Original Article

Health-Related Quality of Life in Children and Adults with Primary Immunodeficiencies: A Systematic Review and Meta-Analysis

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What is already known about this topic? Information on health-related quality of life (HRQOL) in patients with primary immunodeficiency disease (PID) is minimal and no systematic review of existing evidence has been performed to date.

What does this article add to our knowledge? This systematic review confirms that HRQOL in patients with PID is lower than in healthy individuals and in other chronic conditions. Subscales assessing emotional impact were most adversely impacted across all age groups. Parents report child school-related HRQOL as more impaired than do children. There are no disease-specific instruments for HRQOL assessment in children, proxy or self-report, and none evaluating agreement between parent- and child-reported HRQOL.

How does this study impact current management guidelines? Evidence suggests that home-based subcutaneous immunoglobulin is still a preferable method of treatment compared with hospital-based intravenous immunoglobulin, leading to a better HRQOL in patients with PID. Potential discrepancies between child self- and parent-proxy reports of HRQOL measures should be systematically evaluated. Measures of HRQOL should be developed in tandem and include both parent and child self-report versions. A standardized approach to treatment protocols incorporating HRQOL and other relevant patient-reported outcome measures is required to allow for comparison of efficacy of treatments between centers, trials, and countries.

BACKGROUND: Primary immunodeficiency diseases (PIDs) are a group of diseases that have been found to have an adverse impact on quality of life and health-related quality of life (HRQOL).

OBJECTIVE: To systematically assess available evidence on the HRQOL of patients with PID.

METHODS: We performed a literature search of all studies reporting HRQOL assessments in patients with PID published in English from inception to April 11, 2017, using MEDLINE and EMBASE.

RESULTS: Of 1699 articles, 37 met the inclusion criteria. HRQOL was assessed by using various generic instruments. Child Health Questionnaire - Parent Form 50 and short-form 36 were the most frequently used (for children and adults, respectively). No PID-specific HRQOL instruments were used for children. HRQOL is significantly lower in adults with PID

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Abbreviations used
HRQOL- health-related quality of life
MD- *mean score difference*
PedsQL- Pediatric Quality of Life Inventory
PID- primary immunodeficiency disease
PROM- patient-reported outcome measure
SCIG- subcutaneous immunoglobulin

(mean score difference, −24.46; 95% CI, −34.57 to −14.34) and children (−10.06; 95% CI, −12.95 to −7.17) compared with the reference population and lower than in patients with other chronic conditions. There is a general agreement between child- and parent-reported data, although parents report child school-related HRQOL as more impaired than do children (6.19; 95% CI, 0.38 to 11.99). Most studies were of low to moderate quality and had methodological limitations.

CONCLUSIONS: Available evidence suggests that patients with PID have a lower HRQOL than do healthy individuals and patients with other chronic conditions, including diabetes mellitus and juvenile idiopathic arthritis. No disease-specific instruments are available for children, and few options are available for adults. This finding highlights the need for developing PID-specific instruments that would allow for a more sensitive evaluation of PID impact on patient health and psychological well-being, school/work, and social activities. **© 2019 American Academy of Allergy, Asthma & Immunology** **(J Allergy Clin Immunol Pract 2019;7:1929-57)**

Key words: *Primary immunodeficiency diseases; PID; quality of life; Health-related quality of life; Systematic review*

INTRODUCTION

Primary immunodeficiency diseases (PIDs) are a heterogeneous group of inherited disorders with no less than 300 genetically defined single-gene inborn errors of immunity detected to date.[1] Recent data suggest that PID prevalence is much higher than generally thought, with around 6 million people living with a PID worldwide.[2] Patients with PID are generally more prone to develop respiratory and gastrointestinal recurrent infections and/or autoimmune diseases.[3]

PID significantly influences patient life, limiting their working ability and physical and social activities.[4,5] This group of conditions has been linked with a number of negative effects on physical state[6,7] and social activities[8] and is associated with increased anxiety[9] and fatigue.[10] Health-related quality of life (HRQOL) in patients with PID can be also significantly adversely impacted by delays in diagnosis and in treatment for infections.[11]

HRQOL is not assessed as often as it should be, despite the concept being widely used in research articles.[12] Survival rate and number of disease exacerbations are the most frequently used outcome criteria in clinical trials; however, more recently, there has been increasing interest in HRQOL in PID.[13] Within other chronic conditions, HRQOL is widely used as one of the most important outcomes in patient-reported outcome measures (PROMs), and is now an essential part of clinical trials, addressing issues of patient satisfaction, compliance with treatment, and treatment preferences. PROMs are normally designed to measure a specific concept in a standardized way, providing a means of quantifying qualitative information.[12]

HRQOL measures are inherently multidimensional and can be generic or disease specific. A generic measure is a broad outcome indicator including physical, mental, and social health; a specific measure is used to assess the impact of a disease or condition. Generic measures can be used to compare across different types of diseases but often lack the sensitivity or responsiveness needed to pick up small but important changes following an intervention or medical treatment. Evidence shows that HRQOL measures developed specifically for a particular condition are more reliable indicators of the positive and negative impact of that disease and treatment than is clinical opinion or the measurement of objective symptoms.[14]

Despite an increasing number of articles on HRQOL in patients with PID, far too little attention has been paid to the systematic evaluation of available data. The aim of this systematic review was to provide up-to-date evidence on the HRQOL of patients with PID, on qualitative analysis of actual information, and on identification of the strengths and weaknesses in existing approaches to HRQOL assessment. It is hoped that our findings will provide an impetus for further research in the field and improve our understanding of patient needs.

METHODS

Search strategy

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement for Reporting Systematic Reviews and Meta-Analyses (www.prisma-statement.org).[15] The review was registered with the National Institute for Health Research's PROSPERO (CRD42017062380). Studies were identified through comprehensive literature searches of OVID MEDLINE and Embase databases from inception to April 11, 2017, using both free text and medical subject headings (MESH) terms. The search strategies are supplied as Online Repository material (see Figures E1 and E2 in this article's Online Repository at www.jaci-inpractice.org). In addition, the publications cited in the reference lists of the included studies and previously published review articles on the topic were carefully screened to ensure that no original published data had been missed in the initial search. Any prospective, retrospective, and cross-sectional studies assessing HRQOL in patients with PID were considered. There was no limitation on the geographical location, age of participants, publication date, and publication status restrictions, but final data extraction was limited to articles published in English. Primary outcome measures included HRQOL evaluation in patients with PID, measured using validated and/or newly developed instruments.

Eligibility and selection criteria

Original studies were included if they (1) assessed the HRQOL of patients with PID; (2) collected self-reported and/or proxy-reported data; (2) used validated generic or condition-specific HRQOL instruments; and (3) were published in English. The search strategy is provided in Online Repository materials.

All included articles were transferred into EndNote reference manager. To reduce potential selection bias, 2 independent investigators (E.T. and D.P.) independently screened the titles and abstracts of the identified studies and reviewed all the studies for suitability for full-text assessment. Any disagreements were resolved

through discussion involving additional reviewers (I.K. and D.M.) until consensus was reached.

Data extraction

The data from each study were extracted in duplicate, tabulated, and included author and year of publication, descriptive information concerning the study design, country and setting, characteristics of the study population, HRQOL instrument used, outcome measure, and details on statistical analysis. The data on interventional trials also included characteristics of the intervention used, as well as timing of intervention and follow-up.

Quality assessment

Methodological quality of the included studies was independently assessed by E.T. and D.P. on the basis of criteria commonly used in other systematic reviews.[16-18] The final score was obtained by consensus. A checklist with criteria relating to recruitment, study design, outcome, and statistical analyses was used. Each criterion was rated on a 2- or 3-step scale indicating the degree of agreement with the respective criterion. Overall scores ranged from 0 to 11 points, with higher scores indicating a better study quality. In case of disagreement between the 2 reviewers, consensus was achieved. In addition, 3 quality groups were formed: good (score, 9-11), moderate (score, 6-8), and poor (score, 0-5) quality.

Quantitative analysis methodology

Quantitative analysis was performed to obtain the estimate for the mean difference in the HRQOL scores between the following groups: (a) self-reported HRQOL in children with PID versus self-reported HRQOL in healthy controls; (b) self-reported HRQOL in children with PID versus parental proxy-reported children HRQOL; and (c) self-reported HRQOL in adults with PID versus self-reported HRQOL in healthy controls. Subgroup analysis for different HRQOL domains was undertaken when possible.

The decision to undertake a meta-analysis was made after ensuring that there was a sufficient number of studies in each subgroup analysis. All analyses were carried out using the package meta of the R Statistical Software (version 3.5.1).[19] Because of obvious differences between the studies in several parameters, such as year of study and geographical location, the pooled estimates of the mean differences and the 95% CIs were calculated using the random-effects model with Der Simonian-Laird estimate for the between-study variance (τ^2).

To determine the degree of variation between the studies, heterogeneity tests with Higgins' I^2 statistic were used. These measure the proportion of the observed variance due to heterogeneity rather than chance.[20] These were reported together with corresponding P values and between-study variance.

RESULTS

Synthesis

The initial searches found 1699 publications; after removing duplicates (n = 259), 1440 records were identified, and titles and abstracts were screened. Of these, 43 met the inclusion criteria and were eligible for full-text assessment. Six studies were further excluded (Figure 1), with 37 articles included in the qualitative synthesis. Overall, 23 observational[4,6-10,21-37] and 14 interventional[5,38-50] studies were included in the systematic review.

