AUS DEM LEHRSTUHL FÜR EPIDEMIOLOGIE UND PRÄVENTIVMEDIZIN
Prof. Dr. Michael Leitzmann
DER FAKULTÄT FÜR MEDIZIN
DER UNIVERSITÄT REGENSBURG

WHAT ARE THE BEST QUALITY OF LIFE MEASUREMENT INSTRUMENTS FOR ECZEMA? PERSPECTIVES ON POPULARITY AND QUALITY AS A CONTRIBUTION TO DEVELOPING A CORE OUTCOME SET.

Inaugural – Dissertation
zur Erlangung des Doktorgrades
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Zusammenfassung

Einleitung

Das atopische Ekzem (AE, Synonyme: Neurodermitis, atopische Dermatitis) ist eine chronisch bzw. chronisch-rezidivierend verlaufende, entzündliche Hauterkrankung, die Kinder und Erwachsene betrifft. Ihr Leitsymptom ist Juckreiz. Da die AE einen negativen Einfluss auf die Lebensqualität (LQ) der Betroffenen ausübt, werden in einigen randomisierten kontrollierten Studien (RCTs) u.a. auch LQ-Messinstrumente verwendet, um die Wirksamkeit der untersuchten Therapie(n) zu bewerten. Allerdings werden in den RCTs zahlreiche verschiedene LQ-Instrumente angewandt, wodurch die sich auf Metaanalysen und systematische Übersichtsarbeiten stützende evidenzbasierte Entscheidungsfindung erschwert wird. Aus diesem Grunde strebt die Initiative Harmonising Outcome Measures for Eczema (HOME) den Aufbau eines core outcome set (COS), d.h. einer in jeder RCT zu erhebender Mindestauswahl an Outcomes, an. Ziel meiner Dissertation war es, durch die Vorlage dreier systematischer Übersichtsarbeiten in Bezug auf die LQ eine Grundlage für dieses COS zu schaffen.

Material und Methoden

In der ersten systematischen Übersichtsarbeit untersuchte ich, welche LQ-Instrumente bislang in RCTs bei AE-Patienten verwendet wurden. Hierzu wurde die Datenbank Global Resource of Eczema Trials (GREAT) nach RCTs bei AE-Patienten durchsucht. Aus den die Einschlusskriterien erfüllenden Studien extrahierte ich anschließend Informationen zu patientenberichteten Outcomes, vor allem zur LQ. Die zweite Übersichtsarbeit bestand aus einer systematischen Begutachtung der Messeigenschaften aller existierender Messinstrumente, die für die LQ-Messung bei Erwachsenen mit AE entwickelt und/oder validiert wurden. Im Anschluss an eine systematische Literatursuche in Pubmed und Embase nach Studien zu den Messeigenschaften von LQ-Instrumenten für erwachsene AE-Patienten wurden die inhaltliche und die methodische Qualität der Messeigenschaften mit Hilfe der COSMIN-Checkliste (COnsensus-based Standards for the selection of health status Measurement Instruments) bewertet. Eine Synthese der besten Evidenz, die die Ergebnisse verschiedener Studien zusammenfasste, bildete die Grundlage zur Einordnung der LQ-Instrumente in vier Empfehlungskategorien (A-D). Ziel der dritten Übersichtsarbeit war es, die Messeigenschaften aller existierender Messinstrumente, die für die LQ-Messung bei Kleinkindern, Kindern und Jugendlichen mit AE entwickelt und/oder validiert wurden,

systematisch zu untersuchen. Ähnlich wie schon bei der zweiten Übersichtsarbeit fanden wir auch hier mittels einer systematischen Literatursuche in PubMed und Embase Studien zu den Messeigenschaften von LQ-Instrumenten für Kleinkinder, Kinder und Jugendliche mit AE. Wieder erfolgte die Bewertung von inhaltlicher und methodischer Qualität mit Hilfe der COSMIN-Checkliste; eine anschließende Synthese der besten Evidenz ermöglichte weitere Empfehlungen.

Ergebnisse

287 Volltextartikel, in denen über 303 Studien berichtet wurde, sowie 72 Abstracts erfüllten die Einschlusskriterien der ersten Übersichtsarbeit. 63 der 303 Studien (20,8 %) erfassten die LQ der Patienten und setzten hierfür 18 benannte und vier namenlose LQ-Instrumente ein, wobei die am häufigsten benützten Instrumente der Dermatology Life Quality Index (DLQI) für Erwachsene, der Children's Dermatology Life Quality Index (CDLQI) für Kinder, der Infants' Dermatitis Quality of Life Index (IDQoL) für Kleinkinder und der Dermatitis Family Impact (DFI) für Angehörige waren. Die zweite Übersichtsarbeit schloss 15 Artikel und 17 LQ-Instrumente ein. Kein Instrument erfüllte alle Voraussetzungen für eine Anwendungsempfehlung. Sechs Instrumente wurden in Kategorie B eingruppiert, d.h. abhängig von den Ergebnissen weiterer Validierungsstudien gibt es Potential für eine Empfehlung derselben. Drei Instrumente wiesen eine schlechte inhaltliche Qualität in mindestens einem erforderlichen Kriterium auf und wurden daher in Kategorie C eingeordnet. Die verbliebenen acht Instrumente waren nur unzureichend validiert und fielen folglich unter Kategorie D. In die dritte Übersichtsarbeit schlossen wir 17 Artikel ein, die über die Messeigenschaften von 24 LQ-Instrumenten berichteten. Kein Instrument erfüllte alle erforderlichen inhaltlichen Qualitätskriterien. Für die US-Version der Childhood Atopic Dermatitis Impact Scale (CADIS) ist eine zukünftige Empfehlung in Abhängigkeit von weiteren Studienergebnissen möglich. Alle anderen Instrumente waren unzureichend validiert.

Schlussfolgerung

Zusammenfassend gibt es zwei Hauptergebnisse meiner Dissertation. Erstens erfasst nur eine von fünf RCTs LQ. Zahlreiche verschiedene Instrumente werden dafür eingesetzt, wodurch Vergleichs- und Synthesemöglichkeiten der einzelnen Studienergebnisse deutlich eingeschränkt werden. Zweitens kann z. Z. kein LQ-Instrument für die Aufnahme in das geplante COS empfohlen werden, bis nicht weitere Validierungsdaten zur Verfügung stehen.

Bis auf weiteres sollte sich die Forschung auf den Quality of Life Index for Atopic Dermatitis (QoLIAD) und den DLQI für Erwachsene sowie den CADIS und selbstberichtete Instrumente für Kleinkinder, Kinder und Jugendliche fokussieren.

1. Introduction

Eczema (synonym: atopic dermatitis (AD)) is a common inflammatory skin disease that affects both children and adults. It is characterized by a chronic or chronically relapsing course, with pruritus being the main symptom.[1] The prevalence of eczema has increased in the two preceding decades, with up to 20% of children in industrialized countries now affected.[2] Likewise, recent studies in European and US populations suggest that prevalence rates in adults are in excess of 10%.[3,4] Eczema places a considerable economic burden on patients and society and exerts a negative impact on the quality of life (QoL) of the patients and their families.[5,6]

To understand what is meant when talking about impaired QoL of eczema patients, some general considerations on the construct QoL are necessary. The World Health Organization (WHO) defines QoL as "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns".[7] From this definition, it is obvious that QoL is a patient-reported outcome (PRO), typically assessed by filling in a questionnaire or responding to an investigator's questions. QoL is usually referred to as a multidimensional construct, encompassing the domains of somatic sensation, physical and cognitive functioning, psychological well-being, and social interaction.[8] However, it has to be noted that these holistic definitions may not be very useful to harmonize the mostly diverging views of researchers with respect to operational QoL definitions and QoL domains.[9] In an attempt to create a more tangible concept of QoL for medical research and practice, the term "health-related quality of life" (HRQoL) has been used. HRQoL focuses on the effects of a health condition on an individual's QoL, as perceived by that individual; it is therefore a medical and health-care-related interpretation of QoL, whereas QoL goes beyond this and includes also non-medical aspects such as occupation, family and social life, and other influencing factors of an individual's life.[9,10]

Adding to the confusion, there are not only various definitions of QoL, but also different conceptual models. One approach is the utility model, derived from economic decision theory, where patients are asked to balance a shorter life with less dysfunction against a longer life with more dysfunction: The utility model allows transforming responses into Quality Adjusted Life Years (QALY).[11] Another major conceptual model is health status measurement which is closer to the aforementioned definitions of QoL, since it proposes a multidimensional construct consisting of several domains for QoL measurement. While QoL

is quantified in a single numeric index (QALY) in the utility model, each QoL domain is assessed independently in health status measurement, with results often aggregated into a profile score.[11]

Researchers started to think about QoL in the early 1970s, resulting in the development of a few early adult QoL instruments that were mostly generic, i.e. applicable across different diseases and different fields of medicine, such as the Sickness Impact Profile (SIP).[12] A broader interest in QoL research was not observed until the 1990s, when many scientists began to expand and enhance the available conceptual considerations and developed numerous new QoL instruments.[13] In this decade, a growing research interest in QoL measurement in children led to the inauguration of a number of QoL instruments specific to pediatric populations;[14] also, the first dermatology-specific QoL measurement instruments were developed at that time.[15,16] Since then, many QoL instruments for use in dermatology and eczema patients have been proposed. Rehal *et al.* found in a review that 14 different QoL scales were applied in eczema trials from 1985-2010.[17]

As the measurement of QoL in clinical trials is particularly relevant for chronic skin disease such as eczema,[18] it may at first glance seem very positive that researchers and clinicians can now choose from a wide array of QoL measurement instruments. However, some of the QoL instruments used are inadequately validated in eczema. As a result, evidence-based decision making is hampered because treatment effects may be over- or underestimated. Moreover, the use of different QoL scales in randomized controlled trials (RCTs) renders their comparison and evidence synthesis in systematic reviews and meta-analyses difficult. Consequently, important uncertainties remain in the treatment of eczema, requiring the conduct of high quality randomized controlled trials (RCTs).[19,20] An internationally acknowledged way to improve the quality of RCTs and to increase researchers' possibilities to compare the results of RCTs is the development of a core outcome set (COS).[21]

A COS is a consensus-derived minimum set of outcomes to be assessed in a specific situation.[22] In other words, COS cover a minimum of outcomes that should be measured and reported in all clinical trials of a specific medical condition. As their sole intention is to facilitate the comparison of outcomes across trials in systematic reviews and meta-analyses, COS do not preclude researchers from including additional outcomes in their studies. Many clinicians, methodologists, and other volunteers from all over the world are thus actively working to develop COS for various diseases, guided by the recommendations published by the Core Outcome Measures in Effectiveness Trials (COMET) initiative.[23] The COMET initiative aims to promote COS research by providing guidance on developmental and

methodological issues, and by connecting researchers who are interested in COS development.

With the goal of developing a COS for eczema trials, the Harmonising Outcome Measures for Eczema (HOME) initiative was founded in 2008. A multi-perspective Delphi study conducted by the initiators of the HOME initiative defined clinical signs measured by means of a physician-assessed instrument, symptoms of eczema, and the long-term course of eczema as the core outcome domains to be applied in all future eczema trials.[24,25] At the HOME II meeting in Amsterdam in 2011, the international community confirmed these core outcome measures and also added QoL to the core set of outcome domains.[26] The next crucial step in the process of standardizing eczema outcome measurements is to identify appropriate instruments to measure each of the four core outcome domains of eczema. For two domains, this process has been completed and the Eczema Area Severity Index (EASI) has been identified as the currently most adequate measurement instrument to assess clinical signs and the Patient-Oriented Eczema Measure (POEM) as the most adequate instrument to assess symptoms in eczema.[27,28]

In an attempt to standardize processes and to provide a standard for COS development in dermatology, the HOME initiative has published a roadmap.[29] According to this roadmap, the first step for each core outcome domain is a comprehensive review of what outcome measurement instruments have actually been used *(review 1).* After completing this review, a systematic review of validation studies of the identified instruments ensues, in order to highlight gaps in validation and to inform clinicians and researchers about the appropriateness of the existing outcome measurement instruments *(review 2 and 3).* Therefore, the aim of this MD thesis was to complete the aforementioned steps for the core outcome domain QoL, separately for adults, and infants, children, and adolescents.

2. Material and methods

This MD thesis consists of three systematic reviews. Subsequently, material and methods are presented separately for the systematic review on what QoL instruments have been used in eczema trials *(review 1),* for the systematic review on the measurement properties of adult QoL instruments for eczema *(review 2),* and for the systematic review on the measurement properties of QoL instruments for infants, children and adolescents with eczema *(review 3).* This mode of presentation will also be applied to the results section.

2.1 Review 1

This systematic review investigated what QoL instruments have thus far been used in eczema RCTs. We searched the Global Resource of Eczema Trials (GREAT) database,[30] which includes records of all RCTs of eczema treatments,[31] for reports of RCTs, published in English or German language, from 2000 to May 2014. Detailed information on PROs, particularly QoL, was extracted. To ensure consistency in the data extraction, guidelines on what information should be gathered and how this information should be evaluated was agreed on beforehand. A second data extraction was performed for a random sample of 10% of the papers as a measure of quality assurance. For this sample, results were compared between the first and the second data extraction and discrepancies were resolved within the whole team. If only an abstract was available, we assessed QoL only.

Our main outcomes were: i) the proportion of articles that assessed a QoL outcome, ii) the proportion of articles that assessed a PRO, iii) whether the inclusion of a QoL measure was related to whether the primary endpoint was a PRO, iv) what QoL instruments were used, v) the number of QoL instruments per study and vi) the number of studies published and the proportion including QoL instruments over time. A PRO was defined according to Patrick *et al.* as any report coming directly from patients, without interpretation by physicians or others, about how they function or feel in relation to a health condition and its therapy.[32] The term ‘composite index’ was used to describe any score or index that is composed of both a PRO and a non-PRO part.

2.2 Review 2

This systematic review investigated the measurement properties of adult QoL instruments for eczema and was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[33] A study protocol was published

beforehand and has also been registered in the International Prospective Register of Systematic Reviews (PROSPERO): CRD42015017138.[34]

We conducted a systematic literature search in PubMed and Embase identifying studies on measurement properties of adult eczema QoL instruments. The eligibility criteria laid out in the protocol were applied.[34] Only self-reported disease- or dermatology-specific, and not generic QoL measurement instruments, were eligible. We regarded different language versions of the same questionnaire separately because we consider these to be distinct instruments.

We compared the content of each instrument on content domain level. For all eligible studies, we assessed the adequacy of the measurement properties using the predefined criteria for rating the adequacy of measurement properties recommended by the COSMIN group in a slightly modified version.[35] The methodological quality of the included studies was evaluated with the COnsensus-based Standards for the selection of health status Measurement INstruments (COSMIN) checklist.[36–38] In the COSMIN checklist (cf www.cosmin.nl), four domains are distinguished (reliability, validity, responsiveness, and interpretability) with related measurement properties and aspects of measurement properties. For each of the measurement properties, the COSMIN checklist consists of 5 to 18 items covering methodological standards (organized in nine boxes for the nine measurement properties). In addition, each item can be scored on a four-point rating scale (that is, 'poor', 'fair', 'good', 'excellent'). Taking the lowest rating for each item in one box, an overall quality score ('poor', 'fair', 'good', 'excellent') is obtained for each measurement property separately. The measurement property 'criterion validity' was not considered for the purpose of this systematic review since no gold standard exists for QoL.

Where an instrument was evaluated in multiple studies, the findings were synthesized ('best evidence synthesis') provided the characteristics of the included studies were sufficiently similar and the methodological quality of the included studies was sufficient.[39] The results of this best evidence synthesis were the basis to assign four degrees of recommendation (A-D) to the included QoL instruments. Finally, we aimed to identify one most appropriate (currently available) instrument to assess QoL in adults with eczema.

2.3 Review 3

This systematic review investigated the measurement properties of QoL instruments for infants, children and adolescents with eczema and was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

statement.[33] A study protocol was published beforehand and has also been registered in the International Prospective Register of Systematic Reviews (PROSPERO): CRD42015023483.[40]

For this systematic review, we applied in large parts the same methodology as we did for the second review. An important difference concerned the eligibility criteria: To be eligible, a study's population needed to consist of patients younger than 16 years of age. A study with a mixed patient sample was eligible either if it presented a subgroup analysis for infants, children and adolescents with eczema or if infants, children and adolescents with eczema constituted at least 50% of the study population. The measurement instrument had to be a self- or proxy-reported questionnaire. The eligibility criteria laid out in the protocol were applied.[40] Finally, we aimed to identify one best (currently available) instrument to assess QoL in infants, one best (currently available) instrument to assess QoL in children, and one best (currently available) instrument to assess QoL in adolescents with eczema.

