	−0.27 [−2.26/1.72]	
Informants			6.60**
Self-report	20	−1.21 [−1.96/−0.47]***	
Parent-report	4	−3.17 [−4.46/−1.88]***	
Methodological quality			0.36
Low (scores ≤ 4)	2	−0.38 [−4.07/3.31]	
Average (scores between 5 and 6)	17	−1.54 [−2.44/−0.63]***	
High (scores ≥ 7)	5	−1.51 [−2.77/−0.26]*	

*$p \leq .05$; ** $\leq .01$; *** $p \leq .001$, two-tailed

and metabolic diseases and diseases of the nervous system, which have been consistently associated with significant HrQoL impairments [2, 44, 72]). These results suggest that, independent of diagnosis, profile measures accounting for the multidimensionality of the HrQoL construct might be more sensitive for detecting the most impaired domains of children's HrQoL [25]. Finally, a major trend in the use of self-reports was observed, but studies that relied on parent-reports were more likely to identify significant HrQoL differences between cases and controls. This result is aligned with previous findings on parent–child agreement, which have consistently shown that parents are more prone to underrate the HrQoL of their children with chronic conditions [73–76].

Limitations

Some limitations should be considered at the levels of both the individual studies and the review. First, our literature search was restricted to papers published in peer-reviewed journals and written in English, and the "grey literature" (i.e., literature that has not been formally published in books or journal articles [33]) was not considered, which may have introduced publication bias. Second, the first screening of titles and abstracts was performed by only one author, although it was over-inclusive to decrease the chance of rejecting relevant records. In addition, the moderate inter-rater agreement for the selection of papers in the second screening may reflect the complexity of the eligibility criteria and should be considered a limitation. Third, potential publication bias was not verified in each meta-analysis because tests for detecting funnel plot asymmetry have low power when fewer than 10 studies are included and are prone to lead to false-positive test results in the presence of substantial between-study heterogeneity [33, 77, 78]. Fourth, although participant and methodological diversity were addressed using random-effects models and subgroup analyses, other potential factors explaining between-study heterogeneity (e.g., the health state of the controls, disease severity, treatment status) could not be examined across studies. Finally, the small

number of studies precluded subgroup analyses for each HrQoL dimension and forced the use of total scores, even though the computation of total scores was not foreseen for the long versions of the KIDSCREEN. Although the focus on a single instrument ensured that the operationalization of the HrQoL construct was comparable across studies, the high correlations among instrument versions do not imply a similar ability to detect important changes/differences and might have introduced heterogeneity into the study results [79].

Conclusions and practical implications

This meta-analytic review identified some shortcomings in the existing literature and allowed the establishment of guidelines for future research and clinical practice. First, our review identified few studies meeting the eligibility criteria, although the comparison between healthy and chronically ill populations is one of the major applications of generic HrQoL assessment [25, 80]. Therefore, further comparative studies are still needed in the pediatric context [11], particularly studies investigating different diagnoses (e.g., rare diseases) and examining HrQoL changes in the course of child development. Second, our results contribute to a better understanding of the differential impact of specific clinical features (e.g., neurological compromise, external visibility, pain/discomfort) on physical, psychological, social, family and school functioning, which is essential for identifying and planning comprehensive interventions in pediatric healthcare. HrQoL assessment and psychosocial intervention should be routinely implemented in general pediatric healthcare, prioritizing oncology, endocrinology and neurology services [72]. Third, profile assessments are particularly relevant in guiding targeted interventions for children with chronic conditions. The KIDSCREEN-27 provides a health profile based on 27 items clustered into the most accepted HrQoL dimensions, thus preventing response burden [25]. Finally, a multi-informant approach is highly recommended, particularly in the clinical setting, to better understand patients' and parents' participation in clinical decision-making and disease management.

Acknowledgements We would like to thank the authors of the original articles included in this meta-analysis, specifically to those who kindly supplied additional data upon our request: H. Moreira (Faculty of Psychology and Education Sciences, University of Coimbra, Portugal); L. Hedman (Department of Public Health and Clinical Medicine, Occupational and Environmental Medicine, The OLIN Unit, Umeå University; Department of Health Sciences, Division of Nursing, Luleå University of Technology, Sweden), and I. Duarte (Department of Community Medicine, Information and Health Decision Sciences, Faculty of Medicine, University of Porto, Portugal).

Funding This study was funded by a Post-doctoral Fellowship (Grant No. SFRH/BPD/116841/2016) from the Portuguese Foundation for Science and Technology, and conducted at the Centre for Research in Neuropsychology and Cognitive Behavioral Intervention (CINEICC), Faculty of Psychology and Education Sciences of the University of Coimbra, and at the Department of Medical Psychology, University Medical Center Hamburg-Eppendorf.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

Ethical approval This study was approved by the Scientific Council of the Faculty of Psychology and Education Sciences of the University of Coimbra. All studies included in this meta-analytic review were approved by their institutional and/or national ethical committees and were in accordance with the 1964 Helsinki Declaration and its subsequent amendments and with their national ethical and legal requirements, including parental informed consent and, for some studies, additional assent from the children.

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