Most studies did not report SD or CI values, thus making data ineligible for meta-analysis. However, some studies used short-form 36 (SF-36) in an adult population[6,23,25] and Pediatric Quality of Life Inventory (PedsQL) in children[5,9,31,34,37] and reported sufficient data so that it could be pooled using a random-effects meta-analysis.

Key characteristics of observational studies

Populations. The studied populations, instruments used for HRQOL assessment, and reported outcomes of the observational studies are summarized in Table I. Twelve of the 23 observational studies assessed HRQOL in adults,[4,6,8,21-29] 6 in children,[7,9,30-32,37] and 5 in both adults and children.[10,33-36] Sample size varied from 16 patients[24] to 309 patients.[6]

PID type. Focus of the PID type in HRQOL assessment studies differed largely, with common variable immunodeficiency being the most popular selection for inclusion[4,6-10,21,22,24,25,28-30,32-36] followed by X-linked agammaglobulinemia,[7,9,10,22,25-28,30-32,34-36] various types of selective immunoglobulin deficiencies,[7,9,22,23,28,33-36] hyper-IgM syndrome,[7,25,28,32-36] agammaglobulinemia,[10,22] and hypogammaglobulinemia.[22,32,33,35]

Other, less commonly selected PIDs included chronic granulomatous disease,[7,9,37] severe combined immunodeficiency,[22,36] humoral immunodeficiencies,[33] combined immunity deficiency,[33] unspecified immunodeficiencies,[33] CD40 ligand deficiency,[10,30] antibody deficiency,[10,36] congenital neutropenia,[7,36] Wiskott-Aldrich syndrome,[36] X-linked lymphoproliferative syndrome,[36] hyper-IgE syndrome,[36] ataxia-telangiectasia,[7,9] Nijmegen syndrome,[7,9] DiGeorge syndrome,[9,32] transient hypogammaglobulinemia of infancy,[30] and chronic inflammatory demyelinating polyneuropathy.[32] Some studies mentioned other PIDs but did not specify the type.[6,22,35,36]

Key characteristics of interventional studies

Populations. Data on interventional studies included in this systematic review are summarized in Table II. Seven[5,38-43] of the 14 interventional studies investigated HRQOL in both children and adults, with 4 studying adults only[44-47] and 3 focusing on children.[48-50]

Most interventional trials examined the effects of transition to subcutaneous immunoglobulin (SCIG) or medication change, 2 assessed intravenous immunoglobulin use,[44,45] 1 IgG treatment,[5] and 1 inspiratory muscle training.[48] Intervention duration varied from 3 months[44] to 18 months.[47] Control groups were reported in only a third of interventional studies.[5,43,46-48]

PID type

In a similar pattern to observational studies, HRQOL was assessed in a large variety of PID types in interventional research. HRQOL was most often assessed in patients with common variable immunodeficiency,[5,38-40,42,43,47,49,50] X-linked agammaglobulinemia,[5,38,39,47,49,50] hypogammaglobulinemia,[40,42,43,49,50] and agammaglobulinemia.[5,39,40,42,43] Selective immunoglobulin deficiencies[39,43,45,49,50] and hyper-IgM syndrome[39,40,49,50] were also among the most frequently studied PIDs.

A few studies investigated patients with antibody deficiency,[5,45] DiGeorge syndrome,[49,50] ataxia-telangiectasia,[48] severe combined immunodeficiency,[39] or other PIDs.[38,40] Three studies did not provide any specific information on PID type at all.[41,44,46]

Quality of included studies

The methodological quality of both interventional and observational studies is presented in Table E1 in this article's

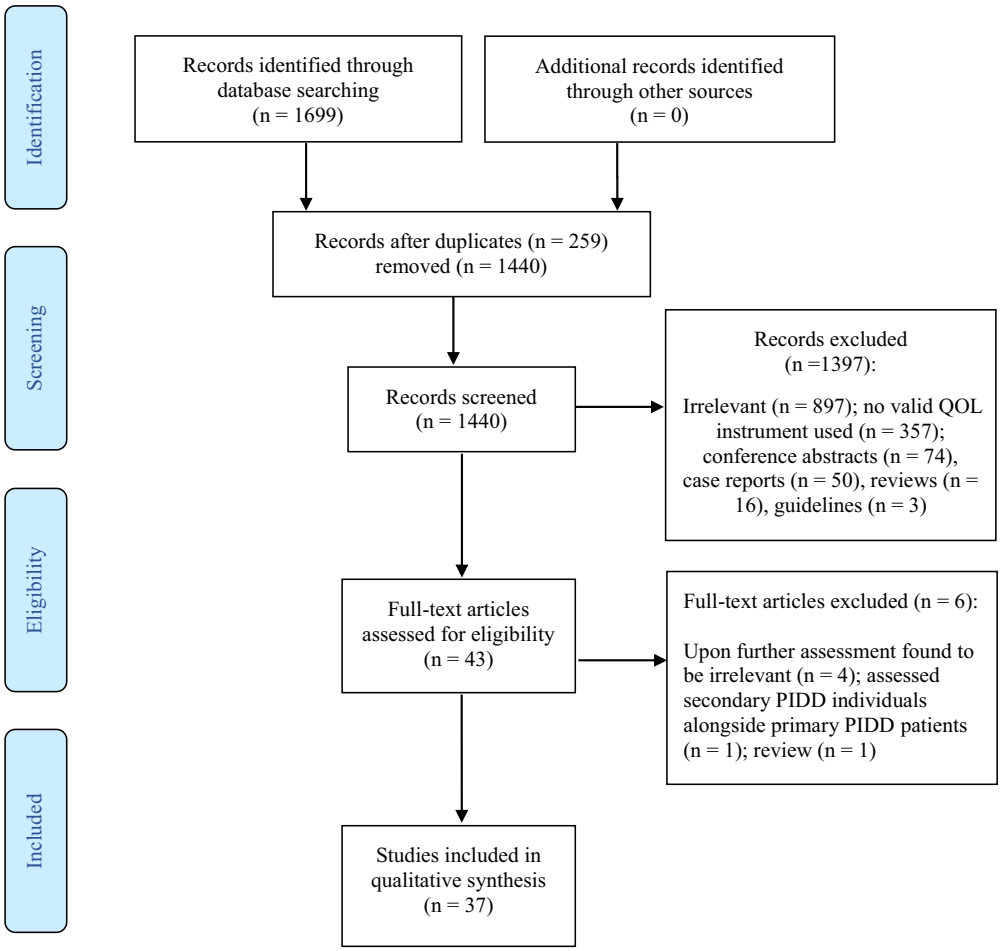


FIGURE 1. PRISMA flowchart of selection of articles for systematic review. *PID*, Primary immunodeficiency diseases; *QOL*, quality of life.

Online Repository at www.jaci-inpractice.org. Many of the included studies had methodologic limitations, which resulted in a low total average score of 5.78 out of 11. Only 2 of the 37 studies were evaluated as "good," 19 were classified as "moderate," and 16 were of "poor" quality. Quality was rated as "poor" more often among interventional studies.

The main limitations were attributed to (a) absence of information about nonresponders in 27 of the 37 studies[4-6,8,9,21,22,24-27,30-32,34,37-43,45,47-50]; (b) lack of description of confounding and effect modifications in 21 studies[5,10,24-26,29,32-34,36-40,43-45,47-50]; (c) use of single-informant only in 28 studies[4,6-8,10,21-29,32,33,36,38-48]; (d) lack of any control group in 14 studies[10,21,22,33,38-42,44-46,49,50]; and (e) prolific use of convenience samples in 21 studies.[4,7-10,21,25,27,29,30,32,34,39-41,43,45,47-50]

Instruments used for quality-of-life measurements

Quality of life was assessed using self- and proxy-reported measurements (Table III). Apart from the disease-specific CVID_QoL questionnaire developed by Quinti et al for adults with common variable immunodeficiency, no other disease-specific instruments were used. The short-form 36 was the most frequently used instrument investigating adult HRQOL and was used in 21 studies.[4-6,8,21-23,25,28,29,33,34,36,38,40-44,46,48] The Child Health Questionnaire - Parent Form 50 was the most frequently used instrument (9 studies) for assessing HRQOL in children.[32,36,38,40-43,49,50] Three studies used HRQOL instruments that were not validated.[10,39,45]

Three child self-report measures,[7,40,48] 2 parent-proxy measures,[41,43] and 10 parent-proxy and child self-report measures[5,9,30-32,34,35,37,49,50] were found. HRQOL in all adult studies was patient-reported with no proxy reports found.

Quality-of-life impairment in patients with PID

Studies included in this systematic review used a diversity of approaches for a reference group selection but could be generally grouped into 2 main categories: (a) comparing HRQOL in patients with PID with that in healthy individuals/national reference data and (b) HRQOL in patients with PID compared with that in individuals with other conditions.

Healthy individuals. Sixteen studies reported more impaired HRQOL[4-9,25,28,30-32,34-37,46] in patients with PID when compared with healthy individuals/national reference data. Only 2 studies[26,27] did not find statistically significant differences in HRQOL between patients with PID and healthy people. Both used national reference data as a comparison source.