3. Results

3.1 Review 1

287 full texts reporting on 303 trials and 72 abstracts were included. 63/303 studies (20.8%) assessed QoL and used 18 named and 4 unnamed QoL instruments. PROs were assessed by 85.9% of articles. We found a statistically significant association between a PRO or a composite index as the primary endpoint and the inclusion of QoL (p=0.002). Likewise, study authors that used a distinct non-PRO as primary endpoint were more likely to include QoL measurement than study authors that did not specify their primary endpoint in more detail.

The Dermatology Life Quality Index (DLQI) (20/36 studies), the Children's Dermatology Life Quality Index (CDLQI) (18/20 studies) and Infant's Dermatology Quality of Life Index (IDQoL) (14/15 studies) were the most common measures in adults, children and infants, respectively. QoL of adult caregivers of children with eczema was most often assessed with the Dermatitis Family Impact (DFI, 14/20 studies). Of the 63 trials that assessed QoL, we found that the majority of studies (n=41, 65.1%) used only one QoL measurement instrument. Two QoL instruments were applied in 16 studies (25.4%) and the remaining 6 studies (9.5%) included three QoL measurement instruments. Analysis over time showed that although there were fluctuations from year to year, the proportion of trials that include QoL measures has remained largely static since 2000.

For the studies which were reported in abstract form only, only 4 out of 72 (6%) assessed QoL. The CDLQI was used in 2 abstracts and the DFI in 1 abstract. Three further QoL instruments were reported, but were not named.

3.2 Review 2

15 articles reporting on 17 instruments were included. No instrument fulfilled the criteria for category A because there was none for which all measurement properties had been evaluated. Measurement error and cross-cultural validity of the QoL instruments in question were not evaluated in any of the included studies. Five language versions of the Quality of Life Index for Atopic Dermatitis (QoLIAD) were placed in category B, meaning that they have the potential to be recommended depending on the results of further validation studies. The QoLIAD was found to have adequate content and construct validity and proved to be internally consistent; its reliability, structural validity and cross-cultural validity are unclear, while responsiveness and measurement error have not been investigated at all. Because of adequate reliability and responsiveness, the Spanish DLQI also fulfilled the criteria for

category B, although less information is available for this questionnaire compared to the QoLIAD. The UK version of the DLQI was shown to have poor internal consistency, content and structural validity in eczema patients and was thus put in category C. Construct validity of both the Impact of Chronic Skin Disease on Daily Life (ISDL) and the Dutch QoLIAD was found inadequate, hence they were also placed in category C. Instruments in that category had poor adequacy in at least one required adequacy criterion and are therefore considered problematic for further use in eczema patients. The remaining eight instruments, namely Deutsches Instrument zur Erfassung der Lebensqualität bei Hauterkrankungen (DIELH), Danish DLQI, German DLQI, Freiburg Life Quality Assessment core module (FLQA-c), Freiburg Life Quality Assessment for Dermatoses (FLQA-d), Italian QoLIAD, English Skindex-29 and German Skindex-29, were minimally validated and were thus placed in category D; since their performance in most measurement properties is largely unclear, further usage cannot be recommended until more validation data is available.

3.3 Review 3

17 articles, three of which were found by hand search, were included. These 17 articles reported on 24 instruments. No instrument can be recommended for use in all eczema trials because none fulfilled all required adequacy criteria. Among the tested instruments for pediatric eczema, the U.S. version of the Childhood Atopic Dermatitis Impact Scale (CADIS), a proxy-reported instrument, was the only one to be placed in category B, meaning it has the potential to be recommended depending on the results of further validation studies. While three of its measurement properties, i.e. internal consistency, reliability and hypothesis testing, were found to be adequate, the assessments of content validity and responsiveness were of poor methodological quality. Measurement error, structural validity and cross-cultural validity of the U.S. version of the CADIS have not yet been investigated. All other instruments including all self-reported ones, namely Italian CADIS (long version), Italian CADIS (short version), Dutch Childhood Impact of Atopic Dermatitis (CIAD), English CIAD (U.K.), English CIAD (U.S.), French CIAD, German CIAD, Italian CIAD, Spanish CIAD, Brazilian Portuguese DISABKIDS Atopic Dermatitis Module (DISABKIDS-ADM) in self- and proxy-reported version, Arabic IDQoL, Dutch IDQoL, English IDQoL (U.K.), Italian IDQoL, Swedish IDQoL, Danish CDLQI, English CDLQI (U.K.), Malay CDLQI, Serbian CDLQI, Spanish CDLQI (Mexico), Swedish CDLQI and an unknown language version of the DISABKIDS-ADM lacked significant validation data and were consequently grouped in

category D, meaning they should not be used until more validation data is available because their performance in most measurement properties is unclear.

4. Discussion

Our first systematic review showed that study authors conducting eczema RCTs take apparently only little interest in measuring QoL, with only about one out of five trials including QoL instruments. To our disappointment, there is also no reason for optimism that the situation might improve in the near future, as our findings suggest that QoL measurement in eczema RCTs has not increased over time, which is in contrast to what we had initially assumed according to a previous review.[17] A more recent study found that 33% of eczema RCTs conducted between 2010 and 2015 included QoL outcome measures, a figure markedly higher than ours (20.8%).[41] However, in that review the authors counted also instruments like for instance the Beck Depression Inventory or State-Trait Anxiety Inventory among QoL instruments. This may at least partly explain the difference since we did not consider these for our review because they do not specifically measure QoL but other constructs (i.e. depression and anxiety in the example above). Nonetheless, the findings of Hill *et al.* on the most frequently applied QoL instruments in eczema are in accordance with the results of our systematic review.

Our first systematic review showed that in adult sufferers of eczema, a multitude of 16 different QoL instruments was used in 36 trials assessing QoL. However, the DLQI, and to a lesser extent the Skindex-29, were applied in the large majority of these studies, with all other questionnaires only used in one study each. According to our second review, the Skindex-29 is almost not validated in eczema, which is why its appropriateness for eczema RCTs is unclear. In contrast, it has become obvious from our findings that the appropriateness of the DLQI for eczema patients is at least doubtful. While the Spanish DLQI was proven reliable and responsive and was thus placed in category B, the UK version of the DLQI was found to have poor internal consistency, content and structural validity in eczema and is therefore suggested not to be used anymore in eczema trials. Although internal consistency, content and structural validity of the Spanish DLQI in eczema patients are yet unknown, the results obtained in the instrument's UK version challenge the applicability of the DLQI to eczema patients in general, and raise the question whether the Spanish version will perform better with respect to these measurement properties. Furthermore, 4 out of 36 trials assessing adult QoL applied modified or self-provided instruments which have not been validated at all. The most appropriate instrument to measure QoL in eczema currently available, the QoLIAD, was used in only one eczema RCT, though. Altogether, we could demonstrate that the overwhelming majority of eczema RCTs assessing adult QoL have thus far relied on

inappropriate or insufficiently validated measurement instruments to evaluate the QoL of the included patients, clearly demonstrating the necessity of an eczema-specific quality of life measurement instrument with sufficient validity evidence.

In stark contrast to the findings for adults, only four QoL questionnaires were used in trials in infants, children and adolescents with eczema. When focusing on the validated ones only, two instruments are left over: the proxy-reported IDQoL, an eczema-specific measure for infants, and the self-reported CDLQI, a dermatology-specific QoL questionnaire. The included studies did not apply any QoL instruments specifically designed for adolescents. Findings from our third review suggest that both the IDQoL and the CDLQI are poorly validated in eczema, whereas the only instrument having the potential to be recommended for pediatric eczema in the future, the U.S. version of the CADIS, was not used in any of the studies assessed in our first review. Similar to the situation in adult patients, these results underline how urgently a quality of life instrument with sufficient evidence for its validity is needed for pediatric eczema.

The fact that none of the investigated QoL instruments for infants, children, adolescents and adults could be recommended for inclusion in the COS being developed by the HOME initiative will delay its finalization for at least two years. However, our systematic review helped to reveal substantial validation gaps of most QoL instruments and forms the basis for prioritizing future research needs. One of the validation studies to be carried out should focus on clarifying the performance of the QoLIAD with respect to measurement error, reliability, structural validity, cross-cultural validity, and responsiveness; also, another examination of its construct validity seems advisable in light of a negative rating that the Dutch QoLIAD obtained for this measurement property. Except reliability and responsiveness, all other measurement properties of the Spanish DLQI need to be evaluated in another validation study, with particular attention to internal consistency, content and structural validity, where the English DLQI (UK) failed. With respect to pediatric patients, further validation studies of the CADIS, including all available language versions, are necessary; these should investigate measurement error, content validity, structural validity, cross-cultural validity, responsiveness and interpretability. Furthermore, we recommend performing additional validation studies for the IDQoL, which is the most frequently used QoL instrument in infants. Eventually, better validation of self-reported questionnaires for children and adolescents, particularly the CDLQI and the DISABKIDS-ADM, is desirable.

Nevertheless, clinicians and researchers should include a QoL measurement instrument in all their upcoming eczema trials because QoL is one of the core outcome domains of the

proposed COS. As no distinct instrument for measuring QoL in eczema trials can be recommended at the moment, the HOME initiative suggests using any QoL instrument that is at least valid, reliable and feasible in eczema patients.[42] Unfortunately, one result of our second and third review is that currently no such instrument is available. There is no optimal solution to this dilemma. Clinicians and researchers need to weigh up validity, reliability and feasibility. With respect to adult patients, we suggest that researchers should include one of the two instruments from category B, i.e. the QoLIAD in several language versions or the (Spanish) DLQI, in their trials. For infants and younger children, we recommend using the proxy-reported CADIS, whereas no clear advice can be given for older children and adolescents. In older adolescents, the suggested QoL instruments for adults may be used.

Probably the most important question for the HOME initiative to be successful is how to increase the acceptance of the proposed COS in the scientific community. Although continually rising attendance figures of the HOME meetings indicate that many stakeholders, including dermatologists, patients, methodologists, and representatives from industry, are interested in developing a COS for eczema trials, there has also been criticism. Besides other reservations, a major point of concern is the (ostensibly) one-sided preference of methodologically questionable systematic reviews as basis for decision-making instead of focusing on original research and taking into account clinicians' views.[43,44] The assertion of an underrepresentation of clinicians at the HOME meetings and in the HOME processes can easily be refuted by the fact that at the third and fourth HOME meeting clinicians made up the majority of voters;[45,46] moreover, the HOME initiative is open to anyone interested in a COS for eczema trials, invalidating the alleged dominance of methodologists.[47] However, it is true that the processes used by HOME are puzzling for many clinicians. The methods are complicated and differ greatly from the ones used in RCTs and traditional systematic reviews. Moreover, the results of the reviews may indeed not be helpful for dermatologists in research and clinical practice to decide on the most appropriate instrument, as is demonstrated by review 2: the meaning of the result that two instruments were placed in category B grows not immediately apparent and probably leaves most clinicians none the wiser. Consequently, HOME's most important challenge is to spell out its methods in more detail and to translate the findings of its processes into meaningful guidelines easily comprehensible for the practicing dermatologist. Nonetheless, there is a germ of truth in the criticized methodological weakness of the systematic reviews that the HOME initiative is relying on.

While there is general agreement in medicine that systematic reviews are vital for evidence based decision making,[48–50] deficiencies in their methodology are considered to render their results less conclusive.[51,52] Despite considerable differences to "traditional" systematic reviews which evaluate for instance information obtained in RCTs, methodological weaknesses are also found in systematic reviews of measurement properties such as ours. One of these weaknesses concerns the COSMIN checklist that we used to assess the methodological quality of the included studies. The inter-rater reliability of the COSMIN checklist was found to be poor,[53] which is particularly relevant for our systematic reviews where two reviewers independently completed the COSMIN checklist for each study. Notably, the findings on poor inter-rater reliability refer to the initial version of the COSMIN checklist with a dichotomous response format; however, we used the refined version with a 4-point rating system.[54] Although the inter-rater reliability of the latter version has not been investigated, it can be assumed that this checklist would perform even worse than the dichotomous one because rating the methodological quality from "excellent" to "poor" is much more open to subjective judgment than only opting for "yes" or "no", particularly since many of the response options to the items of the 4-point COSMIN checklist are formulated vaguely (e.g., distinction between "Multiple hypotheses formulated a priori" and "Minimal number of hypotheses formulate a priori"). Taking into account our experience from review 2, we tried to minimize inter-rater reliability in review 3 by involving the same reviewer in every pair that completed COSMIN boxes. However, this approach cannot overcome other problems associated with the COSMIN checklist such as the need for subjective judgment, the difficulty for the two reviewers to agree on a common rating, the fact that only for the initial dichotomous version a manual is available,[55] and general criticism of the COSMIN checklist's ostensibly unjustified rejection of well-established measures, e.g. effect sizes for responsiveness, as inappropriate.[56]

The COSMIN checklist's stringent requirements, which lead to the mentioned negative judgment of certain measures, are reflected in the fact that 25% of the evaluated measurement properties obtained a "poor" rating in the second review, as compared to 76% in the third review. As these measurement properties are not taken into account for the best evidence synthesis, there arises the question whether the high standards of the COSMIN checklist are justified or if less strict requirements would also be sufficient in order not to lose such a large amount of possibly valuable data. For instance, some of the checklist items judge reporting standards instead of methodological quality, and insufficient reporting can even lead to a "poor" rating for a measurement property despite adequate methodological quality (e.g., item

8 in box F, where missing information on the measurement properties of the comparator instruments results in a "poor" rating for hypothesis testing). Although good reporting in studies is of course desirable and sometimes even the prerequisite for adequate methodological quality, the COSMIN checklist should not evaluate the quality of reporting where it is not a requirement for methodological quality. As a result, some of the checklist's standards are indeed too high and may unduly bar findings for some measurement properties from further analysis. This may also lead to a delayed finalization of COS development since the completion of additional validation studies often takes several years. A potential way out of that dilemma could be the findings of a recent Delphi study on how to select outcome measurement instruments for a COS. The participating experts reached consensus on minimum requirements for including an outcome measurement instrument in a COS; these are at least high quality evidence for good content validity and good internal consistency, and the instrument has to be feasible.[57] Applying these minimum requirements in COS development could open the way for suggesting at least a provisional COS in situations where the COSMIN checklist would still require further validation before an outcome measurement instrument can be recommended.

Nevertheless, it has to be noted that the COSMIN checklist was developed in a Delphi study involving 57 international experts in the field of psychology, epidemiology, statistics, and clinical medicine, whose consensus-based decisions determined items and response options of the checklist.[38] Therefore, although a critical appraisal of the stringency of the COSMIN checklist's standards is lacking in the literature, it can be assumed that most of the requirements formulated in the COSMIN checklist are reasonably high.

Altogether, the COSMIN checklist – despite a number of shortcomings - is a useful instrument for evaluating the methodological quality of studies on measurement properties. However, a critical revision of its content in order to increase inter-rater reliability and to lower standards where they are unreasonably high seems to be required; the use of agreed minimum requirements may be useful for the time being.

When discussing methodological deficiencies, attention must also be drawn to the adequacy criteria proposed by Terwee *et al.*[35] The criteria used for our reviews are based on those presented by Terwee *et al.* in a template protocol available upon request from the COSMIN initiative.[58] Importantly, these criteria have not been published in a scientific journal; however, they deviate from the ones Terwee *et al.* had previously suggested.[35] As authors can only cite the latter ones, the transparency of reviews in this respect is suboptimal. New

adequacy criteria agreed upon by experts in the field in a Delphi study have been recently published and could be used in upcoming systematic reviews in order to avoid that problem.[57] Eventually, the criteria for best evidence synthesis applied by the HOME initiative[59] appear to be suboptimal. According to these criteria, any measurement property of a QoL instrument which conflicting ratings are obtained for will be assigned the rating "+/-", irrespective of the number of positive and negative ratings for that measurement property. Consequently, these criteria do not allow for improvement of QoL instruments that obtained negative ratings for some measurement properties. Even if further validation studies would result in a positive rating for the measurement properties in question, the overall rating according to the criteria for best evidence synthesis would only change from negative to conflicting, but could never become positive. In the light of the results of review 2, where we identified the need for further validation studies for two questionnaires that had obtained negative ratings for some measurement properties in some language versions, these criteria seem irrational and should thus be enhanced accordingly in the future. Improved criteria for best evidence synthesis that could be adopted by the HOME initiative have recently been proposed.[57]

In conclusion, the three reviews that we conducted could clearly demonstrate the need for a COS in eczema that includes QoL instruments. Although some parts of the methodology applied were not optimal and could still be improved, our findings are based on evidence judged according to established and internationally acknowledged criteria. For both pediatric and adult eczema patients, no distinct QoL instrument can be recommended for inclusion in the proposed COS. Further validation work should focus on the QoLIAD and the DLQI for adults, the CADIS for infants, and the CDLQI and DISABKIDS-ADM for children and adolescents.

The results of our systematic reviews informed the fourth and the fifth international consensus meeting to harmonize core outcome measures for atopic eczema.[60] Due to the substantial validation gaps of the investigated QoL instruments, the attendants of the meetings felt not able to recommend one distinct QoL instrument for inclusion in the COS proposed by the HOME initiative, neither for adult nor for pediatric eczema. Further validation studies may hopefully increase the evidence base and thus enable the group to agree on a specific QoL instrument to be included in the COS. A well thought-out COS is essential to improve eczema treatment – both clinicians and patients will benefit in the end.