Meta-analysis of 3 studies in adults[6,23,25] using the SF-36 showed that adults with PID have significantly more impaired

TABLE I. Data on studied populations, instruments used, and effects on the HRQOL in the observational studies

Author, Year	Country	Sample size*	Age (y)	Response rate	Control group	PID type(s)	Instruments used	Impact on quality of life according to authors	Study quality
Adults									
Barlogis et al,[6] 2016	France	309	Mean ± SD, 27.6 ± 0.49	56.9%	HI	CVID, other PIDs	SF-36	Patients with PID reported lower scores for all HRQOL domains compared with controls. According to the PID diagnosis, no difference was observed in the physical or mental composite scores. Antibody disorders have higher difficulties in mental subscale. HRQOL was strongly associated with the burden of health conditions. Patients who received HSCT had significantly higher HRQOL compared with the non-HSCT group in the physical domain.	Moderate
Bienvenu et al,[22] 2016	France	116	Range, 15-84	NR	NA	Aγ, XLA, Hγ, CVID, SCID, SIgGD with recurrent infections, other PIDs	SF-36, LQI	No difference in HRQOL between hospital-based IVIG, home-based IVIG, or SCIG. HRQOL did not change in patients switching from IVIG to SCIG or treatment modalities. Patients with concomitant disease reported lower HRQOL (physical functioning, role physical, bodily pain, and social functioning domains). No impact on the mental component reported.	Moderate

(continued)

TABLE I. *(Continued)*

Author, Year	Country	Sample size*	Age (y)	Response rate	Control group	PID type(s)	Instruments used	Impact on quality of life according to authors	Study quality
Quinti et al,[21] 2016	Italy	118	NR	92.9%	NA	CVID	SF-36, EQ-5D, SGRQ, GHQ-12, PhGA, CVID_QoL questionnaire	Older patients (>50 y) reported worse CVID_QoL Global and emotional functioning scores. No difference between males and females; patients with higher or lower education level. Lower BMI (18.5) was associated with a higher CVID_QoL Global score and emotional functioning when compared with those having normal and/or high BMI. Infections had a significant impact on CVID_Qol Global score and on Emotional and Relational functioning. No correlation found between the CVID_QoL score and IgG, IgA, and IgM serum levels.	Moderate
Jorgensen et al,[23] 2014	Iceland	32	Mean ± SD, 48 ± 13	100%	HI	SIgAD	SF-36, Gardulfs Infection-related HRQOL questionnaire, Study-specific questionnaire with 122 items	No statistically significant difference in HRQOL between patients and controls at baseline. Compared with baseline, patients with SIgAD reported more bodily pain at 6 mo, poorer general health, and summarized physical HRQOL at 6 and 12 mo and decreased vitality at 12 mo. The summarized mental scale remained stable over time.	Good

Tabolli et al,[8] 2014	Italy	96	Mean ± SD, 48 ± 17	85.70%	DM, HF, C, COPD, MenD	CVID	SF-36, GHQ-12	HRQOL in patients with CVID was low, with mental health scales less affected than physical scales. One-third of the patients were at risk of anxiety/ depression (GHQ positive status). A decline in the HRQOL scores (SF-36) over time was reported (physical functioning, body pain, general health, social functioning, role-emotional). General health scale score was lower in patients with CVID, when compared with that in controls. Low PF and SF subscale scores were predictive of mortality.	Moderate
Jones et al,[24] 2012	USA	16	Mean ± SD, 47.2 ± 14.46	76.1	GP	CVID	SF-36, EQ-5D, LQI	SF-36 domains were close to the US healthy people apart from general health domain scores. The EQ-5D Index Score did not differ from that in US healthy individuals.	Moderate

(continued)

TABLE I. *(Continued)*

Author, Year	Country	Sample size*	Age (y)	Response rate	Control group	PID type(s)	Instruments used	Impact on quality of life according to authors	Study quality
Quinti et al,[4] 2012	Italy	96	Mean ± SD, 48.2 ± 17	85.70%	HI	CVID	SF-36, GHQ-12	The HRQOL of patients with CVID did not differ from that of normal subjects in all age groups in the mental domain (vitality, social functioning, role-emotional, mental health). Physical mean values (physical functioning, role-physical, bodily pain, general health) were lower compared with those in controls. Patients with concomitant disease (chronic lung disease and chronic diarrhea) reported lower HRQOL. No difference in patients on IVIG and patients on SCIG as an in-home therapy HRQOL.	Moderate
Aghamohammadi et al,[25] 2011	Iran	36	Range, 15-45	NR	HI	CVID, HIgM, XLA	SF-36	Patients with PID reported lower scores in physical and mental components. Physical and mental components of HRQOL negatively correlated with the number of infection episodes, hospitalizations, and involved organs. Patients with delay in diagnosis showed lower HRQOL, whereas those diagnosed and managed appropriately reported less complications and better HRQOL.	Poor

Winkelstein et al,[26] 2008	USA	25	NR	30.1%	GP	XLA	SF-12v2	No significant differences were found in the HRQOL of patients with PID compared with US general population.	Poor
Howard et al,[27] 2006	USA	41	Mean (range), 33 (21-63)	79%	GP, DM	XLA	SF-12 (SF-12v2, 4-wk recall)	The HRQOL did not differ from that in the general US male population. Patients with XLA had a better HRQOL than did patients with DM.	Poor
Sigstad et al,[28] 2005	Norway	55	Mean (range), 41.6 (20-76)	60.40%	HI, Ps, C	CVID, XLA, SIgAD, HIgM	SF-36, Ferrans and Powers Quality of Life Index	Lower HRQOL scores were associated with unemployment, infections in more than 4 organs, >2 additional diseases, and >2 specific occurrences of stress in the past 2-3 mo. Men reported higher HRQOL than did women in bodily pain, social functioning, and vitality. Patients with selective IgA deficiency had significantly higher QLI scores than did those with other antibody deficiencies and significantly lower total, Health and Functioning, and Socio-economic QLI scores compared with newly diagnosed cancer patients. Patients with PID reported lower SF-36 HRQOL in general health, role limitations, social functioning, and vitality compared with healthy volunteers and scored higher in bodily pain and lower in general health compared with patients with psoriasis.	Moderate

(continued)

TABLE I. *(Continued)*

Author, Year	Country	Sample size*	Age (y)	Response rate	Control group	PID type(s)	Instruments used	Impact on quality of life according to authors	Study quality
Tcheurekdjian et al,[29] 2004	USA	58	Mean ± SD, 49.9 ± 15.7	100%	DM and HF	CVID	SF-36	Patients with CVID reported lower HRQOL scores in all dimensions compared with DM and in 4 of 8 dimensions (bodily pain, general health, social activity level, and mental health) compared with patients with HF. Older age and female sex were negatively associated with HRQOL (physical functioning, role restrictions due to physical limitations, social activity).	Moderate
Children and adults									
Ataeinia et al,[34] 2017	Iran	69	*Adults:* Range, 18-52 *Children:* Mean (range), 10.81 (3-17)	NR	GP	CVID, XLA, HIgM, SIgAD	*Adults:* SF-36 *Children:* PedsQL 4.0	Patients with PID reported lower HRQOL in mental and physical components. Adults with PID had lower HRQOL particularly in general health. HRQOL in children was lower than in control (particularly in physical, emotional, and school functioning in self-report and in school functioning in proxy-reports). Patients with longer follow-up periods reported higher HRQOL in the mental component but physical component was still low. No significant correlation reported between sex, age, disease types, and HRQOL.	Poor

Kearns et al,[33] 2017	USA	134	NR	95.8%	NA	Humoral ID, Hγ, SIgD, congenital Hγ, HIgM, CVID, other humoral IDs, CID, unspecified ID	SF-36, LQI	*Baseline:* 16% of patients reported good health (GH); 44% reported fair health (FH); and 40% reported poor health (PH) (SF-36). *6-mo follow-up:* 92% of the patients in PH at baseline improved (47%) or did not decline (45%). Of patients in GH at baseline, 52% improved or did not change. Of patients reporting health decline, 75% reported FH. *12-mo follow-up:* Of those reporting GH at baseline: 31% GH; 38% FH; 31% PH. Of this reporting FH at baseline: 28% GH; 53% FH; 19% PH. Of those reporting PH at baseline: 9% GH; 33% FH; 58% PH.	Moderate
Espanol et al,[35] 2014	21 Countries via IPOPI	300	Median, 36	100%	GP	CVID, Hγ, XLA, SIgGD, HIgM, other PIDs	EQ-5D Adults: SF-12v2 Children: SF-10v2 for caregivers of children <19 y old	Average HRQOL scores in patients with PID were lower compared with general population norms in physical and mental components. No difference in HRQOL between those receiving IVIG and SCIG.	Good
Reid and Pires,[10] 2014	Canada	91	Mean ± SD, 23 ± 15	54%	NA	XLA, Aγ, CD40 ligand deficiency, CVID, ABd	None	Patients preferred switching to home IVIG rather than to SCIG. Concerns regarding home health care costs were more prominent with IVIG.	Poor

(continued)