5. Abstract

5.1 Introduction

Eczema (synonym: atopic eczema (AE), atopic dermatitis (AD)) is an inflammatory skin disease with a chronic or chronically relapsing course and is common among adults and children. Its main symptom is pruritus. Because it negatively impacts the patients' quality of life (QoL), some eczema randomized controlled trials (RCTs) include QoL measurement instruments to assess treatment efficacy. However, the use of numerous different QoL instruments, many of which are insufficiently validated, hampers evidence-based decision making through meta-analyses and systematic reviews. Therefore, the Harmonising Outcome Measures for Eczema (HOME) initiative seeks to establish a core outcome set (COS), i.e. a minimum set of outcomes to be assessed in every eczema RCT. In my MD thesis, I aimed to lay the ground for the QoL part of that COS by providing three systematic reviews on QoL instruments in eczema.

5.2 Material and methods

The first systematic review investigated which QoL instruments have thus far been used in eczema RCTs. The Global Resource of Eczema Trials (GREAT) database was searched for reports of eczema RCTs. Information on patient-reported outcomes, particularly QoL, was extracted from eligible studies. In the second systematic review, a systematical assessment of the measurement properties of existing measurement instruments developed and/or validated for the measurement of QoL in adult eczema was performed. After a systematic literature search in PubMed and Embase for studies on measurement properties of adult eczema QoL instruments, the adequacy of the measurement properties and the methodological quality was evaluated using the COSMIN checklist. A best evidence synthesis summarizing findings from different studies was the basis to assign four degrees of recommendation (A–D). The third systematic review aimed to systematically evaluate the measurement properties of existing measurement instruments developed and/or validated for the measurement of QoL in infants, children and adolescents with eczema. Similar to the second review, a systematic literature search in PubMed and Embase retrieved studies on measurement properties of eczema QoL instruments for infants, children and adolescents. Again, adequacy and methodological quality were assessed using the COSMIN checklist, with an ensuing best evidence synthesis as basis for further recommendations.

5.3 Results

287 full texts reporting on 303 trials and 72 abstracts were eligible for the first systematic review. 63 of the 303 studies (20.8%) assessed QoL and used 18 named and 4 unnamed QoL instruments, with the most common instruments being the Dermatology Life Quality Index (DLQI) for adults, the Children's Dermatology Life Quality Index (CDLQI) for children, the Infants' Dermatitis Quality of Life Index (IDQoL) for infants and the Dermatitis Family Impact (DFI) for caregivers. The second systematic review included 15 articles reporting on 17 QoL instruments, none of which fulfilled all requirements for recommendation. Six instruments were placed in category B, meaning that they have the potential to be recommended depending on the results of further validation studies. Three instruments had poor adequacy in at least one required adequacy criterion and were therefore put in category C. The remaining eight instruments were minimally validated and were thus placed in category D. In the third systematic review, 17 articles reporting on 24 QoL instruments were included, none of which fulfilled all required adequacy criteria. The U.S. version of the Childhood Atopic Dermatitis Impact Scale (CADIS) was found to have the potential to be recommended depending on the results of further validation studies. All other instruments lacked significant validation data.

5.4 Conclusion

In conclusion, there are two main findings of my MD thesis. Firstly, only one out five eczema RCTs assesses QoL. Many different instruments are used, limiting the possibilities of comparing and synthesizing individual trials' findings. Secondly, no QoL instrument can currently be recommended for inclusion in the proposed COS until further validation data is available. For the time being, research should focus on the Quality of Life Index for Atopic Dermatitis (QoLIAD) and the DLQI for adults as well as the CADIS and self-reported instruments for infants, children and adolescents.

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8. Veröffentlichte Artikel

Nachfolgend finden sich Abdrucke der von mir veröffentlichten Arbeiten, die in Verbindung mit diesem Manteltext meine Dissertation bilden. Bis auf die hinzugefügten Seitenzahlen sind die Abdrucke identisch mit den Originalveröffentlichungen in den jeweiligen Journals.

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SPECIAL REPORT

Eczema Trials: Quality of Life Instruments Used and Their Relation to Patient-Reported Outcomes. A Systematic Review

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It is unclear which quality of life instruments have thus far been used in eczema trials. Therefore, we aimed to identify these instruments. We searched the Global Resource of Eczema Trials (GREAT) database for reports of randomized controlled trials. Information on patient-reported outcomes, particularly quality of life, was extracted from eligible studies. Two-hundred and eighty-seven full texts reporting on 303 trials and 72 abstracts were included. Of the 303 studies, 63 (20.8%) assessed quality of life and used 18 named and 4 unnamed instruments. The Dermatology Life Quality Index (DLQI), the Children's Dermatology Life Quality Index (CDLQI), the Infants' Dermatitis Quality of Life Index (IDQOL), and the Dermatitis Family Impact (DFI) were the most common measures in adults, children, infants, and caregivers, respectively. In conclusion, only about one fifth of eczema trials include a quality of life measure as outcome. Many different instruments are used, limiting the possibilities of comparing and synthesising individual trials' findings. ***Key words: eczema; atopic dermatitis; quality of life; patient-reported outcomes; HOME initiative.***

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Eczema (synonym: atopic dermatitis (AD)) is a common skin disease that affects both children and adults. It exerts a negative impact on the quality of life (QoL) of the patients and their families and places a considerable financial burden on patients and society (1, 2). The disease is characterized by a chronic or chronically relapsing course, with pruritus being the main symptom (3). The prevalence of eczema has increased over recent years (4).

Despite a multitude of available treatment options, important uncertainties remain in the treatment of eczema requiring the conduct of high quality randomized controlled trials (RCTs) (5, 6). The use of non-standardized and inadequately validated outcome measurement instruments (OMIs) in eczema trials hampers evidence-based decision making because treatment effects may be over- or underestimated. Furthermore, comparison and evidence synthesis is rendered difficult when outcome measurement is not standardized.

Therefore, the Harmonising Outcome Measures for Eczema (HOME) initiative set out to define a core outcome set (COS) that should be assessed in all eczema trials in the future (7). A COS is a consensus-derived minimum set of outcomes to be assessed in a specific situation (8). HOME agreed to consider clinical signs, symptoms, long term control and QoL as core outcome domains (9). For each of these domains an adequate OMI needs to be identified. For the signs domain, this process has been completed and the Eczema Area and Severity Index (EASI) has been identified as the currently most adequate measurement instrument to assess clinical signs in eczema (10).

To standardize processes and to provide a standard for COS development in dermatology, the HOME initiative has published a roadmap (11). According to this roadmap, the first step for each core outcome domain is a comprehensive review of what OMIs have actually been used.

QoL, as one of these core outcome domains, is usually classified as a patient-reported outcome (PRO). A PRO is defined as any report coming directly from patients, without interpretation by physicians or others, about how they function or feel in relation to a health condition and its therapy (12). Where clinical trials use a PRO as primary endpoint, this is a reflection of the importance that study authors place on PROs. Thus, with QoL being a PRO, we hypothesized that authors who used PROs as primary endpoints in eczema trials would also be more likely to apply QoL questionnaires.

In accordance with the HOME roadmap (11), the primary aim of this systematic review was to identify the QoL measurement instruments used in eczema trials from the year 2000 onwards. We were also interested in whether there were any time trends in their usage. A secondary aim was to find out whether the consideration of a PRO as a primary endpoint in eczema trials was related to the inclusion of a QoL instrument as an outcome measure.

METHODS

Sample article selection

To obtain a comprehensive selection of eczema trials, we searched the Global Resource of Eczema Trials (GREAT) Database (13), which includes records of all RCTs of eczema treatments (14). An article was considered eligible if it was an eczema treatment trial published since 2000, was indexed in the GREAT database by 31 May 2014 and if a full text or an abstract was available in either English or German language. We did not consider any other sources of eczema trials besides the GREAT database.

Outcomes

The outcomes of interest were: *i*) the proportion of articles that assessed a QoL outcome, *ii*) the proportion of articles that assessed a PRO, *iii*) whether the inclusion of a QoL measure was related to whether the primary endpoint was a PRO, *iv*) what QoL instruments were used, *v*) the number of QoL instruments per study and *vi*) the number of studies published and the proportion including QoL instruments over time.

A patient-reported outcome (PRO) was defined according to Patrick et al. (12) as any report coming directly from patients, without interpretation by physicians or others, about how they function or feel in relation to a health condition and its therapy. Any outcome used in the included studies that fulfilled this definition was recorded as a PRO. We did not categorize PROs according to content or type. The term 'composite index' was used to describe any score or index that is composed of both a PRO and a non-PRO part.

Data extraction

Data extraction was carried out by D.H. To ensure consistency in the data extraction, guidelines on what information should be gathered and how this information should be evaluated was agreed on beforehand by D.H. and C.A. Where these guidelines were not applicable to certain studies, the whole team decided about how to evaluate the information from those studies. A second data extraction was performed for a random sample of 10% of the papers by J.C. as a measure of quality assurance. For this sample, results were compared between the first and the second data extraction and discrepancies were resolved within the whole team. Where a resolution of a discrepancy within this random sample meant that changes were necessary to the initially extracted information by D.H., these changes were also made in the data extractions of the rest of the studies where applicable. Where the study was reported only in an abstract, only data on QoL was extracted.

Data analysis

Statistical data analysis was split into a descriptive and an analytical part.

Descriptive analysis

We determined the absolute number and the percentage of articles assessing QoL. To get an overview of the most common QoL measures, we recorded which questionnaires were used by how many studies. Moreover, we determined the number of QoL instruments used per article (only regarding articles which assessed QoL) and explored changes in the usage of QoL measures over time, which we visualized in diagrams created with Microsoft Excel.

We also calculated the proportion of PROs (with/without composite indices) in relation to all outcomes, the absolute number and percentage of articles assessing PROs (with/without composite indices) in relation to all articles, the median number (and interquartile range (IQR)) of outcomes per article, the median number (and IQR) of PROs per article (with/without composite indices; only regarding articles which assess PROs) and the number of composite indices per article (only regarding articles which assess composite indices). Furthermore, we analysed changes in the total number of outcomes over time and depicted our findings in a diagram.

Analytical analysis

We hypothesized that authors who are generally in sympathy with the integration of PROs in eczema trials would also be more likely to apply QoL questionnaires. Therefore, we computed the absolute and relative frequency of articles assessing QoL in articles with PROs as primary endpoint, in articles with composite indices as primary endpoint, in articles which did not specify their primary endpoint and in articles with non-PROs as primary endpoint. A chi-square test was conducted to test our hypothesis about the connection between a study's primary endpoint and QoL assessment. The results of this chi-square test were presented in a contingency table. Level of significance was set at 5%.

For all analyses, IBM SPSS 22.0 was used. Data was extracted and figures were designed with Microsoft Excel 2013. We used EndNote X6 to manage references.

RESULTS

Our search yielded 378 papers that were published since 2000 and indexed in the GREAT database by no later than 31 May 2014. References to these papers can be found in Appendix S1[1]. Nineteen articles were not eligible. The reasons for exclusion were: paper was protocol only ($n=9$), no English or German abstract or full text was available ($n=5$), paper reported on a study already included ($n=4$), paper was conference publication and not available as abstract or full text ($n=1$). Of the 359 eligible articles, we were able to obtain the full text for 287 papers, and an abstract only for the remaining 72 articles. The 287 full text papers reported on 303 studies. The distribution of publications over time is shown in Fig. 1. As can be seen from Fig. 1, 2011 saw the highest number of trials. Despite some minor differences, similar numbers of studies were found eligible for every publication year.

Descriptive analysis

Overall, only 63 (20.8%) studies assessed QoL. The QoL instruments that were applied in these studies are listed in Table I for adults and children and families, respectively. In adults, the Dermatology Life Quality Index (DLQI) (15) was the most frequently used self-reported QoL measure; in children, the Children's Dermatology Life Quality Index (CDLQI) (16) was the most popular self-reported questionnaire and the

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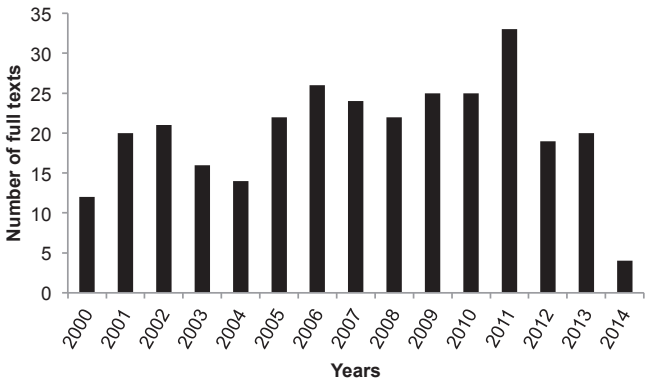


Fig. 1. Distribution of included full text studies over time.

Infants' Dermatitis Quality of Life Index (IDQOL) (17) was the proxy-reported instrument most often used. QoL of carers of children was predominantly assessed with the Dermatitis Family Impact (DFI) questionnaire (18). Altogether, 18 named and 4 unnamed QoL questionnaires were used; of these, 4 were infant- or children-specific measures, 4 assessed the QoL of carers and 16 instruments were applicable to adult patients with eczema. Six instruments, 4 of which are validated, were eczema-specific.

Of the 63 trials that assessed QoL, we found that the majority of studies ($n = 41$, 65.1%) used only one QoL measurement instrument. Two QoL instruments were applied in 16 studies (25.4%) and the remaining 6 studies (9.5%) included 3 QoL measurement instruments. Analysis over time showed that although there were fluctuations from year to year, the proportion of trials that include QoL measures has remained largely static since 2000 (Fig. 2). For instance, none of the 22 studies that were published in 2005 included a QoL instrument whereas studies from 2006 with an inclusion rate of QoL measurement instruments of 31% are even above average. The highest percentage of studies assessing QoL (50%) was observed in 2014; however, this finding needs to be put into context as only 4 studies from 2014 were included in total.

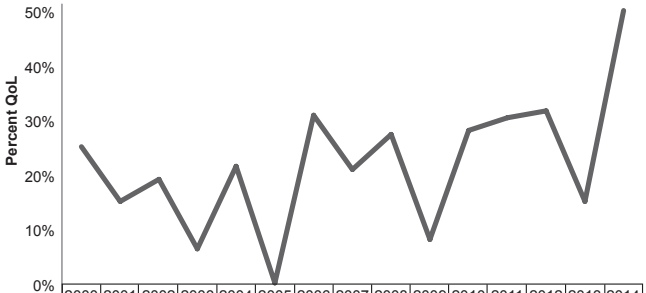
Similarly, we could not observe any clear trends towards increased or reduced usage of the most frequently applied specific QoL instruments (Fig. S1[1]). In most years, less than 10% of the included full texts

Table I. *Quality of life instruments used in adults and children and families/carers*

Instrument, Ref.	Studies *n* (%), Ref.	Type	Full name
*Adults (*n = *36)*			
DLQI (15)	20 (56) (19–38)	Dermatology-specific	Dermatology Life Quality Index
Skindex-29 (39)	2 (6) (40, 41)	Dermatology-specific	
EDLQ (42)	1 (3) (43)	Generic	Everyday Life Questionnaire/Alltagsleben
EQ-5D (44)	1 (3) (45)	Generic	EuroQoL-5D
SF-36 (46)	1 (3) (47)	Generic	Short form 36
SIP (48)	1 (3) (49)	Generic	Sickness Impact Profile
WTP (50)	1 (3) (49)	Generic	Willingness To Pay
DIELH (51)	1 (3) (52)	Dermatology-specific	Deutsches Instrument zur Erfassung der Lebensqualität bei Hauterkrankungen
DLQI (modified)* (15)	1 (3) (53)	Dermatology-specific	Dermatology Life Quality Index
FLQA-d (54)	1 (3) (49)	Dermatology-specific	Freiburg Life Quality Assessment for Dermatoses
ISDL (modified)* (55)	1 (3) (36)	Dermatology-specific	Impact of Chronic Skin Disease on Daily Life
Self-provided*	1 (3) (56)	Dermatology-specific	Unnamed
Skindex-16 (57)	1 (3) (58)	Dermatology-specific	
Skindex-17 (59)	1 (3) (60)	Dermatology-specific	
EDI* (61)	1 (3) (62)	Eczema-specific	Eczema Disability Index
QoLIAD (63)	1 (3) (26)	Eczema-specific	Quality of Life Index for Atopic Dermatitis
Children and families/carers			
Proxy-reported instruments[a] *(*n = *15)*			
IDQOL (17)	14 (93) (36, 64–76)	Eczema-specific	Infants' Dermatitis Quality of Life Index
Self-provided*	1 (7) (77)	Eczema-specific	Unnamed
Self-reported instruments[b] (n = *20)*			
CDLQI (16)	18 (90) (28, 65, 69, 72–75, 78–88)	Dermatology-specific	Children's Dermatology Life Quality Index
CDLQI (modified)* (16)	2 (10) (89, 90)	Dermatology-specific	Children's Dermatology Life Quality Index
*Instruments assessing the quality of life of adult carers of children with eczema (*n = *20)*			
DFI (18)	14 (70) (45, 64–67, 69–73, 81, 86, 87, 91)	Dermatology-specific	Dermatitis Family Impact
Questionnaire by Rüden et al. (92)	3 (15) (43, 93, 94)	Eczema-specific	Unnamed
PIQoL-AD (95)	2 (10) (88, 96)	Eczema-specific	Parents' Index of Quality of Life in Atopic Dermatitis
Self-provided*	1 (5) (83)	Unknown	Unnamed

*Instruments marked with an asterisk have not been validated at all.