TABLE I. *(Continued)*

Author, Year	Country	Sample size*	Age (y)	Response rate	Control group	PID type(s)	Instruments used	Impact on quality of life according to authors	Study quality
Kirch et al,[36] 2012	Germany	117	*Adults:* Mean ± SD, 10.4 ± 10.5 *Children:* Mean ± SD, 7.9 ± 4.3	100%	GP	CVID, SCID, congenital neutropenia, XLA, WAS, SIgD, ABd, CSR/HIgM, XLP, HIgE, other PIDs	*Adults:* SF-36, LQI, WHO-5 *Children:* EQ-5D-Y, CHQ-PF-50, Kidscreen-27, Disabkids-37	HRQOL in patients with PID was lower than in controls in social functional capability, physical functional capability, and physical role function subscales.	Moderate
Children									
Kuburovic et al,[9] 2014	Serbia	25	Mean ± SD, 11.3 ± 4.2	NR	JIA and HI	XLA, SIgAD, CVID, CGD, AT, SIgGD, Nijmegen, DGS	PedsQL	Patients with PID reported lower PedsQL Inventory total scores compared with patients with JIA and healthy children (child-rated and parent-rated). Lower emotional functioning found in children with PID than in children with JIA, and social functioning compared with both children with JIA and healthy children. Lower school functioning was seen in patients with PID (parent-rated). Lower PedsQL total score in patients with high anxiety rate (child-rated and parent-rated).	Moderate

Titman et al,[30] 2014	UK	43	Range, 5-16	80.0%	DM and HI	CVID, XLA, CD40 ligand deficiency, THI	PedsQL, SDQ	Increased psychological difficulties (particularly emotional and peer relationship) in patients with PID vs healthy children. Lower HRQOL in patients with PID compared with healthy children (all subscales) both child-reported and parent-reported. Lower HRQOL in patients with PID than in patients with DM on all subscales except for emotional (both child-reported and parent-reported). THI reported lowest HRQOL of PID studied.	Moderate
Cole et al,[37] 2013	UK	47	*Non-HSCT:* Median (range), 9 (3-15) *Post-HSCT:* Median (range), 10 (4-14)	67	HI	CGD	PedsQL, SDQ	Those with CGD had lower HRQOL (total score, psychosocial score, and all individual domains except the emotional score) compared with healthy children. Decreased parent and self-reported HRQOL in nontransplanted vs transplanted children. Increased parental-reported emotional difficulties in nontransplanted compared with healthy children. PedsQL and SDQ scores in transplanted children did not differ from those in healthy individuals.	Moderate

(continued)

TABLE I. *(Continued)*

Author, Year	Country	Sample size*	Age (y)	Response rate	Control group	PID type(s)	Instruments used	Impact on quality of life according to authors	Study quality
Soresina et al,[31] 2009	Italy	25	Range, 4.1-17.7	NR	HI, RD	XLA	PedsQL	*Child-reported:* Patients with XLA had lower total HRQOL compared with healthy controls but no significant difference with patients with rheumatic diseases. Patients with XLA had better physical HRQOL than did patients with rheumatic diseases but no difference in mental domain. *Parent-reported:* Patients with XLA had lower total HRQOL compared with healthy controls but higher than compared with patients with rheumatic diseases. No difference in physical domain between patients with XLA and healthy controls but lower HRQOL in psychosocial health domain. Positive correlation between proxy- and child-report total scores.	Moderate
Mozaffari et al,[7] 2006	Iran	50	Mean ± SD, 12.62 ± 3.65	100%	HI	CVID, XLA, CGD, HIgM, AT, Congenital neutropenia, SIgGD, Nijmegen	PedsQL	Patients with PID (all age groups) reported lower total HRQOL score, physical score, and psychosocial score compared with healthy subjects. No correlation reported between patient sex and HRQOL.	Moderate

Zebracki et al,[32] 2004	USA	36	Range, 4-18	83%	JIA and HI	CVID, XLA, Hγ, DGS, HIgM,	CHQ-PF50	Compared with children with JIA, children with PID were similar in many aspects of their HRQOL. *Parent-reported:* Reduced perceptions of child's health, parental time, family activities, but less bodily pain and discomfort than parents of children with JIA. Children with PID scored lower on most QOL domains compared with healthy children. *Parent-reported*: Lower HRQOL in physical functioning, limitations in school-related and social activities, general health, greater limitations in parental time, greater parental emotional distress, and greater limitations in family activities compared with healthy children.	Poor

ABd, Antibody deficiency; *Aγ*, agammaglobulinemia; *AT*, ataxia-telangiectasia; *C*, cancer; *CHQ-PF50*, Child Health Questionnaire - Parent Form 50; *CID*, combined immunity deficiency; *CGD*, chronic granulomatous disease; *COPD*, chronic obstructive pulmonary disease; *CVID*, common variable immunodeficiency; *DGS*, DiGeorge syndrome; *DM*, diabetes mellitus; *GP*, national general population data; *Hγ*, hypogammaglobulinemia; *HI*, healthy individuals; *HF*, heart failure; *HIgE*, hyper-IgE syndrome; *HIgM*, hyper-IgM syndrome; *HSCT*, hematopoietic stem cell transplant; *ID*, immunity deficiency; *IPOPI*, International Patient Organisation for Primary Immunodeficiencies; *IVIG,* intravenous immunoglobulin; *JIA*, juvenile idiopathic arthritis; *MenD*, mental disorders; *NA*, not available; *NR*, not reported; *PF*, physical functioning; *PID*, primary immunodeficiency disease*; Ps*, psoriasis; *QLI*, Quality of Life Index; *RD*, rheumatic diseases; *SCID*, severe combined immunodeficiency; *SDQ*, Strengths and Difficulties Questionnaires; *SIgAD*, selective IgA deficiency; *SIgD*, selective immunoglobulin deficiency; *SIgGD*, selective IgG deficiency; *THI*, transient hypogammaglobulinemia of infancy; *WAS*, Wiskott-Aldrich syndrome; *XLA*, X-linked agammaglobulinemia; *XLP*, X-linked lymphoproliferative syndrome.
*Included in the final analysis.

TABLE II. Data on studied populations, instruments used, and effects on the HRQOL in the interventional studies

Author, Year	Country	Sample size*	Age (y)	Response rate (%)	Control group	PID type(s)	Instruments used	Treatment before enrollment	Intervention	Impact on QOL according to authors	Study quality
Adults											
Spadaro et al,[44] 2017	Italy	30	Mean ± SD, 43.9 ± 14.6	97.7	NA	ABd	SF-36	IVIG (≥6 mo)	IVIG, high infusion rates	No changes in HRQOL.	Moderate
Abdou et al,[45] 2009	USA	10	Mean (range), 49 (19-72)	NR	NA	SIgGD and/or ABd	WHO QOL- based instrument for patients with immune deficiency	UT	IVIG, monthly	Improved HRQOL after 12 mo of treatment.	Poor
Nicolay et al,[46] 2006	Sweden	34	*P.Home:* Mean ± SD, 35.5 ± 13.2 P.Hosp Mean ± SD, 36.1 ± 13.6	73.8	GP	NR	SF-36, LQI	IVIG, home- or hospital-based (≥4 mo)	SCIG, weekly home-based	The mean baseline LQI scores for the adults in P.Hosp. were lower than in adults in P.Home. LQI improved on SCIG in P.Hosp with no changes in P.Home. *P.Home:* General health improved after 12 mo of SCIG. *P.Hosp.:* Improved in 4 SF-36 scales ("role-physical," "general health," "vitality," and "health transition") after 12 mo of SCIG. "Role-physical," "vitality," and "social functioning" were lower than in the general US population at baseline but exceeded reference group after 12 mo. "General health" did not reach the reference group levels.	Moderate

Gardulf et al,[47] 1993	Sweden	25 (15 PT and 10 UT)	*PT:* Mean ± SD, 43 ± 16 *UT:* Mean ± SD, 38 ± 14	89.2	HI, KT, RD, HD, D, BP	CVID, XLA	GHRI	IMT or UT	SCIG, weekly home-based	UT had poorer functional status, compared with a reference group. UT reported increased fear of getting infections. Weekly, self-administered SCIG improved general health in PT and UT.	Moderate
Children											
Felix et al,[48] 2014	Brazil	11	Mean ± SD, 14.64 ± 4.22	NR	HI	AT	SF-36	Standard of care	Inspiratory muscle training	HRQOL improved in the general health and vitality domains.	Poor
Fasth and Nystrom,[49] 2008, and Fasth and Nystrom,[50] 2007	Sweden	12	Median (range), 10.9 (1.7-17.1)	NR	NA	Hγ, SIgGD, SIgAD, CVID, DGS, XLA, HIgM	CHQ	IVIG, hospital-based	SCIG, twice a week-every 2 wk	CHQ improved (child-rated global health and social limitations, child general health and emotional impact, and parent-rated mental health) from baseline. *Proxy-report:* Improvements after 6 mo for mental health, change in health, and family activities. *Child-report:* Significant improvements for role/social limitations-emotional at 3 and 6 mo and global health at 6 mo. No significant improvements in	Poor

(continued)

TABLE II. *(Continued)*

Author, Year	Country	Sample size*	Age (y)	Response rate (%)	Control group	PID type(s)	Instruments used	Treatment before enrollment	Intervention	Impact on QOL according to authors	Study quality
										other concepts. Subcutaneous IgG treatment significantly reduced absence days, days spent on hospital/ physician visits, and health care—related expenses.	
Children and adults											
Routes et al,[5] 2016	USA, Brazil, and UK	25 at baseline 20 at 12 mo	*Adults:* Mean ± SD, 47.7 ± 12.9 *Children:* Mean SD,5.1 ± 4.8	NR	GP, RD, BP, C, HF, COPD	CVID, XLA or Aγ, or ABd	SF-36, PedsQL	UT	IgG	*Adults:* lower baseline physical component scores compared with GP, adults with chronic back pain or cancer; lower mental component summary scores compared with GP. *Children:* lower baseline PedsQL total, physical summary, psychosocial summary scores compared with GP. *Post-IgG treatment adults:* improved role-physical, general health, and social functioning *Post-IgG treatment caregivers:* improved vitality. *Post-IgG treatment children:* no improvement.	Moderate