[a]Proxy-reported means that the (primary) caregiver of an infant fills in a questionnaire that assesses the quality of life of the infant. Proxy-reported instruments are often used in infants and younger children because they cannot report on their quality of life themselves due to their inability to read and a lack of understanding. [b]Self-reported instruments are used in older children. These questionnaires are filled in by the children themselves, not by their caregiver.



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
% QoL	25%	15%	19%	6%	21%	0%	31%	21%	27%	8%	28%	30%	32%	15%	50%
N	12	20	21	16	14	22	26	24	22	25	25	33	19	20	4

Fig. 2. Percentage of studies assessing quality of life (QoL) over time. N: total number of included studies in the respective year.

applied the DLQI (15), the IDQOL (17), the CDLQI (16) or the DFI (18). In 2014, 25% of the included full texts used the 4 instruments depicted in Fig. S1[1]; however, this result should not be interpreted as a recent rise in usage of these measures since only 4 full texts from 2014 were included in our systematic review.

For the studies which were reported in abstract form only, only 4 out of 72 (6%) assessed QoL. The CDLQI (16) was used in 2 abstracts and the DFI (18) in 1 abstract. Three further QoL instruments were reported, but were not named.

The assessment of the full text articles revealed that a total of 2,633 outcomes were assessed of which 809 (30.7%) were PROs or composite indices (i.e. a scale that is composed of both a PRO and a non-PRO part). Of these, 633 (24.0%) were PROs and 176 (6.7%) were composite indices. The majority of studies (281, 92.7%) included at least one PRO and/or a composite index as any endpoint (primary, secondary, other). A total of 230 (85.9%) studies included at least one PRO, whereas composite indices were assessed in just over half of studies (164, 54.1%).

The median number of outcomes per study was 7 (IQR: 5–11). In studies that assessed PROs and/or composite indices, the median number of PROs was 2 (IQR 1–4). The same values were found when looking at PROs without composite indices. For studies using composite indices, the vast majority of 153 (93.3%) studies included only one composite index, 10 studies (6.1%) two composite indices and only a single study applied 3 composite indices. Analysis over time showed that the median number of outcomes per study has plateaued since 2000. The highest median number of outcomes per study was 9.5 in 2006 whereas the lowest number was 5 in 2013. A median of 6 outcomes was found for 4 years; the same is true for a median of 7 outcomes. In 3 years, the median number of outcomes per study amounted to 8.

Table II. *Association between primary endpoint and assessment of quality of life*

	Primary endpoint				
	PRO	Composite Index	Non-PRO	Not specified	Total
Quality of Life assessed?					
Yes, *n* (%)	14 (43.8)	14 (24.1)	17 (21.0)	18 (13.7)	63 (20.9)
No, *n* (%)	18 (56.3)	44 (75.9)	64 (79.0)	113 (86.3)	239 (79.1)
Total, *n* (%)	32 (100)	58 (100)	81 (100)	131 (100)	302 (100)

χ^2=14.556, p=0.002.
PRO: Patient-reported outcome.

Analytical analysis

We were able to categorise the endpoints for 302 studies: 32 studies (10.6%) chose a PRO as primary endpoint, 58 trials (19.2%) a composite index, 81 studies (26.8%) had a non-PRO as primary endpoint and 131 studies (43.4%) did not specify their primary endpoint. The endpoint for one study could not be categorised.

There was a statistically significant association between the type of primary endpoint (PRO, composite index, non-PRO, not specified) and the assessment of QoL (yes/no) (p=0.002, Table II). Studies with a PRO as primary endpoint were most likely to measure QoL, followed by studies with a composite index as primary endpoint. Likewise, study authors that used a distinct non-PRO as primary endpoint were more likely to include QoL measurement than study authors that did not specify their primary endpoint in more detail.

DISCUSSION

QoL is considered particularly relevant for chronic skin diseases such as eczema. Inclusion of QoL instruments in RCTs is of great importance, given the fact that the patient's perspective on the efficacy of a certain treatment often deviates from clinicians' assessments (97).

Our study demonstrated that the majority of studies (approximately 90%) include at least one PRO. This is in contrast to previous findings that only about 25% of dermatology trials included a participant efficacy outcome (98). However, we did not apply any limitations concerning the type of PRO which may explain these differences. Despite the fact that most studies included a PRO, it was clear from this review that the majority of outcomes (approximately three-quarters) reported are non-PROs.

Even though the QoL of patients and their family is greatly impacted by eczema, respective outcome measures often seem to only play a minor part in eczema trials (99). One study, however, noted a substantial increase in the usage of QoL instruments in eczema trials from 1985 to 2010 (100). We were not able to verify this trend since our findings suggest that the inclusion of QoL measurement instruments has changed very little over time. A reason for this result may be that we looked at the relative frequency of studies assessing QoL instead of absolute numbers, taking into account

the larger quantity of trials in our observation period, compared to the observation period investigated by Rehal & Armstrong (100). Different time intervals in that study and our review may present a further explanation of this discrepancy since the idea of QoL in dermatology emerged in the early 1990s and the development of the first QoL instruments for dermatological conditions falls also in this time period. Consequently, a broader inclusion of QoL measurement instruments in trials did not start until the late 1990s. Rehal & Armstrong (100) reported that 14 different QoL instruments were used in eczema trials from 1985 to 2010. In contrast, we found that from 2000 to 2014, study authors applied 22 different instruments, suggesting a growing number of existing QoL OMIs. Nonetheless, findings on the most frequently applied QoL instruments were similar in both reviews.

The QoL instruments that were mostly used in clinical trials, i.e. the DLQI (15), the IDQOL (17), the CDLQI (16) and the DFI (18), all have been developed at one academic medical centre (see http://www.cardiff.ac.uk/dermatology/quality-of-life/). Reasons for the widespread use of these instruments may be that they are available in many language versions and that they are easy to use. All 4 instruments fit on one A4 page whereas other questionnaires are often longer. A critical review recommends the Skindex-29 (39) rather than the DLQI as dermatology-specific QoL measure (101), but we identified only 2 trials in which it was actually used.

With respect to the lack of "hard" outcomes such as mortality in eczema, QoL measures could fill this gap and provide the necessary evidence to judge the effectiveness and appropriateness of interventions from the patients' perspective. Against this backdrop, it is surprising that only 1 out of 5 eczema trials include QoL instruments, particularly since similar figures are obtained for different diseases in other fields of medicine. For example, one study found that 16% of drug clinical trials published in 2005 in 5 high quality journals included QoL measures (102). However, most of these studies reported on heart disease, cancer or other serious illnesses where "hard" outcomes are available. Authors of future eczema trials should therefore consider the inclusion of a QoL measurement in their trials.

We could show that authors who chose PROs as primary endpoints in their trials were also more likely to include QoL measures than researchers that decided to use any other endpoints. Surprisingly, this observation holds also for composite indices: A significantly higher proportion of studies with a composite index as primary endpoint assessed QoL than did studies with a non-PRO or a not specified endpoint. This implies that the measurement of QoL is not so much dependent on individual characteristics of a trial when opting for or against the inclusion of QoL instruments; instead, the general attitude of study authors towards PROs appears to determine whether or not QoL is measured as well. In addition, this finding may also explain why there was no increase in QoL measurement over time despite ongoing efforts to promote the use of QoL instruments. Moreover, there seems to be an association between how well researchers report on their study results and the measurement of QoL since authors that did not specify their primary endpoint were least likely to use QoL instruments. However, further research is warranted to find out why QoL measurement instruments are not included in more trials.

Some further attention must also be drawn to the high proportion of studies that did not specify their primary endpoint (43.4%). In contrast, Nassar et al. (103) found that only 20% of the RCTs on non-neoplastic skin diseases that were published in 2009 did not state their primary outcome. However, they restricted their search to journals with an impact factor of at least 2. As they also showed that a clear definition of the primary endpoint was significantly associated with a higher journal impact factor, this result may present an explanation for our findings because we did not narrow down our eligibility criteria to high quality journals.

In conclusion, we could demonstrate that a high proportion of trials include some sort of PROs but that QoL was only assessed in about one fifth of all trials. Even though a range of QoL measurement instruments have been used in RCTs of eczema, most studies applied the DLQI (15) for adults, the CDLQI (16) for older children, the IDQOL (17) for infants or the DFI (18) for adult carers of children with eczema.

We provide an up-to-date review on QoL OMIs used for eczema. A strength of this study was the use of the GREAT database, which searches 6 databases, including 3 specialist databases. A recent study showed a high sensitivity of the GREAT database, with 94% of trials cited in systematic reviews on eczema treatments listed in the GREAT database (104). The GREAT database therefore is considered a primary and comprehensive source to identify eczema RCTs. We did not consider any other study designs for inclusion in this systematic review.

Limitations of our study were the language restriction to English and German and our focus on the time interval from 2000 to 2014. In this way, QoL questionnaires in other languages may have been missed or underestimated and older QoL instruments may be underrepresented in our review. Also, we did not consider ongoing trials for this review. As a result, we cannot rule out the possibility that different findings would be obtained when regarding studies that are currently under way.

Results on the number of reported outcomes, the number of reported PROs, the number of reported composite indices, the proportion of validated indices used, the assessment of adverse events and additional safety assessments will be reported elsewhere.

The aim of this systematic review was not to critically appraise the measurement properties of the available QoL scales for eczema patients. Instead, this systematic review is intended to form the basis for further research on the appropriateness of the mentioned QoL instruments for eczema patients. As the use of so many different QoL instruments in eczema trials limits the possibility to synthesize their findings in meta-analyses and systematic reviews, the HOME initiative aims to define a COS including one distinct QoL instrument. A critical appraisal of the measurement properties of existing QoL instruments is the prerequisite for doing so and will be subject to a further systematic review. Our review is the first step to reach the goal of including a QoL instrument in the COS.

Conflict of interest: CA is a member of the HOME executive committee. DH and JC are members of the HOME initiative. The authors declare that they have no further conflicts of interest. The authors did not receive any financial funding to conduct this study.

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SYSTEMATIC REVIEWS

PROTOCOL Open Access

Measurement properties of adult quality-of-life measurement instruments for eczema: protocol for a systematic review

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Abstract

Background: Eczema is a common chronic or chronically relapsing skin disease that has a substantial impact on quality of life (QoL). By means of a consensus-based process, the Harmonising Outcome Measures in Eczema (HOME) initiative has identified QoL as one of the four core outcome domains to be assessed in all eczema trials (Allergy 67(9):1111-7, 2012). Various measurement instruments exist to measure QoL in adults with eczema, but there is a great variability in both content and quality (for example, reliability and validity) of the instruments used, and it is not always clear if the best instrument is being used.
Therefore, the aim of the proposed research is a comprehensive systematic assessment of the measurement properties of the existing measurement instruments that were developed and/or validated for the measurement of patient-reported QoL in adults with eczema.

Methods/Design: This study is a systematic review of the measurement properties of patient-reported measures of QoL developed and/or validated for adults with eczema. Medline via PubMed and EMBASE will be searched using a selection of relevant search terms. Eligible studies will be primary empirical studies evaluating, describing, or comparing measurement properties of QoL instruments for adult patients with eczema. Eligibility assessment and data abstraction will be performed independently by two reviewers. Evidence tables will be generated for study characteristics, instrument characteristics, measurement properties, and interpretability. The quality of the measurement properties will be assessed using predefined criteria. Methodological quality of studies will be assessed using the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist. A best evidence synthesis will be undertaken if more than one study has investigated a particular measurement property.

Discussion: The proposed systematic review will produce a comprehensive assessment of measurement properties of existing QoL instruments in adult patients with eczema. We aim to identify one best currently available instrument to measure QoL in eczema patients.

Systematic review registration: PROSPERO CRD42015017138.

Keywords: Eczema, Measurement instruments, Health-related quality of life, Quality of life, Validity, Reliability, Responsiveness, Interpretability

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Background

Eczema (synonymous with atopic eczema, atopic dermatitis) is an important medical condition not only in children but also in adults. The prevalence of eczema in adults is estimated at 1% to 3% [1]. Various different interventions exist, many of which have been assessed in randomized controlled trials. Due to substantial variation in eczema outcome measures in trials, interventions are not comparable. The lack of standardization of eczema outcome measures currently renders truly evidence-based decision making difficult, if not impossible.

A multi-perspective Delphi study [2] conducted by the initiators of the Harmonising Outcome Measures in Eczema (HOME) initiative [3] defined clinical signs measured by means of a physician-assessed instrument, symptoms of eczema, and the long-term course of eczema as the core outcome domains to be applied in all future eczema trials. At the HOME II meeting in Amsterdam in 2011, the international community confirmed these core outcome measures and also added quality of life (QoL) to the core set of outcome domains [4]. The next crucial step in the process of standardizing eczema outcome measurements is to identify appropriate instruments to measure each of the four core outcome domains of atopic eczema. There was broad international consensus among clinicians, patients, and methodologists that the Outcome Measures in Rheumatology (OMERACT) quality criteria 'Truth, Discrimination, and Feasibility' [5] need to be met for eczema outcome measures to be recommended by the HOME initiative [4].

Objectives

1. To systematically assess the measurement properties of patient-reported measurement instruments of QoL for adults with eczema
2. To identify outcome measurement instruments for QoL in adults with eczema
   2.a. that meet the predefined criteria to be recommended [4,5] for the measurement of QoL in future eczema trials
   2.b. that have the potential to be recommended in the future depending on the results of further validation studies
   2.c. that do not meet the predefined criteria to be recommended [4,5] and therefore should not be used any more.
3. To provide the evidence base
   3.a. for an international consensus process to further standardize the assessment of QoL in adults with eczema in clinical trials.
   3.b. for an international consensus process to prioritize further research concerning QoL assessment in adults with eczema.

Methods/Design

Protocol and registration

The methods for this systematic review have been developed according to recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyes Protocols (PRISMA-P) statement [6]. This protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO): CRD42015017138.

Literature search

A systematic literature search will be performed in PubMed and EMBASE. The search strategy will contain blocks of search terms related to the following aspects:

1. construct of interest: quality of life
2. target population: (atopic) eczema (cf Table 1).
3. measurement properties: the precise PubMed search filter for finding studies on measurement properties developed by Terwee *et al*. will be used to identify relevant articles [7]. This filter has a sensitivity of 93.1% and a precision of 9.4%.
4. interpretability

The entire search strategy is available as an Additional file 1 to this protocol.

The systematic electronic search will be supplemented by hand searching of reference lists of studies included

Table 1 Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	Eczema (synonyms: atopic eczema, atopic dermatitis, neurodermatitis)	Populations with other skin diseases than eczema, populations of children with eczema, and populations of adolescents with eczema
Study design	Development study, validation study	Linguistic validation studies
Outcome	Quality of life, health-related quality of life	Signs, disease severity measure, disease control measure, biomarker, and physiology of the skin
Type of measurement instrument	Self-reported measurement instrument	All others
Publication type	Articles with available full text	Abstracts

and key articles on this topic. Furthermore, an additional search will be performed in each database, including the names of the instruments which are found in the initial search. The PROQOLID (www.proqolid.org) database will be searched.

Eligible measurement instruments

Eligible measurement instruments will include all patient-reported measurement instruments which were designed and/or validated to measure QoL in adults with eczema.

Eligible studies

A study will be included if it is published as a full-text paper and concerns the development ('development paper') and/or evaluation of the measurement properties ('validation paper') of instruments that measure QoL or health-related quality of life (HrQoL) in adult people with eczema. A study with a mixed patient sample will be eligible either if it presents a subgroup analysis for adult patients with atopic eczema or if adult patients with atopic eczema constitute at least 50% of the study population. The measurement instrument must be a self-reported questionnaire. Articles that report indirect evidence, for instance, by using data obtained within the context of a clinical trial, will not be considered eligible. Articles assessing the measurement properties of dermatology-specific instruments in non-eczema samples will not be considered eligible.

Study selection

Two reviewers will independently judge titles and abstracts retrieved in the literature search and, at a second stage, full-text articles for eligibility (Table 1). Disagreements will be resolved by discussion with all reviewers.

Assessment of the methodological quality of included studies

The COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) checklist [8-10] will be used to evaluate the methodological quality of included studies. In the COSMIN checklist (cf www.cosmin.nl), four domains are distinguished (reliability, validity, responsiveness, and interpretability) with related measurement properties and aspects of measurement properties. These are listed in Table 2 (adapted from [8]).

For each of the measurement properties, the COSMIN checklist consists of 5 to 18 items covering methodological standards (organized in nine boxes for the nine measurement properties). In addition, each item can be scored on a four-point rating scale (that is, 'poor,' 'fair,' 'good,' 'excellent'). Taking the lowest rating for each item in one box, an overall quality score ('poor,' 'fair,' 'good,' 'excellent') is obtained for each measurement property separately.

The measurement property 'criterion validity' will not be considered for the purpose of this systematic review since no gold standard exists for QoL.

Data abstraction

Relevant data from all included articles will be summarized in evidence tables. The evidence table will be drafted and pilot tested. Data from each article included will be abstracted independently by two reviewers. All reviewers will participate in this process and will work in pairs on defined sets of articles. Disagreements will be resolved by discussion of all reviewers.

Evidence tables will include the following: reference, geographical location, language, setting, study type, key characteristics of study subjects, name of measure, domains measured, number of items and (sub)scales, number and type of response categories, recall period in the questions, scoring algorithm, time needed for administration, mode of administration, target population for whom the questionnaire was originally developed, how a full copy of the questionnaire can be obtained, the instructions given to those who complete the questionnaire, the available versions and translations of the questionnaire, results of the measurement properties, all items from the COSMIN box Generalisability, and all items from the COSMIN box Interpretability [8,9].

If general characteristics of an instrument (that is, name of measure, number of items and (sub)scales, number and type of response categories, recall period in the questions, scoring algorithm, time needed for administration, mode of administration, target population for whom the questionnaire was originally developed, how a full copy of the questionnaire can be obtained, the instructions given to those who complete the questionnaire, the available versions and translations of the questionnaire) cannot be extracted from the studies included, the original development paper may be consulted to obtain missing information.

Content comparison

An overview of the content of each instrument on item level will be presented in order to visualize which content is covered by the different instruments. The original development paper is going to be consulted to obtain this information.

Quality assessment of the measurement instruments

The predefined criteria for rating the quality of measure recommended by the COSMIN group will be used [11] (cf Table 3). These criteria are in accordance with the OMERACT filter [5] which has been adopted by the HOME initiative [4] and the criteria applied in a previous review on atopic eczema outcome measures [12] (Table 3).

Table 2 Definitions of domains, measurement properties, and aspects of measurement properties

Domain	Measurement property	Aspect of a measurement property	Definition
Reliability			The degree to which the measurement is free from measurement error
Reliability (extended definition)			The extent to which scores for patients who have not changed are the same for repeated measurement under several conditions: for example, using different sets of items from the same HR-PROs (internal consistency) over time (test-retest) by different persons on the same occasion (inter-rater) or by the same persons (that is, raters or responders) on different occasions (intra-rater)
	Internal consistency		The degree of interrelatedness among the items
	Reliability		The proportion of total variance in the measurements which is because of 'true'[a] differences among patients
	Measurement error		The systematic and random error of a patient's score that is not attributed to true change of the construct to be measured
Validity			The degree to which an HR-PRO instrument measures the construct(s) it purports to measure
	Content validity		The degree to which the content of an HR-PRO instrument is an adequate reflection of the construct to be measured
		Face validity	The degree to which (the items of) an HR-PRO instrument indeed looks as though they are an adequate reflection of the construct to be measured
	Construct validity		The degree to which the scores of an HR-PRO instrument are consistent with hypotheses (for instance with regard to internal relationships, relationships to scores of other instruments, or differences between relevant groups) based on the assumption that the HR-PRO instrument validly measures the construct to be measured
		Structural validity	The degree to which the scores of an HR-PRO instrument are an adequate reflection of the dimensionality of the construct to be measured
		Hypothesis testing	Idem construct validity
		Cross-cultural validity	The degree to which the performance of the items on a translated or culturally adapted HR-PRO instrument is an adequate reflection of the performance of the items of the original version of the HR-PRO instrument
Responsiveness			The ability of an HR-PRO instrument to detect change over time in the construct to be measured
	Responsiveness		Idem responsiveness
Interpretability[b]			The degree to which one can assign qualitative meaning - that is, clinical or commonly understood connotations - to an instrument's quantitative scores or changes in scores

Abbreviations: *HR-PROs* health related patient-reported outcomes, *CTT* classical test theory. [a]The word 'true' must be seen in the context of the CTT, which states that any observation is composed of two components - a true score and error associated with the observation. 'True' is the average score that would be obtained if the scale were given an infinite number of times. It refers only to the consistency of the score and not to its accuracy [14]. [b]Interpretability is not considered a measurement property but an important characteristic of a measurement instrument.

Best evidence synthesis

If an instrument has been evaluated in different studies, findings will be synthesized if the characteristics of the included studies are sufficiently similar and if the results of the studies do not show too different or conflicting findings and if the methodological quality of the included studies is sufficient [13]. The criteria for best evidence synthesis are outlined in Table 4.

Generating recommendations for the use of QoL measurement instruments for eczema

For each instrument identified in the review, a standardized recommendation for usage or required future validation work will be made depending on the quality of the instrument and on the methodological quality of included studies (cf Table 5). According to the results of the HOME II meeting [4], all three criteria of the OMERACT filter [5], that is, truth, discrimination, and feasibility, have to be met by an outcome measure to be recommended by the HOME initiative.

Four categories of recommendation will be made:

1. QoL measurement instrument meets all requirements and is recommended for use.
2. QoL measure meets two or more quality items, but performance in all other required quality items is unclear, so that the outcome measure has the potential to be recommended in the future depending on the results of further validation studies.

Table 3 Quality criteria for measurement properties adapted from [11] and [15]

Property	Rating	Quality criteria
Reliability		
Internal consistency	+	Cronbach's alpha(s) ≥ 0.70
	?	Dimensionality not known OR Cronbach's alpha not determined
	–	Cronbach's alpha(s) < 0.70
	+	MIC > SDC OR MIC outside the LOA
	?	MIC not defined
	–	MIC ≤ SDC OR MIC equals or inside LOA
Reliability	+	ICC/weighted Kappa ≥ 0.70, OR Pearson's *r* ≥ 0.80
	?	Neither ICC/weighted Kappa nor Pearson's *r* determined
	–	ICC/weighted Kappa < 0.70 OR Pearson's *r* < 0.80
Validity		
Content validity	+	All items are considered to be relevant for the construct to be measured, for the target population, and for the purpose of the measurement, AND the questionnaire is considered to be comprehensive
	?	Not enough information available
	–	Not all items are considered to be relevant for the construct to be measured, for the target population, and for the purpose of the measurement, OR the questionnaire is considered not to be comprehensive
Construct validity		
Structural validity	+	Factors should explain at least 50% of the variance
	?	Explained variance not mentioned
	–	Factors explain <50% of the variance
Structural validity (IRT methods applied)	+	Residual correlations among the items after controlling for the dominant factor <0.20 OR Q3's < 0.37, item scalability >0.30, IRT model fit: G2 > 0.01, no DIF for important subject characteristics (such as age, gender, education): McFadden's R2 < 0.02
	?	Important characteristics not reported
	–	Residual correlations among the items after controlling for the dominant factor ≥0.20 OR Q3's ≥ 0.37, item scalability ≤0.30, IRT model fit: G2 ≤ 0.01, important DIF for important subject characteristics (such as age, gender, education): McFadden's R2 ≥ 0.02
Hypothesis testing	+	Correlation with an instrument measuring the same construct ≥0.50 OR at least 75% of the results are in accordance with the hypotheses, AND correlation with related constructs is higher than with unrelated constructs
	?	Solely correlations determined with unrelated constructs
	–	Correlation with an instrument measuring the same construct <0.50 OR <75% of the results are in accordance with the hypotheses OR correlation with related constructs is lower than with unrelated constructs
Cross-cultural validity	+	No differences in factor structure OR no important DIF between language versions
	?	Multiple group factor analysis not applied AND DIF not assessed
	–	Differences in factor structure OR important DIF between language versions
Responsiveness		
Responsiveness	+	Correlation with changes on instruments measuring the same construct ≥0.50 OR at least 75% of the results are in accordance with the hypotheses OR AUC ≥ 0.70, AND correlations with changes in related constructs are higher than with unrelated constructs
	?	Solely correlations determined with unrelated constructs
	–	Correlations with changes on instruments measuring the same construct <0.50, OR <75% of the results are in accordance with the hypotheses, OR AUC < 0.70, OR correlations with changes in related constructs are lower than with unrelated constructs
Interpretability	+	MIC calculated and anchor questions clearly described
	?	MIC calculated but anchor questions not clearly labelled
	–	MIC not reported

MIC: minimal important change, SDC: smallest detectable change, LOA: limits of agreement, ICC: intraclass correlation coefficient, AUC: area under the curve. +positive rating, ? indeterminate rating, –negative rating.

Table 4 Levels of evidence for the overall quality of a measurement property [16]

Level	Rating	Criteria
Strong	+++ or −−−	Consistent findings in multiple studies of good methodological quality OR in one study of excellent methodological quality
Moderate	++ or −−	Consistent findings in multiple studies of fair methodological quality OR in one study of good methodological quality
Limited	+ or −	One study of fair methodological quality
Conflicting	+/−	Conflicting findings
Unknown	?	Only studies of poor methodological quality

+positive rating, ? indeterminate rating, −negative rating.

3. QoL measure has low quality in at least one required quality criterion (≥1 rating of 'minus') and therefore is not recommended to be used any more.
4. QoL measure has (almost) not been validated. Its performance in all or most relevant quality items is unclear so that it is not recommended to be used until further validation studies clarify its quality.

Finally, we aim to identify one best (currently available) instrument to assess QoL in adult eczema.

Discussion

The proposed systematic review will yield a comprehensive assessment of measurement properties of existing QoL instruments in adult patients with eczema. We aim to arrive at a recommendation of one best instrument to measure QoL in eczema patients. The processes underlying this systematic review are transparent and systematic. Quality assurance is achieved by involving two independent reviewers at each stage. A strength of the proposed research is the international coverage of the contributing reviewers. This will increase the credibility of any findings. However, coordinating work packages between many reviewers is certainly a challenge. Whether or not we will be able to reach the goal of recommending one best instrument is unclear. It may well be that no instrument will meet all the filter criteria or that several instruments will meet them. In any case, the findings of this systematic review will inform a consensus-finding process at the fourth meeting of the HOME initiative (HOME IV) that will take place in Malmö, Sweden, in April 2015. Based on the findings of this work, we hope to be able to inform group discussion and consensus voting with the ultimate goal to endorse one instrument to be included in the core set of outcome measurement instruments for eczema. If instruments lack important requirements, for instance, in relation to responsiveness or feasibility, further validation work will need to be done before a QoL instrument can be included in the core set.

Table 5 Quality criteria required for recommendation of QoL measures for eczema

Quality item (name)	Inclusion in OMERACT filter	Required rating for recommendation
Content validity	Truth	+
Structural validity	Truth	+
Hypotheses testing	Truth	+
Cross-cultural validity	Truth	+
Internal consistency	Discrimination	+
Reliability	Discrimination	+
Measurement error	Discrimination	+
Responsiveness	Discrimination	+
Interpretability	Feasibility	+

Additional file

Additional file 1: Search strings. The search strings for Medline (via PubMed) and EMBASE.

Abbreviations

COSMIN: COnsensus-based Standards for the selection of health Measurement INstruments; *HrQoL*: health-related quality of life; *PRO*: patient-reported outcome; QoL: quality of life.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

CA initiated the protocol, conceptualized the research plan for the proposed systematic review, wrote the manuscript, and reviewed it for important intellectual content. DH conceptualized the research plan for the proposed systematic review, wrote the manuscript, and reviewed it for important intellectual content. CP wrote the manuscript and reviewed it for important intellectual content. SD helped with the methodology section and reviewed the manuscript for important intellectual content. JC reviewed the manuscript for important intellectual content. RO helped with the methodology section and reviewed the manuscript for important intellectual content. RH reviewed the manuscript for important intellectual content. TS reviewed the manuscript for important intellectual content. SC reviewed the manuscript for important intellectual content. JS conceptualized the research plan for the proposed systematic review and reviewed it for important intellectual content. All authors read and approved the final manuscript.

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Measurement properties of adult quality-of-life measurement instruments for eczema: a systematic review

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core outcome set; eczema; Harmonising Outcome Measures for Eczema initiative; measurement properties; quality of life.

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Abstract

Background: The Harmonising Outcome Measures for Eczema (HOME) initiative has identified quality of life (QoL) as a core outcome domain to be evaluated in every eczema trial. It is unclear which of the existing QoL instruments is most appropriate for this domain. Thus, the aim of this review was to systematically assess the measurement properties of existing measurement instruments developed and/or validated for the measurement of QoL in adult eczema.

Methods: We conducted a systematic literature search in PubMed and Embase identifying studies on measurement properties of adult eczema QoL instruments. For all eligible studies, we assessed the adequacy of the measurement properties and the methodological quality with the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist. A best evidence synthesis summarizing findings from different studies was the basis to assign four degrees of recommendation (A–D).

Results: A total of 15 articles reporting on 17 instruments were included. No instrument fulfilled the criteria for category A. Six instruments were placed in category B, meaning that they have the potential to be recommended depending on the results of further validation studies. Three instruments had poor adequacy in at least one required adequacy criterion and were therefore put in category C. The remaining eight instruments were minimally validated and were thus placed in category D.

Conclusions: Currently, no QoL instrument can be recommended for use in adult eczema. The Quality of Life Index for Atopic Dermatitis (QoLIAD) and the Dermatology Life Quality Index (DLQI) are recommended for further validation research.

Abbreviations
COS, Core outcome set; COSMIN, COnsensus-based Standards for the selection of health Measurement INstruments; DIF, Differential item functioning; HOME, Harmonising Outcome Measures for Eczema; HrQoL, health-related quality of life; ICC, Intraclass Correlation Coefficient; IRT, Item response theory; MIC, Minimal important change; MID, Minimal important difference; OMERACT, Outcome Measures in Rheumatology; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QoL, quality of life.

Eczema (synonymous with atopic eczema, atopic dermatitis) is a common, chronic, relapsing skin disease that affects both children and adults. Recent studies suggest that eczema prevalence rates in adults are in excess of 10% (1, 2). There are numerous treatments for eczema, many of which have been studied in randomized controlled trials. However, the lack of standardization of eczema outcome measurement instruments in clinical trials currently limits the possibility to compare and synthesize results in order to determine the best treatments, hampering evidence-based decision-making and rendering the generation of treatment recommendations difficult.

Therefore, the Harmonising Outcome Measures for Eczema (HOME) initiative (www.homeforeczema.org) set out to define a core outcome set (COS) to be applied in all future eczema trials. A COS is an agreed minimum set of outcomes that should be measured and reported in all clinical trials of a specific disease or trial population (3). Clinical signs, symptoms, long-term control of flares and quality of life (QoL) have been identified as the core outcome domains by the HOME initiative (4–6).

In accordance with the HOME roadmap (7), we set out to perform a systematic review of the measurement properties of all instruments that were developed and validated to measure QoL in eczema patients.

Methods

Protocol and registration

This systematic review was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (8). A study protocol was published beforehand (9) and has also been registered in the International Prospective Register of Systematic Reviews (PROSPERO): CRD42015017138.

Literature search

On 9 January 2015, we performed a systematic literature search in PubMed and EMBASE, as described in detail in the previously published protocol (9).

It was supplemented by hand searching of reference lists of included studies and key articles on this topic. We also searched the PROQOLID database (http://www.proqolid.org).

Eligible studies

The eligibility criteria laid out in the protocol were applied (9). In accordance with a consensus-based decision of the HOME initiative (10), only disease- or dermatology-specific, and not generic QoL measurement instruments, were eligible.

Assessment of the methodological quality of included studies

The COnsensus-based standards for the selection of health Measurement INstruments (COSMIN) checklist was used to evaluate the methodological quality of the included studies (11–14).

Assessment of measurement properties and further characteristics of QoL instruments

We assessed all measurement properties from the COSMIN checklist in this review, with the exception of criterion validity since no gold standard exists for QoL. Interpretability and feasibility data were collected where available. With the exception of content comparison and instrument characteristics, we regarded different language versions of the same questionnaire separately because we consider these to be distinct instruments. Our main reason for this approach was the fact that it cannot be assumed that different language versions of measurement instruments show the same measurement properties. Strictly speaking, it is the measurements that are valid, reliable and responsive and not the instruments *per se*.

Content comparison

We compared the content of each instrument at content domain level. In QoL questionnaires, subsets of items belonging together based on their content are often referred to as content domains. The original development paper for each instrument was consulted to obtain this information. We largely adopted the domains mentioned therein.