Niebur et al,[39] 2015	USA	32	Mean (range), 14,5 (2-75)	94.1	NA	XLA, Aγ, X-linked SCID, CVID, SigGD, and HIgM	Likert scale	16% SCIG	16% SCIG or 20% SCIG	20% SCIG was rated more favorably than 16% SCIG in the domain of side effects. No significant difference in satisfaction scores for effectiveness, convenience, or global satisfaction were recorded.	Poor
Vultaggio et al,[38] 2015	Italy	39	Mean ± SD, 31.7 ± 15.7	NR	NA	CVID, XLA, other PID	CHQ-PF50, SF-36, LQI	IVIG	SCIG	A significant decrease in both days of hospitalization and days off school/work was recorded at 24 mo. No HRQOL improvement during the SCIG treatment at 6, 12, and 24 mo in both adults and children. The total mean score of LQI improved at 6 mo.	Poor
Berger et al,[40] 2010	USA	45	Mean ± SD, 37.8 ± 19.40	98	NA	CVID, congenital Aγ or Hγ, HIgM, other PIDs	SF-36, CHQ-PF50	IVIG	SCIG	Switching to SCIG for 12 mo improved perceptions of general health in both adults and children with PID. Adults improved in the mental health and vitality assessments. Parents of children reported improved perceptions of personal and family activities.	Poor

(continued)

TABLE II. *(Continued)*

Author, Year	Country	Sample size*	Age (y)	Response rate (%)	Control group	PID type(s)	Instruments used	Treatment before enrollment	Intervention	Impact on QOL according to authors	Study quality
Gardulf et al,[41] 2008	Sweden	87	*Children:* Mean (range), 8.1 (3-13) *Adults:* Mean (range), 34.7 (13-74)	84.8	NA	NR	SF-36, CHQ-PF50, LQI	IVIG, home- or hospital-based (≥4 mo)	SCIG	*Previous IVIG therapy in the hospital/ doctor's office adults:* improvement in health transition, role-physical, general health, vitality (all SF-36) and LQI scales I, II, and III. *Previous IVIG at home adults:* improvement in general health (SF-36). No changes in the LQI. *Children:* improvements in family activities, global general health, general health perceptions, parental impact-emotional, parental impact-time, role/social-emotional behavioral (all CHQ-PF50) and LQI scales I and III.	Poor
Nicolay et al,[42] 2005	Germany	51	Mean ± SD, 27.4 ± 20.1	NR	NA	CVID, Aγ, or Hγ	CHQ-PF50, SF-36, LQI	IVIG, home- or hospital-based (≥6 mo)	SCIG, weekly	Score values significantly increased for scales I, III, and IV in patients switching from IVIG to SCIG. Positive correlations between CHQ-PF50 and the	Poor

										LQI scales. No significant correlations between SF-36 and the LQI scales, except for bodily pain and scale III.	
Gardulf et al,[43] 2004	Sweden	58	*Children:* Median (range), 7 (3-13) *Adults:* Median (range), 33.5 (14-74)	96.6	Patients already on SCIG therapy	CVID, SIgGD, Aγ, or Hγ	CHQ-PF50, SF-36, LQI	IVIG	SCIG	*Children:* improvements in role/social-emotional, behavioral, general health, parental impact-emotional, parental impact-time, family activities, global health (all CHQ-PF50) *Adults:* improved vitality, mental health, and social functioning. LQI improved for both adults and children.	Poor

ABd, Antibody deficiency; *AT*, ataxia-telangiectasia; *Aγ*, agammaglobulinemia; *BP*, back pain; *C*, cancer; *CHQ-PF50*, Child Health Questionnaire - Parent Form 50; *COPD*, chronic obstructive pulmonary disease; *CVID*, common variable immunodeficiency; *D*, dialysis; *DGS*, DiGeorge syndrome; *GP*, national general population data; *HD*, hemodialysis; *HF*, heart failure; *Hγ*, hypogammaglobulinemia; *HI*, healthy individuals; *HIgM*, hyper-IgM syndrome; *IMT*, inspiratory muscle training; *IVIG,* intravenous immunoglobulin; *KT*, kidney transplant; *NA*, not available; *NR*, not reported; *P.Home*, previously home-based treatment; *P.Hosp*, previously hospital-based treatment; *PID*, primary immunodeficiency diseases; *PT*, previously treated; *RD*, rheumatic diseases; *SCID*, severe combined immunodeficiency; *SIgAD*, selective IgA deficiency; *SIgD*, selective immunoglobulin deficiency; *SIgGD*, selective IgG deficiency; *UT*, untreated; *XLA*, X-linked agammaglobulinemia.
*Included in the final analysis.

HRQOL than do healthy individuals (Figure 2) in general health (mean score difference [MD], −24.46; 95% CI, −34.57 to −14.34; heterogeneity [I^2 = 91%]) and in all domains: physical functioning (MD, −9.26; 95% CI, −13.96 to −4.56; I^2 = 52%), role-physical limitations (MD, −19.71; 95% CI, −23.18 to −16.25; I^2 = 94%), bodily pain (MD, −10.20; 95% CI, −16.14 to −4.26; I^2 = 58%), vitality (MD, −9.53; 95% CI, −13.98 to −5.09; I^2 = 49%), and social functioning (MD, −11.98; 95% CI, −15.26 to −8.70; I^2 = 24%).

Meta-analysis of 5 studies in children[5,9,31,34,37] using PedsQL showed that children with PID reported significantly lower HRQOL when compared with healthy individuals (Figure 3) in total score (MD, −10.06; 95% CI, −12.95 to −7.17; I^2 = 0%) and in every domain: psychosocial score (MD, −11.15; 95% CI, −16.54 to −5.77; I^2 = 31%), physical functioning (MD, −10.73; 95% CI, −16.06 to −5.41; I^2 = 49%), emotional functioning (MD, −9.32; 95% CI, −13.05 to −5.58; I^2 = 0%), social functioning (MD, −8.96; 95% CI, −14.43 to −3.49; I^2 = 50%), and school functioning (MD, −14.23; 95% CI, −18.39 to −10.06; I^2 = 0%).

Child self-report versus parent (proxy-) report

Overall, 11 observational and 9 interventional studies collected information on HRQOL in children. Approaches to HRQOL assessment in children varied between studies and included child self-report, proxy-report, and both self- and proxy-report. Two main approaches for data analysis were used: (a) assessment of correlation between proxy- and child-report; and (b) description of differences between patients with PID and reference group according to self- and/or proxy-report. Some studies did not provide information on HRQOL assessment.

Observational studies. Five[9,30,31,34,37] of 11 observational studies provided some comparison between proxy- and child-reported data. Of these, 2 assessed relationships between child- and proxy-reported HRQOL, finding moderate[31] to strong[30] correlations. Three studies highlighted some discrepancies in HRQOL perception between the children and their parents. Patients with PID reported more impaired HRQOL in physical and emotional functioning compared with healthy individuals, which had not been reported by their parents[34]; children with X-linked agammaglobulinemia reported better emotional functioning compared with patients with rheumatic diseases, whereas no difference was found when proxy-reported data were analyzed.[31] Patients with chronic granulomatous disease did not report a more impaired HRQOL on the emotional subscale, compared with healthy children, whereas proxy reports suggested significant and negative differences.[37]

The remaining studies either did not report simultaneous data collection by child and proxy[7,10,32,33,36] or did not provide specific analysis of the data.[35]

Meta-analysis of 4 studies[9,31,34,37] using PedsQL showed that self-reported HRQOL in children with PID did not significantly differ from proxy-reported HRQOL (Figure 4) in total score (MD, 4.87; 95% CI, −0.17 to 9.92; I^2 = 26%) and in the following domains: psychosocial score (MD, 2.75; 95% CI, −6.29 to 11.78; I^2 = 53%), physical functioning (MD, 5.45; 95% CI, −0.67 to 11.57; I^2 = 12%), emotional functioning (MD, 2.15; 95% CI, −4.48 to 8.78; I^2 = 39%), and social functioning (MD, 3.59; 95% CI, −1.67 to 8.86; I^2 = 0%). The only significant difference was found in school functioning (MD, 6.19; 95% CI, 0.38 to 11.99; I^2 = 0%), with parents reporting more impaired HRQOL compared with their children.

Interventional studies. There was substantial variation between intervention studies in sample size and in approaches to data analysis and presentation. Only 1 of 13 studies reported no changes in HRQOL upon intervention,[44] with others highlighting HRQOL improvement, particularly with the use of SCIG. We failed to find comparison of child- and proxy-reports in all interventional studies assessing HRQOL in children included in our systematic review.[5,38-43,48] The only exception was a study by Fasth and Nystrom; however, any meaningful conclusions cannot be drawn due to a very small sample size.[49,50]

Other conditions

Studies used a wide range of conditions as a reference group, including diabetes mellitus,[8,27,29,30] heart failure,[5,8,29] cancer,[5,8] chronic obstructive pulmonary disease,[5,8] mental disorders,[8] kidney transplant/dialysis,[47] back pain,[5,47] psoriasis,[28] juvenile idiopathic arthritis,[9,32] and other rheumatic diseases.[5,31,47] Overall, patients with PID tend to report lower general HRQOL compared with patients with other chronic conditions including diabetes mellitus and juvenile idiopathic arthritis, with emotional subscales on multidimensional questionnaires particularly affected, in both children and adults.