Adequacy of the measurement properties

The predefined criteria for rating the adequacy of measurement properties recommended by the COSMIN group were used in a slightly modified version (15) (Table 1). Hypothesis testing was split into the aspects convergent/divergent [defined as the correlation between instruments measuring similar/different constructs (16)] and discriminative validity [defined as the ability of a measurement instrument to distinguish between different subgroups of patients (16)] throughout the review. Findings from both aspects were integrated into an overall rating in the end (see also 'Differences between protocol and review'). Where studies applied item response theory (IRT) methods in the evaluation of measurement properties, rather than in the development of measurement instruments, we were able to evaluate the adequacy and methodological quality for internal consistency, construct validity, structural validity and cross-cultural validity.

Best evidence synthesis

Where an instrument was evaluated in multiple studies, the findings were synthesized provided the characteristics of the included studies were sufficiently similar and the methodological quality of the included studies was sufficient (18). The criteria for best evidence synthesis are outlined in Table 2.

Table 1 Adequacy criteria for measurement properties adapted from (15) and (17)

Property	Rating	Adequacy criteria
Reliability		
Internal consistency	+	Cronbach's alpha(s) ≥0.70
(CTT methods applied)	?	Cronbach's alpha not determined
	−	Cronbach's alpha(s) <0.70
Internal consistency	+	Person Separation Index ≥0.70
(IRT methods applied)	?	Person Separation Index not determined
	−	Person Separation Index <0.70
Measurement error	+	MIC > SDC OR MIC outside the LoA
	?	MIC not defined
	−	MIC ≤ SDC OR MIC equals or inside LoA
Reliability	+	ICC/weighted Kappa ≥0.70, OR Pearson's $r \geq 0.80$
	?	Neither ICC/weighted Kappa, nor Pearson's r determined
	−	ICC/weighted Kappa < 0.70 OR Pearson's $r < 0.80$
Validity		
Content validity	+	All items are considered to be relevant for the construct to be measured, for the target population, and for the purpose of the measurement AND the questionnaire is considered to be comprehensive
	?	Not enough information available
	−	Not all items are considered to be relevant for the construct to be measured, for the target population and for the purpose of the measurement OR the questionnaire is considered not to be comprehensive
Construct validity		
Structural validity	+	Factors should explain at least 50% of the variance
(CTT methods applied)	?	Explained variance not mentioned
	−	Factors explain < 50% of the variance
Structural validity	+	Residual correlations among the items after controlling for the dominant factor < 0.20 OR Q3's < 0.37, item scalability >0.30, IRT model fit: G2 > 0.01, no DIF for important subject characteristics (such as age, gender, education): McFadden's R2 < 0.02, OR no nonuniform DIF
(IRT methods applied)	?	Important statistics not reported
	−	Residual correlations among the items after controlling for the dominant factor ≥0.20 OR Q3's ≥0.37, item scalability ≤0.30, IRT model fit: G2 ≤ 0.01, important DIF for important subject characteristics (such as age, gender, education): McFadden's R2 ≥ 0.02, OR nonuniform DIF
Hypothesis testing	+	Correlations with instruments measuring the same construct ≥ 0.50 OR at least 75% of the results are in accordance with the hypotheses AND correlation with related constructs is higher than with unrelated constructs
(convergent/divergent validity)	?	Solely correlations determined with unrelated constructs
	−	Correlations with instruments measuring the same construct <0.50 OR < 75% of the results are in accordance with the hypotheses OR correlation with related constructs is lower than with unrelated constructs
Hypothesis testing	+	Differences in scores on the measurement instrument for all evaluated patient subgroups are statistically significant OR ≥75% of results in accordance with hypotheses
(discriminative validity)	?	Some differences statistically significant, others not
	−	Differences in scores on the measurement instrument for all evaluated patient subgroups are not statistically significant OR <75% of results in accordance with hypotheses
Cross-cultural validity	+	No differences in factor structure OR no important DIF between language versions
	?	Multiple group factor analysis not applied AND DIF not assessed
	−	Differences in factor structure OR important DIF between language versions
Responsiveness		
Responsiveness	+	Correlation with changes on instruments measuring the same construct ≥0.50 OR at least 75% of the results are in accordance with the hypotheses OR AUC ≥0.70 AND correlations with changes in related constructs are higher than with unrelated constructs
	?	Solely correlations determined with unrelated constructs
	−	Correlations with changes on instruments measuring the same construct <0.50 OR < 75% of the results are in accordance with the hypotheses OR AUC < 0.70 OR correlations with changes in related constructs are lower than with unrelated constructs

DIF, Differential item functioning; ICC, Intraclass correlation coefficient; IRT, Item response theory; LoA, Limits of agreement; MIC, Minimal important change; SDC, Smallest detectable change; +, positive rating; ?, indeterminate rating; −, negative rating.

Table 2 Levels of evidence for the overall adequacy of a measurement property, adapted from (19)

Level	Rating	Criteria
Strong	+++, ? (strong) or −−−	Consistent findings in multiple studies of good methodological quality OR in one study of excellent methodological quality
Moderate	++, ? (moderate) or −−	Consistent findings in multiple studies of fair methodological quality OR in one study of good methodological quality
Limited	+, ? (limited) or −	One study of fair methodological quality
Conflicting	+/−	Conflicting findings
Unknown	Weak	Only studies of poor methodological quality

+, positive rating; ?, indeterminate rating; −, negative rating.

Generating recommendations for the use of QoL measurement instruments for eczema

For each reviewed instrument, a standardized recommendation for usage or required future validation work was made depending on the adequacy of the instrument and the methodological quality of the included studies.

Four categories of recommendation were made (9):

(A) QoL measurement instrument meets all requirements and is recommended for use.

(B) QoL measure meets two or more adequacy items, but performance in all other required adequacy items is unclear, so that the outcome measure has the potential to be recommended in the future depending on the results of further validation studies.

(C) QoL measure has low adequacy in at least one required adequacy criterion (≥1 rating of 'minus') and therefore is not recommended to be used any more.

(D) QoL measure has (almost) not been validated. Its performance in all or most relevant adequacy items is unclear so that it is not recommended to be used until further validation studies clarify its adequacy.

Finally, we aimed to identify one most appropriate (currently available) instrument to assess QoL in adults with eczema.

Differences between protocol and review

In this manuscript, we specified that generic instruments are not eligible for our review. Unlike what was planned in the original protocol (9), we did not perform a content comparison at item level because the resulting comparison table would have been too large and thus not informative. Instead, we compared the content of the different QoL instruments at content domain level.

For reasons of clarity, we decided to use the term 'adequacy of the measurement properties' instead of 'quality of the measurement properties'. For studies applying IRT methods, only internal consistency, construct validity, structural and cross-cultural validity were evaluated, if applicable. In addition, as the review was conducted, it was clear that some minor alterations were required to the adequacy criteria presented in Table 3 of the protocol and Table 1 of this review, respectively:

- For internal consistency, the indeterminate rating ('?') was changed from 'Dimensionality not known OR Cronbach's alpha not determined' to 'Cronbach's alpha not determined' in order to avoid redundancy between the adequacy criteria and the COSMIN criteria for methodological quality. Adequacy criteria for IRT methods were added.
- Although the adequacy criteria for content validity refer to a questionnaire's target population (which may be other than eczema), we applied the same inclusion criteria for content validity studies like for the other measurement properties, that is at least 50% eczema patients in the sample or subgroup analysis for eczema patients presented, because we were interested in the instruments' content validity in eczema patients.
- The IRT criteria for structural validity were amended with information on differential item functioning (DIF) (20). A positive rating can now also be obtained if a study shows that there is no nonuniform DIF. Occurrence of nonuniform DIF results in a negative rating according to the new criteria.
- The criteria suggested by Terwee et al. (15) for hypothesis testing were only applied to convergent and divergent validity. Self-developed criteria for discriminative validity, which is another aspect of hypothesis testing, were added. The adequacy criteria for interpretability were omitted since interpretability is not considered to be a formal measurement property by the COSMIN initiative (12).

The best evidence synthesis ratings were complemented by an indeterminate rating for strong, moderate and limited levels of evidence each. This was done for scenarios where a QoL instrument would obtain an indeterminate rating for a certain measurement property. An indeterminate rating was assigned where no clear evidence was available for either a positive or negative rating.

In order to obtain an overall rating for hypothesis testing, findings from best evidence synthesis for convergent/divergent and discriminative validity were synthesized according to the following criteria: in case of conflicting ratings, the worse rating determined the overall rating for hypothesis testing; if either convergent/divergent or discriminative validity obtained an indeterminate rating, the rating for the other

Table 3 Comparison of the content of the different QoL instruments on content domain level

Domain	DIELH	DLQI	FLQA-c	FLQA-d	ISDL*	QoLIAD	Skindex-29†
Symptoms	X	X	X	X	X		X
Emotions	X	X	X	X	X		X
Activities of daily living	X	X	X	X	X		
Leisure	X	X					
Work/study	X	X					
Social life	X	X	X	X	X		
Treatment	X	X	X	X			
Functioning							X
Satisfaction			X	X			
Stigmatization					X		
Illness cognitions					X		
Need for mental and emotional stimulation						X	
Need for physical and emotional stability						X	
Need for security						X	
Need to share and belong						X	
Esteem needs						X	
Need for personal development and fulfilment						X	

DIELH, Deutsches Instrument zur Erfassung der Lebensqualität bei Hauterkrankungen; DLQI, Dermatology Life Quality Index; FLQA-c, Freiburg Life Quality Assessment core module; FLQA-d, Freiburg Life Quality Assessment for Dermatoses; ISDL, Impact of Chronic Skin Disease on Daily Life; QoLIAD, Quality of Life Index for Atopic Dermatitis.

*The ISDL distinguishes several higher level domains that contain a number of subordinate domains each. The subordinate domains were used for this content comparison. The exact domains are (subordinate domains in brackets): physical functioning (skin status; physical symptoms of itch, pain and fatigue; scratch response), psychological functioning (anxiety; negative mood; positive mood), stressors (disease impact on daily life; stigmatization), illness cognitions (helplessness; acceptance; perceived benefits), social support (perceived support; social network).

†Content comparison of Skindex-29 is based on dimensions empirically derived from factor analysis and not on content-related domains.

aspect of hypothesis testing determined the overall rating for hypothesis testing.

Results

In total, we found 16 eligible articles (21–36) (Fig. 1). Of these, we were able to obtain 15 full-text papers. One manuscript pertaining to the Ukrainian versions of the Dermatology Life Quality Index (DLQI) and the Skindex-16 could not be procured and was thus excluded (25).

Most of the included studies reported on the DLQI ($n = 6$) (23, 24, 28–30, 35) and the Quality of Life Index for Atopic Dermatitis (QoLIAD, $n = 3$) (31, 34, 36). Two studies presented information on the Deutsches Instrument zur Erfassung der Lebensqualität bei Hauterkrankungen (DIELH) (32, 33). Skindex-29 was evaluated in two studies (22, 26). One study each was available for the Freiburg Life Quality Assessment core module (FLQA-c) (21), the Freiburg Life Quality Assessment for Dermatoses (FLQA-d) (23) and the Impact of Chronic Skin Disease on Daily Life (ISDL) (27). An overview of the content of these different instruments is shown in Table 3. Symptoms and emotions are captured by six out of seven questionnaires, whereas all other content domains are included in a lower number of instruments. Four instruments (DIELH, DLQI, FLQA-c, and FLQA-d) share the most content domains, whereas the QoLIAD does not have any content domain in common with the other QoL instruments. Other characteristics of the included instruments are shown in Table 4. The number of items ranges from 10 to 54. Almost all instruments use a 4- or 5-point Likert scale. Only the ISDL applies a visual analogue scale (VAS) in addition, whereas the QoLIAD has a dichotomous response format.

Characteristics of the included studies

Table 5 contains information on the settings and the study populations in the included studies. All included studies were conducted in Europe with the exception of the validation studies of the US versions of the QoLIAD and the Skindex-29. Most studies recruited their participants in a secondary care setting, while primary care patients were included in only two studies. Additionally, there was significant variation with respect to sample size, with 15 patients being the smallest and 286 patients the largest sample size of a single study.

Validity of the instruments and recommendations

The number of studies assessing the different measurement properties of each QoL instrument identified is given in Table 6. From the 15 included studies, we were able to rate the methodological quality of 67 measurement properties. One measurement property (1%) was rated as having excellent, 18 (27%) as having good, 31 (46%) as having fair and 17 (25%) as having poor methodological quality according

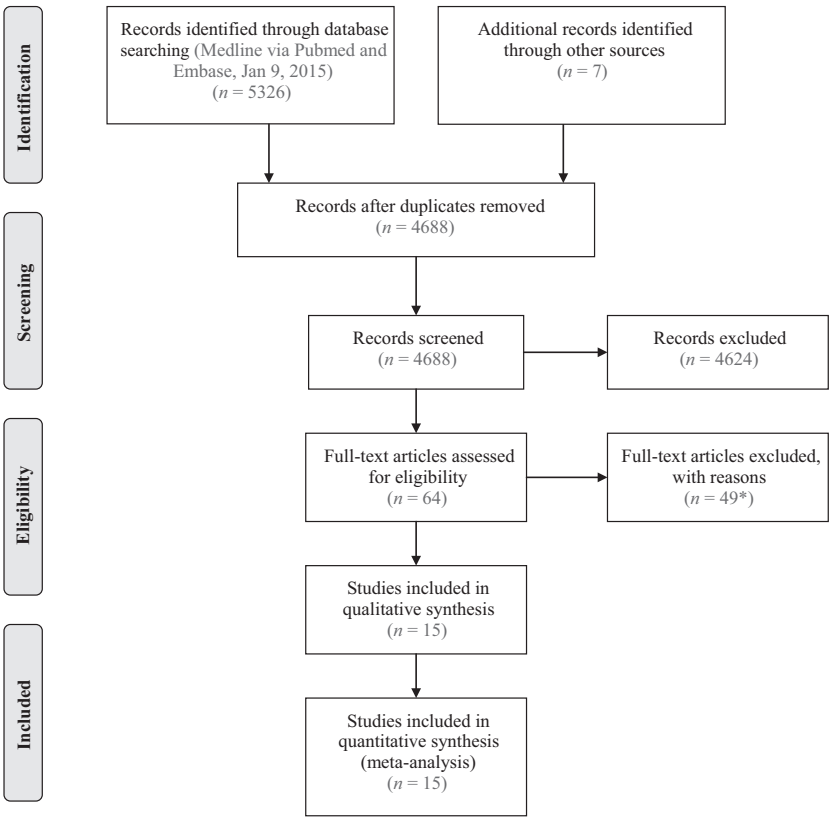

Figure 1 Diagram of article flow during literature search and article screening according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards. *One article was found eligible, but could not be procured and was thus excluded.

to the COSMIN checklist. Our synthesis of the results and level of evidence for the properties of each instrument is presented in Table 7. There was no instrument for which all measurement properties of interest have been examined. As a result, none of the instruments complied with all of our prespecified requirements of truth, discrimination and feasibility. Detailed results for every single instrument and study included are available as an Appendix S1 to this publication (Tables S1–S55).

Internal consistency was good for most language versions of the QoLIAD, with Cronbach's α ranging from 0.88 to 0.94 (36). In a population of 146 eczema patients, the Person Separation Index of the DLQI amounted to 0.63, resulting in a negative rating for internal consistency (35). For all other instruments, there was either no evidence on internal consistency or only evidence from methodologically poor studies. Measurement error was not assessed for any of the included instruments. An indeterminate rating was found for most language versions of the QoLIAD in terms of reliability. Of the other instruments, reliability information was available for the Spanish DLQI only; with an Intraclass Correlation Coefficient (ICC) of 0.77 between the two administrations, this instrument showed good reliability (24).