Moderators of HRQOL score include recurrent infections, presence of concomitant disease (chronic lung disease and chronic diarrhea), and high anxiety rate.[4,6,9,22,25,28]

DISCUSSION

HRQOL has been found to predict and influence processes and health outcomes and has therefore become an important outcome in medical care and in clinical trials. This systematic review found evidence that HRQOL in children and adults with PID is more adversely impacted than in healthy individuals and people with other chronic conditions, including diabetes mellitus and juvenile idiopathic arthritis. There was general agreement between child- and proxy-reports of HRQOL in PID, except in a school-related domain, where parents reported HRQOL as more impaired. With reference to clinical interventions, home SCIG use is associated with a better HRQOL score. We found a lack of disease-specific instruments, with a single questionnaire available for adults with common variable immunodeficiency and no instruments available for children. The availability of only a small number of high-quality studies and data reporting issues prevented a proper data collation.

Unlike many rare diseases, patients with PID benefit from available treatment options, with replacement immunoglobulin given at frequent intervals for life being a standard approach.[51] Immunoglobulin treatment may lead to reduced incidence of bacterial infections and possible improved long-term survival rates.[52] However, despite treatment, patients with PID, particularly those with a late diagnosis, experience recurrent infections.[25,28] Cumulative evidence presented in this systematic review confirms that HRQOL in children and adults with PID is significantly lower than in a healthy population. High heterogeneity between the studies (including different population samples, PID types assessed, instruments used, statistical approaches, lack of information) did not allow us to perform quantitative analysis of all included studies. However, a limited number of studies in adults[6,23,25] and children[5,9,31,34,37]

TABLE III. Instruments for HRQOL assessment used in the included studies

QOL assessment instrument	Items/domains	No. of studies using the instrument	Reference
SF-36	36/8	21	4-6,8,21-23,25,28,29,33,34,36,38,40-44,46,48
Child Health Questionnaire - Parent Form 50	50/14	9	32,36,38,40-43,49,50
Life Quality Index	15/3	8	22,24,33,38,41-43,46
PedsQL version 4.0	23/4	7	5,9,30,31,34,37
EuroQol (EQ-5D)	5/5	3	21,24,36
Short Form-12 (SF-12)	12/8	3	26,27,35
General Health Questionnaire (GHQ-12)	12 items	3	4,8,21
Strengths and Difficulties Questionnaires (SDQ)	25/5	2	30,37
WHO QoL instrument-based questionnaire for patients with immune deficiency	NR	1	45
PEDQOL	50/2	1	7
The General Health Rating Index (GHRI)	23/4	1	47
Study-specific questionnaire	122 items	1	23
Infection-related HRQOL developed by Gardulf	9 items	1	23
CVID_QoL questionnaire	32/3	1	21
St. George's Respiratory Questionnaire (SGRQ)	50/3	1	21
Ferrans and Powers Quality of Life Index (QLI)	66/5	1	28
Nonspecified questionnaire or not clearly reported	NR	1	10,39

EQ-5D, EuroQol five-dimensional questionnaire; *NR*, Not reported.

produced comparable data, which did permit meta-analyses. In support of the findings from our qualitative analysis, the meta-analysis demonstrated impairment of general health HRQOL as well as in all tested subscales across all age groups. School functioning is the most impaired domain in children and may be explained by the high number of days away from school due to recurrent infections and/or more frequent hospitalizations.

The use of HRQOL promotes understanding of disease processes and health outcomes, as well as predicting health service use,[53] and thus it is important that HRQOL measures be developmentally appropriate and validated for the age and population in which they are used. Although researchers have suggested that both parents and children can provide valuable information on a child's condition, proxy reporting of HRQOL is widespread, particularly in pediatric studies where children have been considered unreliable respondents. Although there is evidence suggesting that child-parent agreement on generic measures developed together (such as KIDSCREEN for children with chronic health conditions) is typically good[54] and increases over time, discrepancies have been found. Discrepancies may be attributed to cognitive and reflective abilities in individual children and to findings in studies that use child and parent proxy measures that were developed by different researchers often in different populations.

This review showed that agreement between proxy- and child-report (where these were used) was generally good, with only significant differences found on school-related HRQOL. However, we note that the research reviewed here is cross-sectional and has not assessed changes in child-parent agreement over time. The magnitude of agreement between proxy- and self-report has been shown to increase over time, particularly when time since diagnosis and age are taken into account.[55] Furthermore, most of the studies included did not collect data from children and their parents in parallel, which did not allow us to make definitive conclusions on the level of agreement. Ideally, parent and child reports should be developed in tandem, and considered separate but important information, particularly in the early stages following diagnosis.

HRQOL in PID is more impaired when compared with that in healthy individuals and also when compared with that in patients with other chronic conditions, namely, diabetes mellitus and juvenile idiopathic arthritis, the conditions most commonly used in PID research as a reference group. Subscales assessing emotional impact were most adversely impacted across all age groups.

Although SF-36 is one of the most widely used instruments in adults, with Child Health Questionnaire - Parent Form 50 and PedsQL being widely used in pediatric practice, their psychometric properties have not been rigorously tested in patients with PID. It has been recommended that HRQOL measures developed specifically for a particular condition be used, when available. Both the European Medicines Agency and the US Food and Drug Administration emphasize that outcome measures selected for a study should be well targeted to the specific patient population, which fundamentally rules out the use of generic PROMs.[56,57] Both bodies now consider the most widely used generic PROM, the SF-36, to be unsuitable for making claims about the value of treatments. If comparison across diseases is needed for a particular study design, then both generic and disease-specific measures should be used. Most of the studies in all age groups use generic instruments for HRQOL assessment in

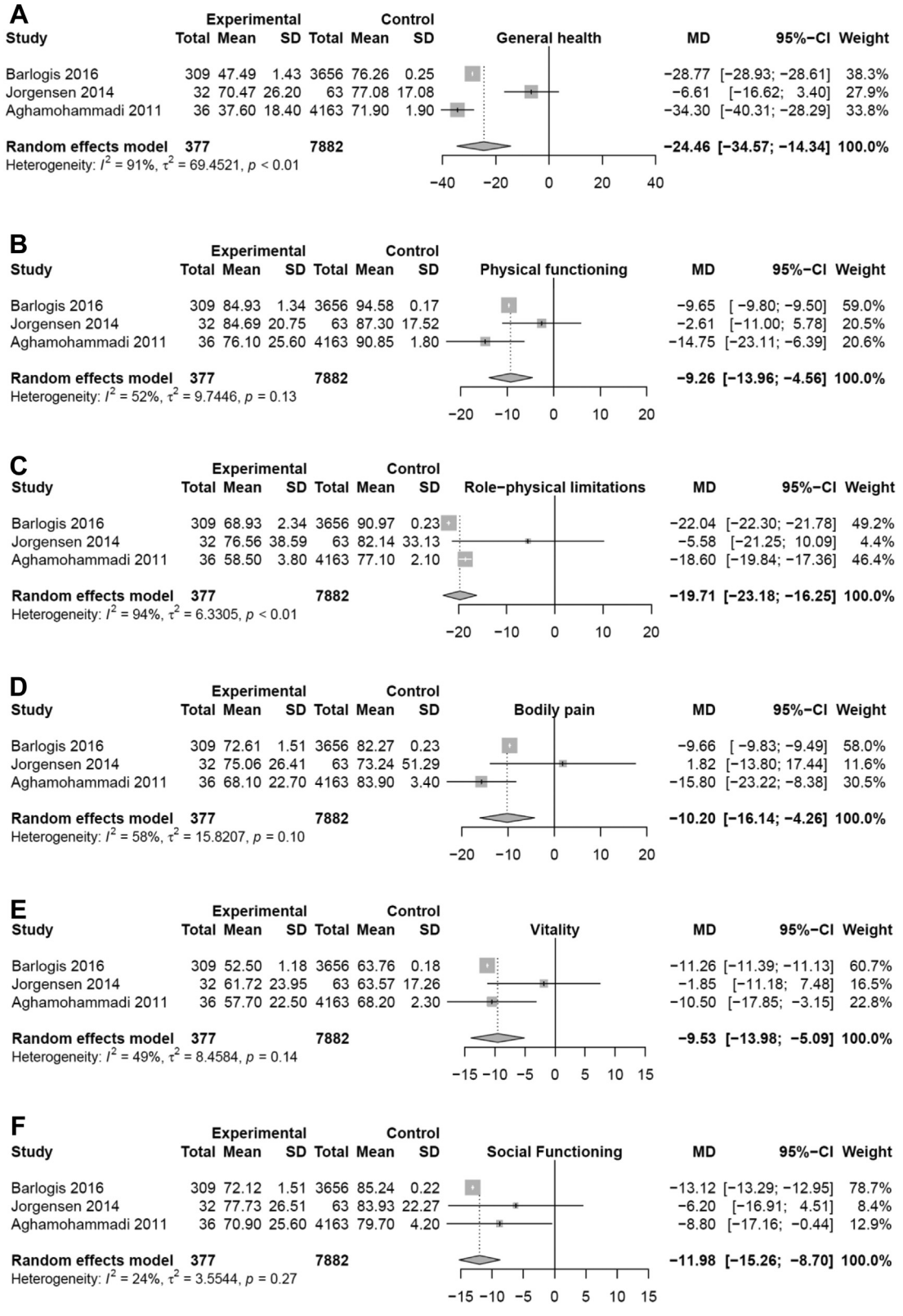


FIGURE 2. Forest plots on the mean difference in the HRQOL in adults with PID versus healthy individuals, using SF-36: (**A**) general health, (**B**) physical functioning, (**C**) role-physical limitations, (**D**) bodily pain, (**E**) vitality, and (**F**) social functioning.

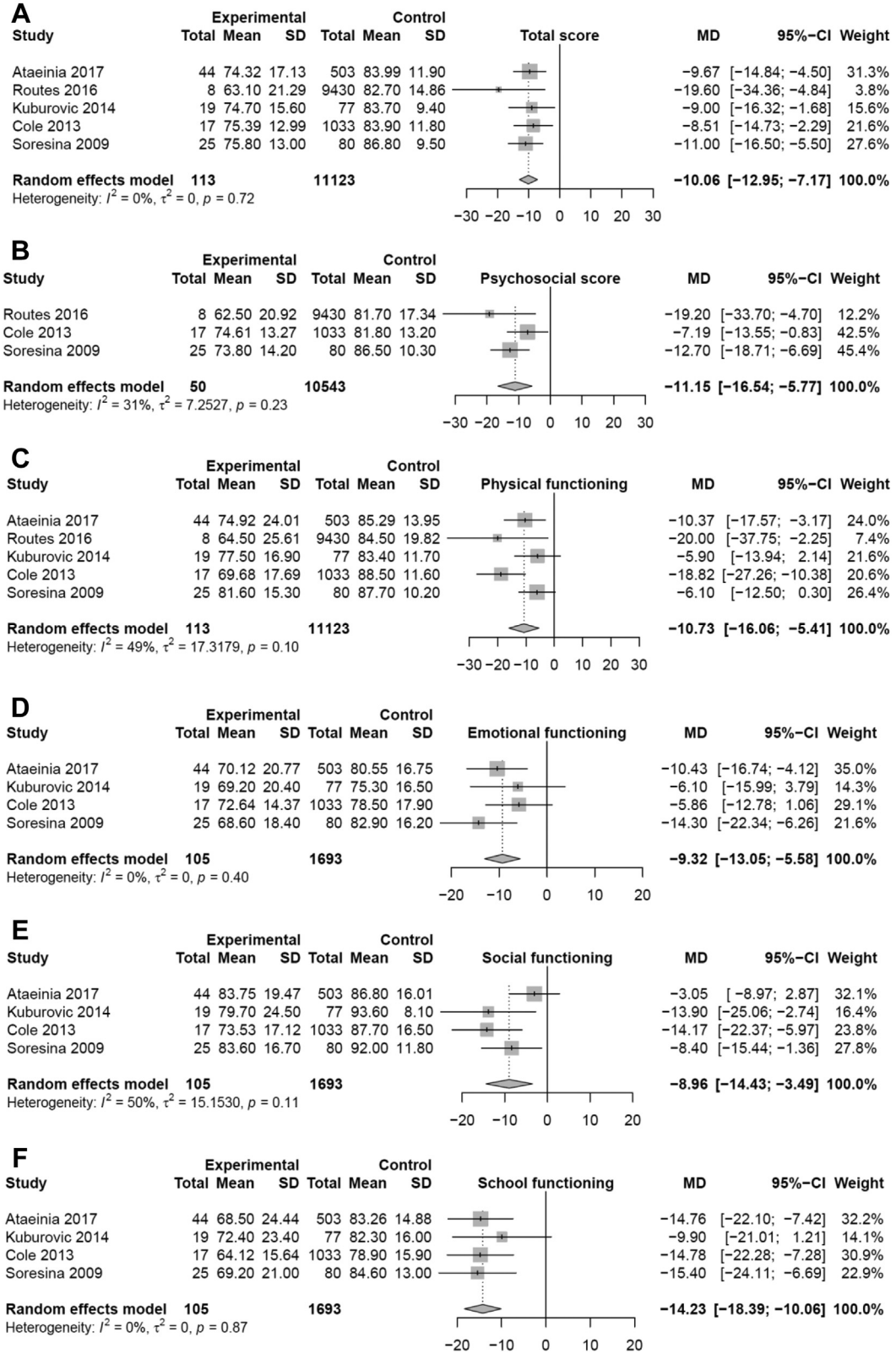


FIGURE 3. Forest plots on the mean difference in the HRQOL in children with PID versus healthy individuals, using PedsQL: (**A**) total score, (**B**) psychosocial score, (**C**) physical functioning, (**D**) emotional functioning, (**E**) social functioning, and (**F**) school functioning.

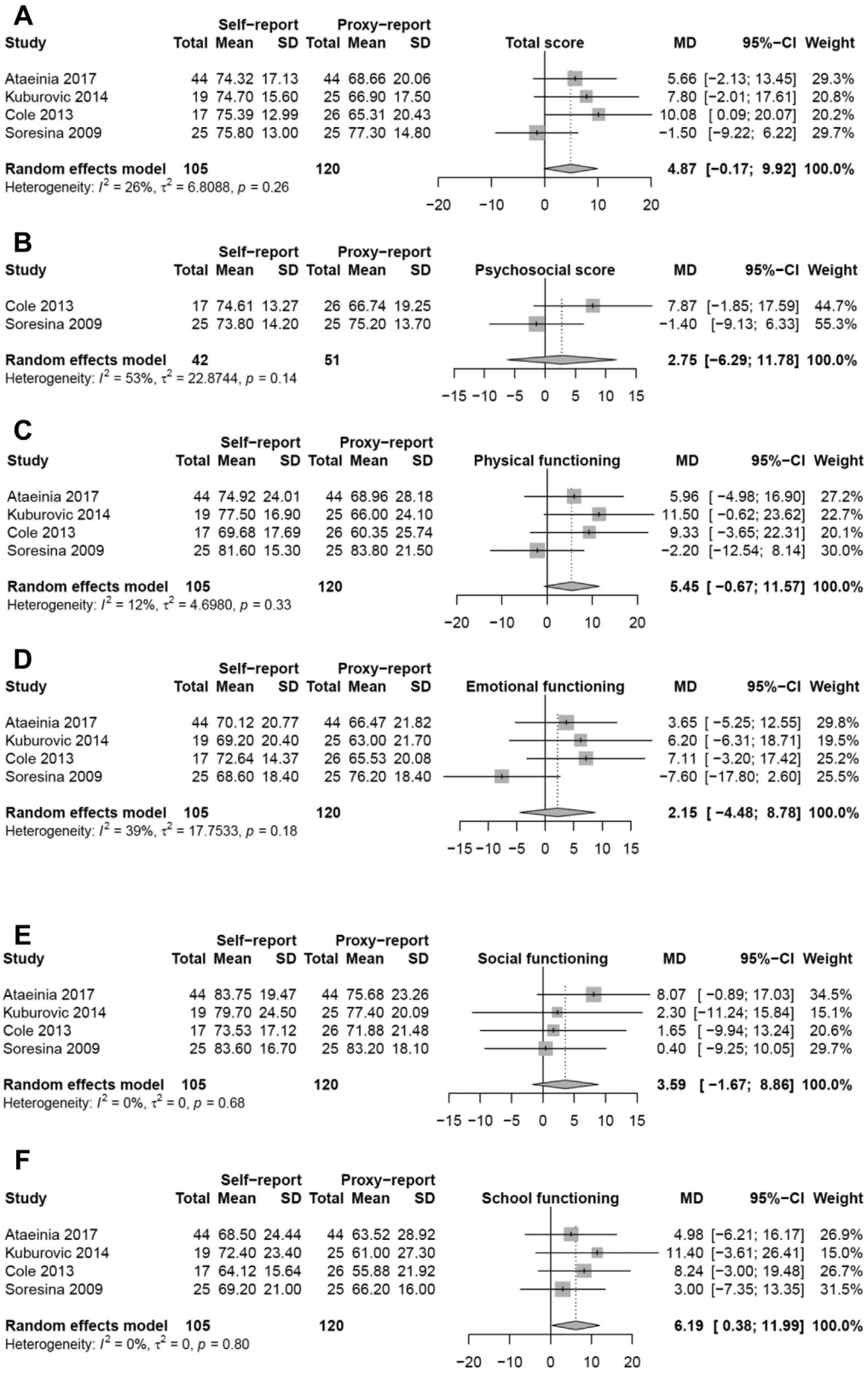


FIGURE 4. Forest plots on the mean difference in self-reported HRQOL in children with PID versus quality of life reported by their parents, using PedsQL: (**A**) total score, (**B**) psychosocial score, (**C**) physical functioning, (**D**) emotional functioning, (**E**) social functioning, and (**F**) school functioning.

patients with PID because few or no PID-specific instruments exist. Recently, Quinti and et al[21] developed and validated the first PID disease-specific instrument for patients with common variable immunodeficiency. The PADQOL-16, a new disease-specific questionnaire, has been developed for patients with primary antibody defect.[58] However, to our knowledge, no study providing data on HRQOL using the measure is available.