There was moderate evidence of good content validity for most QoLIAD versions. There was strong evidence that the Italian QoLIAD has good content validity. Content validity was found to be limited for the UK version of the DLQI in a population of 56 eczema patients; these patients considered the DLQI not comprehensive and found some items irrelevant (for instance, items 1 and 9 were not considered relevant by any patient in that study) (29). Likewise, structural validity of the UK version of the DLQI was found to be poor due to nonuniform differential item functioning (DIF) of items 6 and 7 with respect to gender and age, respectively. Moreover, 2/10 items showed uniform DIF with respect to gender, 3/10 items exhibited uniform DIF with respect to age, and there was disease-specific DIF for 5/10 items when patients with eczema and psoriasis were compared. Item residual statistics were indicative of a misfit to the Rasch model, although item–trait interaction suggested that the DLQI fits a Rasch model for eczema patients (35). Structural validity of the UK version of the QoLIAD as well as of DIELH is unclear. With data available for 15/17 QoL instruments, hypothesis testing (i.e. construct validity) was the measurement property most frequently assessed. Good construct validity was found for the DIELH and most QoLIAD versions. Correlations between QoLIAD (except Dutch and Italian) and DLQI were moderate to high (r = 0.58–0.77) with most values being above 0.70. Similar but lower correlations were found between QoLIAD (except Dutch and Italian) and the Psychological General Well-Being Schedule (PGWB) (r = 0.55–0.79) (36). Good conver-

Table 4 Characteristics of the different instruments

Characteristic	DIELH	DLQI	FLQA-c	FLQA-d	ISDL	QoLIAD	Skindex-29
Target population	Patients with any dermatological condition	Patients with skin disease	Patients with skin disease	Patients with chronic inflammatory skin disease	Patients with chronic skin disease	Eczema patients	Patients with skin disease
Number of items	36	10	28	54	32	25	29
Number of subscales	7	6	6	6	5	None	3
Number/type of response categories	5-point Likert scale (and 'not applicable')	4-point Likert scale	5-point Likert scale	ND	10-cm-VAS for physical symptoms; 5-point Likert scale for positive and negative mood; 4-point Likert scale for all other scales	Dichotomous (true/not true)	5-point Likert scale
Scoring algorithm	Calculation of a sum score, range 0–180	Calculation of a sum score, range 0–30	Calculation of a scale score by averaging the answers within a scale, range 1–5; no total score	ND	Calculation of subscale scores by summing up the subscales' items scores	Calculation of a sum score, range 0–25	Calculation of a scale score by averaging responses to items in a given scale
Recall period in the items	ND	1 week	1 week	ND	ND	ND	ND
Administration costs	ND	No charge for unfunded studies; $9.50 per patient for pharmaceutical companies (37)	ND	ND	ND	No charge for non-commercial studies; Administration fee of £100 for commercial studies (38)	ND
Available translations	German	More than 90 (37)	German	German	Dutch	Dutch, English (UK), English (US), French, German, Italian, Japanese, Spanish (39)	16 language versions (40)

DIELH, Deutsches Instrument zur Erfassung der Lebensqualität bei Hauterkrankungen; DLQI, Dermatology Life Quality Index; FLQA-c, Freiburg Life Quality Assessment core module; FLQA-d, Freiburg Life Quality Assessment for Dermatoses; ISDL, Impact of Chronic Skin Disease on Daily Life; ND, Not described; QoLIAD, Quality of Life Index for Atopic Dermatitis; UK, United Kingdom; US, United States (of America); VAS, visual analogue scale.

Table 5 Important characteristics of the included development and validation studies

		Study characteristics				
					Study population	
QoL instrument	Number of studies	Geographic location(s)	Language(s)	Setting(s)	Number of participants per study	Age range (years)
DIELH	2 (32, 33)	Germany	German	Secondary care	85 (32) ND (33)	ND (32) ND (oldest: 88) (33)
Danish DLQI	1 (30)	Denmark	Danish	Secondary care	66	ND
English DLQI (UK)	3 (28, 29, 35)	United Kingdom	English (UK)	Secondary care (28) Primary care (29) Community (35)	13 (28) 56 (29) 146 (35)	ND (28) 16–53 (29) 20–82 (35)
German DLQI	1 (23)	Germany	German	Tertiary care	80	ND
Spanish DLQI	1 (24)	Spain	Spanish	Secondary care	114	ND
FLQA-c	1 (21)	Germany	German	Tertiary care	253	17–75
FLQA-d	1 (23)	Germany	German	Tertiary care	80	ND
ISDL	1 (27)	Netherlands	Dutch	Secondary care	128	16–77
Dutch QoLIAD	1 (36)	Netherlands	Dutch	Secondary care	15 (item generation) 20 (field testing) 46 (validation)	ND ND 16–67
English QoLIAD (UK)	2 (34, 36)	United Kingdom	English (UK)	Community (34) Community and secondary care (36) Community (36)	146 (34) 36 (item generation) (36) 21 (field testing) (36) 286 (validation) (36)	20–82 (34) ND (36) ND (36) 16–86 (36)
English QoLIAD (US)	1 (36)	United States of America	English (US)	ND Secondary care	ND (item generation) 20 (field testing) 178 (validation)	ND ND 16–78
French QoLIAD	1 (36)	France	French	ND Secondary care Community	ND (item generation) ND (field testing) 213 (validation)	ND ND 18–86
German QoLIAD	1 (36)	Germany	German	ND Secondary care Community and secondary care	ND (item generation) 17 (field testing) 187 (validation)	ND ND 17–77
Italian QoLIAD	1 (36)	Italy	Italian	Secondary care	14 (item generation) 15 (field testing)	ND
Spanish QoLIAD	1 (31, 36)*	Spain	Spanish	ND (36) Community and secondary care (36) Secondary care (31, 36)	ND (item generation) (36) 20 (field testing) (36) 83 (validation) (31, 36)	ND (36) ND (36) 16–81 (31, 36)
English Skindex-29 (US)	1 (26)	United States of America	English (US)	Primary and secondary care	103	ND
German Skindex-29	1 (22)	Germany	German	Tertiary care	76	ND

DIELH, Deutsches Instrument zur Erfassung der Lebensqualität bei Hauterkrankungen; DLQI, Dermatology Life Quality Index; FLQA-c, Freiburg Life Quality Assessment core module; FLQA-d, Freiburg Life Quality Assessment for Dermatoses; ISDL, Impact of Chronic Skin Disease on Daily Life; ND, Not described; QoLIAD, Quality of Life Index for Atopic Dermatitis; UK, United Kingdom; US, United States (of America).

*Two articles on the Spanish QoLIAD were included but regarded as one study due to duplicate publication. From de Lucas 2003, only validation data not presented in Whalley 2004 were taken into account.

gent validity was also demonstrated for the UK version of the DLQI (29). With the exception of the Dutch and the Spanish QoLIAD versions, patients could be clearly discriminated according to perceived severity, current flares of symptoms and general health using the QoLIAD (36). The ISDL and the Dutch QoLIAD got negative ratings for hypothesis testing. While convergent validity of the Dutch QoLIAD was adequate, its discriminative validity was poor and resulted in a negative rating (36). The English Skindex-29 (US version) had good discriminative validity (26). For the

Table 6 Number of studies assessing the measurement properties of QoL instruments for adults with eczema

Measurement property	DIELH	Danish DLQI	English DLQI (UK)	German DLQI	Spanish DLQI	FLQA-c	FLQA-d	ISDL	Dutch QoLIAD	English QoLIAD (UK)	English QoLIAD (US)	French QoLIAD	German QoLIAD	Italian QoLIAD	Spanish QoLIAD	English Skindex-29 (US)	German Skindex-29
Internal consistency	/	/	1 (35)	/	/	/	/	1 (27)	1 (36)	2 (34, 36)	1 (36)	1 (36)	1 (36)	/	1 (36)	/	/
Measurement error	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Reliability	/	/	/	/	1 (24)	/	/	/	1 (36)	1 (36)	1 (36)	1 (36)	1 (36)	/	1 (36)	/	/
Content validity	/	/	1 (29)	/	/	/	/	1 (27)	1 (36)	1 (36)	1 (36)	/	1 (36)	1 (36)	1 (36)	/	/
Structural validity	1 (33)	/	1 (35)	/	/	/	/	/	/	1 (34)	/	/	/	/	/	/	/
Hypothesis testing	2 (32, 33)	1 (30)	2 (28, 29)	1 (23)	/	1 (21)	1 (23)	1 (27)	1 (36)	1 (36)	1 (36)	1 (36)	1 (36)	/	1 (31, 36)	1 (26)	1 (22)
Cross-cultural validity	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Responsiveness	/	/	/	/	1 (24)	1 (21)	/	1 (27)	/	/	/	/	/	/	/	/	/

DIELH, Deutsches Instrument zur Erfassung der Lebensqualität bei Hauterkrankungen; DLQI, Dermatology Life Quality Index; FLQA-c, Freiburg Life Quality Assessment core module; FLQA-d, Freiburg Life Quality Assessment for Dermatoses; ISDL, Impact of Chronic Skin Disease on Daily Life; QoLIAD, Quality of Life Index for Atopic Dermatitis; UK, United Kingdom; US, United States (of America).

remaining questionnaires, hypothesis testing assessments either led to an indeterminate rating or were conducted methodologically poorly.

Responsiveness in eczema patients was investigated for only three questionnaires, but only the Spanish DLQI was proven responsive (24).

Values for the minimal important change (MIC) or minimal important difference (MID) were not available for any of the included questionnaires. Data on floor and ceiling effects (i.e. ≥15% of patients having the lowest/the highest score) were available from one study for the QoLIAD. Only the US version of the QoLIAD showed some floor effects with 17.1% and 18.5% of respondents having the lowest score for visits 1 and 2, respectively. No floor or ceiling effects were observed for the other QoLIAD versions (36). In a sample of 56 eczema patients, the English DLQI (UK) exhibited no ceiling effects (29). Likewise, there were no floor or ceiling effects in the 13 eczema patients taking part in the development study of the English DLQI (UK) (28). Completion time for the Spanish QoLIAD was found to be 5 min or less (36).

Discussion

In this systematic review, the measurement properties of seven different adult eczema QoL instruments were evaluated. None of these instruments fulfilled all predefined filter criteria for truth, discrimination and feasibility, indicating the need for further validation work.

Currently, no QoL instrument can be highly recommended. In general, more validation research on all QoL questionnaires included in this review would be desirable. The QoLIAD (36) in several language versions was placed in category B, meaning that it has the potential to be recommended in the future depending on the results of further validation studies. The same is true for the Spanish language version of the DLQI (24), although less information is available for this instrument compared to the QoLIAD. For the majority of the questionnaires, that is DIELH (33), Danish DLQI (30), German DLQI (23), FLQA-c (21), FLQA-d (23), Italian QoLIAD (36), English Skindex-29 (US) (26) and German Skindex-29 (22), further usage cannot be recommended until more validation data are available since the performance of these instruments is largely unclear. Three instruments, the English DLQI (UK version) (28), ISDL (27) and Dutch QoLIAD (36), were found to have low adequacy in at least one required adequacy criterion and therefore are considered problematic for further use in eczema patients.

The QoLIAD, in several language versions, is a valid and internally consistent QoL instrument applying a needs-based model. According to this model, QoL is determined by an individual's ability and capacity to satisfy their needs, with high QoL when most needs and lowest QoL when few or none of the needs are met. Consequently, instruments based on this model assess the overall impact of a disease and its treatment. This is also reflected by the fact that the QoLIAD is the only instrument that does not have any content domain in common with the other instruments. As a

Table 7 Summary of measurement properties of QoL instruments for adults with eczema

Measurement property	DIELH	Danish DLQI	English DLQI (UK)	German DLQI	Spanish DLQI	FLQA-c	FLQA-d	ISDL	Dutch QoLIAD	English QoLIAD (UK)	English QoLIAD (US)	French QoLIAD	German QoLIAD	Italian QoLIAD	Spanish QoLIAD	English Skindex-29 (US)	German Skindex-29
Internal consistency	/	/	−−	/	/	/	/	Weak	Weak	++	+	+	+	/	Weak	/	/
Measurement error	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Reliability	/	/	/	/	+	/	/	/	Weak	? (limited)	? (limited)	? (limited)	? (limited)	/	? (limited)	/	/
Content validity	/	/	−	/	/	/	/	Weak	++	++	++	/	++	+++	++	/	/
Structural validity	? (limited)	/	−−	/	/	/	/	/	/	? (moderate)	/	/	/	/	/	/	/
Hypothesis testing	+	Weak	+	Weak	/	? (limited)	Weak	−	−	+	+	+	+	/	+	++	? (limited)
Cross-cultural validity	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Responsiveness	/	/	/	/	+	Weak	/	Weak	/	/	/	/	/	/	/	/	/
Recommendation	D	D	C	D	B	D	D	C	C	B	B	B	B	D	B	D	D

DIELH, Deutsches Instrument zur Erfassung der Lebensqualität bei Hauterkrankungen; DLQI, Dermatology Life Quality Index; FLQA-c, Freiburg Life Quality Assessment core module; FLQA-d, Freiburg Life Quality Assessment for Dermatoses; ISDL, Impact of Chronic Skin Disease on Daily Life; QoLIAD, Quality of Life Index for Atopic Dermatitis; UK, United Kingdom; US, United States (of America).

Recommendations are defined as follows: A, QoL measurement instrument meets all requirements and is recommended for use; B, QoL measure meets two or more adequacy items, but performance in all other required adequacy items is unclear, so that the outcome measure has the potential to be recommended in the future depending on the results of further validation studies; C, QoL measure has low adequacy in at least one required adequacy criterion (≥1 rating of 'minus') and therefore is not recommended to be used any more; D, QoL measure has (almost) not been validated. Its performance in all or most relevant adequacy items is unclear so that it is not recommended to be used until further validation studies clarify its adequacy. +++, ++, +, positive rating indicating adequate measurement property; ? (moderate), ? (limited), intermediate rating indicating intermediate measurement property; −, −−, negative rating indicating inadequate measurement property (please refer to Table 2 for further details); Weak = measurement property was assessed only in studies of poor methodological quality; / = not assessed.

result, the QoLIAD may not cover some of the aspects that clinicians might consider important in clinical practice. Floor or ceiling effects of the 25-item questionnaire were almost not observed and it was quickly completed. Although good construct validity was shown for most language versions of the QoLIAD, the negative rating for hypothesis testing for the Dutch QoLIAD indicates that the QoLIAD's construct validity should be further examined. Reliability, structural validity and cross-cultural validity of the QoLIAD are unclear and should also be further investigated. Measurement error and responsiveness of the QoLIAD have not yet been investigated. Moreover, interpretability data (i.e. definition and ranges of the QoLIAD that represent mild, moderate and severe QoL impairments in eczema) are not available.

The Spanish DLQI is a 10-item QoL instrument that was shown reliable and responsive in eczema patients. The validity of this DLQI version has not yet been tested. Even though plenty of information concerning floor and ceiling effects as well as other interpretability data is available for other language versions of the DLQI in populations other than eczema, respective data of the Spanish DLQI obtained in eczema patients are not available.

We found the English (UK) version of the DLQI to have poor internal consistency, content and structural validity in eczema patients. Thus, the English DLQI (UK version) is not suggested to assess QoL in eczema patients. Likewise, the ISDL and the Dutch version of the QoLIAD are not suggested for use either because of a lack of construct validity.

As we included a number of instruments that are dermatology-specific and thus were not specifically developed for patients with eczema, content validity of those instruments in eczema patients is of great importance. Dermatology-specific instruments are more likely to miss issues that eczema patients consider important simply because they were developed for patients with skin disease in general. Whereas good content validity was shown for the QoLIAD, an eczema-specific instrument, content validity of the included dermatology-specific instruments in eczema patients was almost not investigated. One study found limited content validity of the English DLQI (UK) in eczema patients. This finding challenges the applicability of the DLQI to eczema patients and raises the question whether other language versions of this instrument may have better content validity. Particularly for the Spanish DLQI, shown to be adequately reliable and responsive, a thorough examination of its content validity in eczema patients is needed.

As most data on interpretability were not gathered in eczema samples, only little information on interpretability was available for the included instruments. For instance, a MIC of four points has been proposed for the DLQI, but the corresponding studies did not meet our eligibility criteria (41, 42). Banding systems to assign clinical meaning to the scores have been suggested both for the DLQI (43) and the Skindex-29 (44–46), but none of these studies was found eligible. Thus, future validation studies should also look at interpretability in eczema patients.

Strengths and limitations of this review

We registered and published a protocol prior to our systematic review and highlighted differences between the protocol and final review. A validated, precise search filter was used to identify all possibly eligible articles of any language indexed in PubMed, EMBASE or both (47). Aiming to find the best evidence for eczema patients, we used predefined and strict eligibility criteria. We applied the COSMIN checklist to rate the study quality and gather information on interpretability and feasibility (11–14). At least two reviewers were involved in every step of the review process to assure quality. Frequent discussions took place within the research team in order to resolve discrepancies.

A potential limitation of our systematic review is that we only searched PubMed and EMBASE, thus possibly missing articles listed elsewhere. However, we were not able to find any further eligible articles through a thorough hand search. We were not able to retrieve one eligible article providing information on the measurement properties of the Ukrainian versions of the Skindex-16 and the DLQI (25).

Recommendations to researchers, clinicians and decision-makers

This review suggests that currently only the QoLIAD and the DLQI have the potential to be recommended for use depending on the results of further validation studies. These validation studies should investigate several language versions of the QoLIAD and the DLQI, also including the versions that were found inadequate for use in eczema patients in order to possibly confirm the findings of previous studies, thus strengthening the evidence base for the recommendations presented in this systematic review. The Dutch QoLIAD, the ISDL and the UK version of the DLQI are not suggested for use in eczema trials unless future validation studies show – in contrast to the existing evidence – adequate measurement properties for these instruments.

Clinicians and researchers should include a QoL measurement instrument in every future eczema trial because QoL is one of the core outcome domains of the proposed COS. As no instrument for measuring adult QoL in eczema trials can be highly recommended at the moment, the HOME initiative suggests using any QoL instrument that is at least valid, reliable and feasible in eczema patients (48). Unfortunately, we found in our review that currently no such instrument is available. An ideal solution to this quandary does not exist. Clinicians and researchers need to balance validity, reliability and feasibility. We suggest that researchers should include one of the two instruments from category B, i.e. the QoLIAD or the DLQI, in their trials.