A recent systematic review by Abolhassani et al[59] clearly demonstrated a marked improvement in patients' HRQOL when treatment was changed from hospital-based intravenous immunoglobulin to home-based SCIG. Our findings are in line with these findings, and our qualitative analysis has only strengthened this evidence. More recently, an ambitious review by Lingman-Framme and Fasth[60] showed that improvement in HRQOL was largely attributed to the home setting. SCIG not only improves overall HRQOL but has a positive impact on school absence, domain that is strongly impacted in children with PID. Nevertheless, there are patients not willing to switch to SCIG because of perceived inconvenience, apprehension about adverse reactions at home, and concerns over frequent needle procedures.[40] Moreover, it is worth noting that some patients report that treatment negatively impacts HRQOL due to perceived restrictions.

In PID, patient-reported outcomes are poorly defined. A standardized protocol that incorporates HRQOL and other relevant PROMs and agreed definitions of outcomes for different age groups and patient types would allow for the comparison of efficacy of treatments between centers, trials, or countries.[61] Timing of measurement in treatment contexts is also important. To this end, it is vital that patient-related outcomes such as improved HRQOL are seen as a primary outcome, and are measured at multiple intervals during the trial duration and beyond. Because HRQOL has only been studied in relatively few PID treatment trials to date, it is unclear which factors or subscales are most predictive of short- and/or long-term treatment outcomes for which type of patient, and which time points for measurement are most informative.

Despite the comprehensive approach used in this review, it was not possible to collate data from all the studies due to a significant heterogeneity between the studies in their design, methodology, and data presentation. Confidence in our findings was downgraded because meta-analysis was performed using data from only a few studies, which does not allow to draw definitive conclusions. Very few studies were assessed as being of good quality, with the most frequent sources of potential bias including the lack of detailed data presentation; nonreporting of numbers; no statistical adjustment for potential confounding factors included; lack of data provided on the incidence and recurrence of infections; no exclusion criteria reported; and missing data on attrition in the intervention studies.

CONCLUSIONS

In this systematic review we found that HRQOL in adults and children with PID is more impaired compared with that in healthy individuals and in patients with diabetes mellitus and juvenile idiopathic arthritis. Overall, the quality of the studies was poor to moderate. Recommendations to improve future research include a clear descriptive of the sample, the development and use of disease-specific measures, the use of both parent- and child-report measures where appropriate, longitudinal design when possible, and data provided on effect sizes in treatment studies. This will help to evaluate efficacy and allow for interstudy comparability. A wide range of instruments are used for PID HRQOL assessment, although their psychometric properties have not been rigorously tested for this condition.

Available evidence suggests that patients with PID have a more impaired HRQOL than do healthy individuals and patients with other chronic conditions. No disease-specific instruments are available for children (proxy- or self-report), and few options are available for research with adults. There is an urgent need to develop PID-specific instruments and rigorously evaluate existing measures.

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ONLINE REPOSITORY

TABLE E1. Quality assessment of studies

Author, Year	Recruitment: (a) Avoidance of selection bias	Recruitment: (b) Avoidance of nonresponse bias	Description of nonresponders is missing (−1)	Design: (a) Course of measurement	Design: (b) Informants	Design: (c) Type of controls	Outcome assessment	Confounding and effect modification	Summary	Summary*
Observational studies										
Adults										
Barlogis et al,[E1] 2016	2	0	−1	1	0	1	2	1	6	Moderate
Bienvenu et al,[E2] 2016	2	0	−1	1	0	0	2	2	6	Moderate
Quinti et al,[E3] 2016	1	2	−1	1	0	0	2	1	6	Moderate
Jorgensen et al,[E4] 2014	2	2	0	1	0	1	2	1	9	Good
Tabolli et al,[E5] 2014	1	2	−1	1	0	1	2	1	7	Moderate
Jones et al,[E6] 2012	2	1	−1	1	0	1	2	0	6	Moderate
Quinti et al,[E7] 2012	1	2	−1	1	0	1	2	2	8	Moderate
Aghamohammadi etal,[E8] 2011	1	0	−1	1	0	1	2	0	4	Poor
Winkelstein et al,[E9] 2008	2	0	−1	1	0	1	2	0	5	Poor
Howard et al,[E10] 2006	0	0	−1	1	0	1	2	1	5	Poor
Sigstad et al,[E11] 2005	2	0	0	1	0	1	2	1	7	Moderate
Tcheurekdjian et al,[E12] 2004	1	2	0	1	0	1	2	0	7	Moderate
Children and adults										
Ataeinia et al,[E13] 2017	1	0	−1	1	1	1	2	0	5	Poor
Kearns et al,[E14] 2017	2	2	0	1	0	0	2	0	7	Moderate
Espanol et al,[E15] 2014	2	2	0	1	1	1	2	1	10	Good
Reid and Pires,[E16] 2014	1	0	0	1	0	0	0	0	2	Poor
Kirch et al,[E17] 2012	2	2	0	1	0	1	2	0	8	Moderate
Children										
Kuburovic et al,[E18] 2014	1	0	−1	1	1	1	2	2	7	Moderate
Titman et al,[E19] 2014	1	1	−1	1	1	1	2	1	7	Moderate
Soresina et al,[E20] 2009	2	0	−1	1	1	1	2	1	7	Moderate
Mozaffari et al,[E21] 2006	1	2	0	1	0	1	2	1	8	Moderate
Zebracki etal,[E22] 2004	1	1	−1	1	0	1	2	0	5	Poor
Interventional studies										
Adults										
Spadaro et al,[E23] 2017	2	2	0	1	0	0	2	0	7	Moderate
Abdou et al,[E24] 2009	0	0	−1	1	0	0	0	0	1	Poor
Nicolay et al,[E25] 2006	2	1	0	1	0	0	2	1	7	Moderate
Gardulf et al,[E26] 1993	1	2	−1	1	0	1	2	0	6	Moderate
Children										
Felix et al,[E27] 2014	1	0	−1	1	0	1	2	0	4	Poor
Cole et al,[E28] 2013	2	1	−1	1	1	1	2	0	7	Moderate
Fasth et al,[E29] 2008	1	0	−1	1	1	0	2	0	4	Poor
Fasth and Nystrom,[E30] 2007	1	0	−1	1	1	0	2	0	4	Poor
Children and adults										

Routes et al,[E31] 2016	2	0	−1	1	1	1	2	0	6	Moderate
Niebur et al,[E32] 2015	1	2	−1	1	0	0	0	0	3	Poor
Vultaggio et al,[E33] 2015	2	0	−1	1	0	0	2	0	4	Poor
Berger et al,[E34] 2010	0	2	−1	1	0	0	2	0	4	Poor
Gardulf et al,[E35] 2008	0	1	−1	1	0	0	2	2	5	Poor
Nicolay et al,[E36] 2005	2	0	−1	1	0	0	2	1	5	Poor
Gardulf et al,[E37] 2004	0	2	−1	1	0	1	2	0	5	Poor

*Based on criteria, studies were classified into 3 categories: good (score, 9-11), moderate (score, 6-8), and poor (score, 0-5).

1 ((primary or severe or combined or common variable) adj4 immunodeficienc*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
2 immunologic deficiency syndromes/ or agammaglobulinemia/ or common variable immunodeficiency/ or dysgammaglobulinemia/ or hyper-igm immunodeficiency syndrome/ or hyper-igm immunodeficiency syndrome, type 1/ or iga deficiency/ or igg deficiency/ or severe combined immunodeficiency/ or x-linked combined immunodeficiency diseases/
3 (antibod* adj2 deficienc*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4 ((IgA or IgG) adj2 deficienc*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
5 1 or 2 or 3 or 4
6 (HRQoL or HRQL or quality of life or value of life or quality adjusted life year* or CHQ-PF50 or PEDSQL or p?ediatric quality of life or child health questionnaire or SF-36 or 36-Item Short Form Health Survey or sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six or euroqol or "euro qol" or "eq5d" or "eq 5d" or sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty or sf6 or sf 6 or SF 6D or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve or quality of wellbeing or quality of well-being).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7 "Quality of Life"/
8 quality-adjusted life years/
9 "surveys and questionnaires"/ or patient reported outcome measures/ or self report/
10 6 or 7 or 8 or 9
11 5 and 10

FIGURE E1. Search strategy: MEDLINE (via Ovid).

1 ((primary or severe or combined or common variable) adj4 immunodeficienc*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]
2 immune deficiency/ or cellular immunodeficiency/ or combined immunodeficiency/ or humoral immune deficiency/
3 (antibod* adj2 deficienc*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]
4 ((IgA or IgG) adj2 deficienc*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]
5 1 or 2 or 3 or 4
6 (HRQoL or HRQL or quality of life or value of life or quality adjusted life year* or CHQ-PF50 or PEDSQL or p?ediatric quality of life or child health questionnaire or SF-36 or 36-Item Short Form Health Survey or sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six or euroqol or "euro qol" or "eq5d" or "eq 5d" or sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty or sf6 or sf 6 or SF 6D or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve or quality of wellbeing or quality of well-being).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]
7 "quality of life"/ or "international classification of functioning, disability and health"/ or quality adjusted life year/ or "quality of life index"/ or short form 36/ or "quality of life assessment"/ or "quality of working life"/
8 6 or 7
9 5 and 8

FIGURE E2. Search strategy: Embase (via Ovid).

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