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Authors' contributions

DH conceptualized the research plan for the systematic review, screened search results, extracted data, assessed measurement properties, coordinated the work of the other reviewers, wrote the manuscript and reviewed it for important intellectual content. CP screened search results, extracted data, assessed measurement properties, wrote the manuscript and reviewed it for important intellectual content. SD performed the literature search, extracted data, assessed measurement properties, helped with the methodology section and reviewed the manuscript for important intellectual content. JC extracted data, assessed measurement properties and reviewed the manuscript for important intellectual content. AD screened search results, extracted data, assessed measurement properties, wrote the manuscript and reviewed it for important intellectual content. RO screened search results, extracted data, assessed measurement properties and reviewed the manuscript for important intellectual content. RH contributed to the study design and reviewed the manuscript for important intellectual content. TS screened search results, extracted data, assessed measurement properties and reviewed the manuscript for important intellectual content. SC screened search results, extracted data, assessed measurement properties and reviewed the manuscript for important intellectual content. JS conceptualized the research plan for the systematic review, extracted data, assessed measurement properties and reviewed the manuscript for important intellectual content. CA conceptualized the research plan for the systematic review, extracted data, assessed measurement properties, wrote the manuscript and reviewed it for important intellectual content.

Conflicts of interest

Aaron Drucker is involved with the development of a novel quality-of-life assessment instrument for atopic dermatitis that is as yet unpublished. Jochen Schmitt and Christian Apfelbacher are members of the executive committee of the HOME initiative. All authors are ordinary members of the HOME initiative. The authors declare that there are no other conflicts of interests.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Detailed results: Rating of measurement properties of outcome instruments of quality of life of adult eczema patients and assessment of the methodological quality of the included studies.

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Systematic Reviews

PROTOCOL Open Access

Measurement properties of quality of life measurement instruments for infants, children and adolescents with eczema: protocol for a systematic review

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Abstract

Background: Eczema is a common chronic or chronically relapsing, inflammatory skin disease that exerts a substantial negative impact on quality of life (QoL). The Harmonising Outcome Measures for Eczema (HOME) initiative has used a consensus-based process which identified QoL as one of the four core outcome domains to be assessed in all eczema clinical trials. A number of measurement instruments exist to measure QoL in infants, children, and adolescents with eczema, and there is a great variability in both content and quality of the instruments used. Therefore, the objective of the proposed research is to comprehensively and systematically assess the measurement properties of the existing measurement instruments that were developed and/or validated for the measurement of patient-reported QoL in infants, children, and adolescents with eczema.

Methods/design: This study is a systematic review of the measurement properties of patient-reported measures of QoL developed and/or validated for infants, children, and adolescents with eczema. A systematic literature search will be carried out in MEDLINE via PubMed and EMBASE using a selection of relevant search terms. Eligible studies will be primary empirical studies evaluating, describing, or comparing measurement properties of QoL instruments for infants, children, and adolescents with eczema. Two reviewers will independently perform eligibility assessment and data abstraction. Evidence tables will be used to record study characteristics, instrument characteristics, measurement properties, and interpretability. The adequacy of the measurement properties will be assessed using predefined criteria. The COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist will be used to evaluate the methodological quality of included studies. A best evidence synthesis will be undertaken if more than one study has examined a particular measurement property.

Discussion: The proposed systematic review will yield a comprehensive assessment of measurement properties of existing QoL instruments in infants, children, and adolescents with eczema. The results will serve as a basis to recommend a QoL measurement instrument for infants, one for children, and one for adolescents for use in future clinical trials.

Systematic review registration: PROSPERO CRD42015023483

Keywords: Eczema, Atopic dermatitis, Measurement instruments, Health-related quality of life, Quality of life, Validity, Reliability, Responsiveness, Interpretability

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Background

Eczema (synonymous with atopic eczema, atopic dermatitis) represents the most common chronic disease in children in many countries [1]. Its main symptom is persistent pruritus [2]. The disease has a negative impact on the quality of life (QoL) of the patients and their families [3, 4]. Despite the fact that various interventions exist for eczema, uncertainties concerning the best treatment options remain. A major reason for this situation is the inconsistent use of varying eczema outcome measures in randomized controlled trials, making the comparison of interventions across these trials in systematic reviews and meta-analyses difficult. Thus, outcome measures in clinical trials of (pediatric) eczema patients need to be improved [5].

An internationally acknowledged way to ameliorate this unsatisfying situation is the development of a core outcome set (COS) [6]. The Harmonising Outcome Measures for Eczema (HOME) initiative [7] aims to develop a COS for eczema. Clinical signs measured by means of a physician-assessed instrument, symptoms, long-term control of eczema flares, and QoL were agreed on as the core outcome domains to be assessed in all future eczema trials [8, 9]. There was broad international consensus among clinicians, patients, and methodologists that the Outcome Measures in Rheumatology (OMERACT) quality criteria "truth, discrimination, and feasibility" [10] need to be met for eczema outcome measures to be recommended by the HOME initiative [9]. The next crucial step in the process of standardizing eczema outcome measurements is now the identification of appropriate instruments to measure each of the four core outcome domains of atopic eczema [11]. For adult QoL measurement instruments, this has already been undertaken, using methods similar to this proposed review [12]. The results have been published [13]. As the methodology of this systematic review will be in large parts identical to the one applied in the review on adult QoL instruments, content and wording of this protocol are very similar to the published protocol of the review on adult QoL instruments [12]. This pertains specifically to the methods section. To ensure transparency, differences in the methodology of both reviews are highlighted in the "Differences between this review and previously suggested methodology" section.

Objectives

1. To systematically assess the measurement properties of patient- or parent-reported measurement instruments of QoL for infants, children, and adolescents with eczema
2. To identify outcome measurement instruments for QoL in infants, children, and adolescents with eczema
   a. That meet the predefined criteria to be recommended [10, 9] for the measurement of QoL in future eczema trials
   b. That have the potential to be recommended in the future depending on the results of further validation studies
   c. That do not meet the predefined criteria to be recommended [10, 9] and therefore should not be used any more
3. To provide the evidence base for an international consensus process
   a. To further standardize the assessment of QoL in infants, children, and adolescents with eczema in clinical trials
   b. To prioritize further research concerning QoL assessment in infants, children, and adolescents with eczema

Methods/design

Protocol and registration

The methods for this systematic review have been developed according to the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement [14], and a populated PRISMA-P checklist is available as an Additional file 1 to this protocol. This protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO): CRD42015023483.

Literature search

A systematic literature search will be performed in PubMed and EMBASE. The search strategy will contain blocks of search terms related to the following aspects:

1. Construct of interest: quality of life
2. Target population: (atopic) eczema (Table 1)
3. Measurement properties: the precise PubMed search filter for finding studies on measurement properties developed by Terwee et al. will be used to identify relevant articles [15]. This filter has a sensitivity of 93.1 % and a precision of 9.4 %
4. Interpretability

The search will not be restricted with respect to the publication time of retrieved studies. The entire search strategy is available as an Additional file 2 to this protocol. The systematic electronic search will be supplemented by hand searching of reference lists of studies included and key articles on this topic. Furthermore, an additional search will be performed in each database, including the names of the instruments which are found in the initial search. The PROQOLID (www.proqolid.org) database, an online database of QoL instruments, will be searched. The initial search in PubMed and EMBASE will be carried out

Table 1 Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	Eczema (synonyms: atopic eczema, atopic dermatitis, neurodermatitis); populations younger than 16 years of age	Populations with other skin diseases than eczema, populations of adults with eczema, carers of infants/children with eczema
Study design	Development study, validation study	Linguistic validation studies
Outcome	Quality of life, health-related quality of life	Signs, disease severity measure, disease control measure, biomarker, physiology of the skin
Type of measurement instrument	Self- or proxy-reported measurement instrument	All others
Publication type	Articles with available full text	Abstracts

on a single day that will be reported in the final review, whereas the hand searching process will be performed during the eligibility assessment of articles, which may take several weeks. The additional search of each database will be done, after the eligibility assessment has been completed, on a single day.

Eligible studies

A study will be included if it is published as a full-text paper and concerns the development ("development paper") and/or evaluation of the measurement properties ("validation paper") of instruments that measure QoL or health-related quality of life (HrQoL) in infants, children, and adolescents with eczema. Measurement instruments that assess both the QoL of children and caregivers will be included if separate scores for the QoL of the child and for the QoL of the caregiver can be calculated. Generic QoL measurement instruments for infants, children, and adolescents and measurement instruments assessing solely the QoL of caregivers will not be considered eligible. The HOME initiative decided in 2011 that generic QoL measurement instruments are not eligible for the COS [16]. QoL measurement instruments for caregivers will be investigated in a separate review. To be eligible, at least 50 % of a study's population must consist of eczema patients younger than 16 years of age. A study with a mixed patient sample will be eligible either if it presents a subgroup analysis for infants, children, and adolescents with eczema or if infants, children, and adolescents with eczema constitute at least 50 % of the study population. The measurement instrument must be a self- or proxy-reported questionnaire. Articles that report indirect evidence, for instance, by using data obtained within the context of a clinical trial, will not be considered eligible. Articles assessing the measurement properties of dermatology-specific instruments in non-eczema samples will not be considered eligible.

Study selection

Two reviewers will independently judge titles and abstracts retrieved in the literature search and, at a second stage, full-text articles for eligibility (Table 1). Disagreements will be resolved by consensus-seeking discussions within the research team.

Data extraction

Relevant data from all included articles will be summarized in evidence tables. The evidence tables drafted for the adults' review [12] will be slightly adapted. Data from each article included will be extracted independently by two reviewers. Reviewers will work in pairs on defined sets of articles. Disagreements will be resolved by consensus-seeking discussions within the research team.

Evidence tables will include the following: reference, geographical location, language, setting, study type, key characteristics of study subjects, name of measurement instruments, domains measured, number of items and (sub)scales, number and type of response categories, recall period in the questions, scoring algorithm, time needed for administration, mode of administration, target population for whom the questionnaire was originally developed, how a full copy of the questionnaire can be obtained, the instructions given to those who complete the questionnaire, the available versions and translations of the questionnaire, results of the measurement properties, all items from the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) box Generalisability, and all items from the COSMIN box Interpretability [17, 18].

If general characteristics of an instrument (that is, name of measurement instrument, number of items and (sub)scales, number and type of response categories, recall period in the questions, scoring algorithm, time needed for administration, mode of administration, target population for whom the questionnaire was originally developed, how a full copy of the questionnaire can be obtained, the instructions given to those who complete the questionnaire, the available versions and translations of the questionnaire) cannot be extracted from the studies included, the original development paper may be consulted to obtain missing information.

Content comparison

An overview of the content of each instrument on content domain level will be presented in order to visualize the content covered by the different instruments. The original development paper will be consulted to obtain this information.

Assessment of the methodological quality of included studies

The COSMIN checklist [17–19] will be used to evaluate the methodological quality of included studies. In the COSMIN checklist (www.cosmin.nl), four domains are distinguished (reliability, validity, responsiveness, and interpretability) with related measurement properties and aspects of measurement properties. These are listed in Table 2 (adapted from Mokkink LB et al. [18]).

For each measurement property, the COSMIN checklist consists of 5 to 18 items covering methodological standards (organized in nine boxes for the nine measurement properties). In addition, each item can be scored on a 4-point rating scale (that is, "poor," "fair," "good," "excellent"). Taking the lowest rating for each item in one box, an overall quality score ("poor," "fair," "good," "excellent") is obtained for each measurement property separately [20].

Assessment of measurement properties and further characteristics of QoL instruments

We will assess all measurement properties from the COSMIN checklist in this review, with the exception of the measurement property "criterion validity," which will not be considered for the purpose of this systematic review, since there is no gold standard for QoL. Data on interpretability and feasibility will be collected where presented. With the exception of content comparison and instrument characteristics, we will regard different language versions of the same questionnaire separately throughout the review. Our principal reason for doing so is the fact that it is problematic to assume that different language versions of measurement instruments exhibit the same measurement properties. Strictly speaking, it is the measurements themselves that are valid, reliable, and responsive and not the instruments per se.

Assessment of the adequacy of the measurement instruments

The predefined criteria for rating the adequacy of the measurement instruments recommended by the COSMIN group will be used in a slightly modified version [21] (Table 3). These criteria are in accordance with the OMERACT filter [10], which has been adopted by the HOME initiative [9] and applied in a previous review on atopic eczema outcome measures [22]. The measurement property "hypothesis testing" will be split into the aspects convergent/divergent (defined as the correlation between instruments measuring similar/different constructs [23]) and discriminative validity (defined as the ability of a measurement instrument to distinguish between different subgroups of patients [23]) for this review. An overall rating for hypothesis testing will be obtained from both aspects in the end (see "Generating recommendations for the use of QoL measurement instruments for eczema" section). Where studies apply item response theory (IRT) methods in the evaluation of measurement properties, rather than in the development of measurement instruments, we will be able to assess the adequacy and methodological quality of internal consistency, construct validity, structural validity, and cross-cultural validity.

Best evidence synthesis

If an instrument has been evaluated in multiple studies, findings will be synthesized if the characteristics of the included studies are sufficiently similar, if the results of the studies do not show significantly different or conflicting findings, and if the methodological quality of the included studies is sufficient [24]. The criteria for best evidence synthesis are outlined in Table 4.

Generating recommendations for the use of QoL measurement instruments for eczema

For each instrument identified in the review, a standardized recommendation for usage or required future validation work will be made depending on the methodological quality of included studies and on the adequacy of the instrument (Table 5). According to the results of the HOME II meeting [9], all three criteria of the OMERACT filter [10], that is, truth, discrimination, and feasibility, have to be met by an outcome measure to be recommended by the HOME initiative. Although convergent/divergent and discriminative validity will be regarded separately throughout the review, the findings for these two aspects of hypothesis testing will be synthesized according to the following criteria: in case of conflicting ratings, the worse rating determines the overall rating for hypothesis testing; if one of the aspects obtains an indeterminate rating, the rating for the other aspect determines the overall rating for hypothesis testing.

Four categories of recommendation will be made:

A. QoL measurement instrument meets all requirements and is recommended for use.
B. QoL measure meets two or more adequacy items, but performance in all other required adequacy items is unclear, so that the outcome measure has the potential to be recommended in the future

Table 2 Definitions of domains, measurement properties, and aspects of measurement properties

Domain	Measurement property	Aspect of a measurement property	Definition
Reliability			The degree to which the measurement is free from measurement error.
Reliability (extended definition)			The extent to which scores for patients who have not changed is the same for repeated measurement under several conditions: for example, using different sets of items from the same HR-PROs (internal consistency), over time (test-retest) by different persons on the same occasion (inter-rater) or by the same persons (i.e., raters or responders) on different occasions (intra-rater).
	Internal consistency		The degree of interrelatedness among the items.
	Reliability		The proportion of total variance in the measurements which is because of "true"[a] differences among patients.
	Measurement error		The systematic and random error of a patient's score that is not attributed to true change of the construct to be measured.
Validity			The degree to which an HR-PRO instrument measures the construct(s) it purports to measure.
	Content validity		The degree to which the content of an HR-PRO instrument is an adequate reflection of the construct to be measured.
		Face validity	The degree to which (the items of) an HR-PRO instrument indeed looks as though they are an adequate reflection of the construct to be measured.
	Construct validity		The degree to which the scores of an HR-PRO instrument are consistent with hypotheses (for instance with regard to internal relationships, relationships to scores of other instruments, or differences between relevant groups) based on the assumption that the HR-PRO instrument validly measures the construct to be measured.
		Structural validity	The degree to which the scores of an HR-PRO instrument are an adequate reflection of the dimensionality of the construct to be measured.
		Hypothesis testing	Idem construct validity.
		Cross-cultural validity	The degree to which the performance of the items on a translated or culturally adapted HR-PRO instrument are an adequate reflection of the performance of the items of the original version of the HR-PRO instrument.
Responsiveness			The ability of an HR-PRO instrument to detect change over time in the construct to be measured.
	Responsiveness		Idem responsiveness.
Interpretability[b]			The degree to which one can assign qualitative meaning—that is, clinical or commonly understood connotations—to an instrument's quantitative scores or changes in scores.

HR-PROs health-related patient-reported outcomes, *CTT* classical test theory

[a]The word "true" must be seen in the context of the CTT, which states that any observation is composed of two components—a true score and error associated with the observation. "True" is the average score that would be obtained if the scale were given an infinite number of times. It refers only to the consistency of the score and not to its accuracy [26]

[b]Interpretability is not considered a measurement property but an important characteristic of a measurement instrument

Table 3 Adequacy criteria for measurement properties adapted from [21] and [27]

Property	Rating	Adequacy criteria
Reliability		
Internal consistency (CTT methods applied)	+	Cronbach's alpha(s) ≥0.70
	?	Cronbach's alpha not determined
	–	Cronbach's alpha(s) <0.70
Internal consistency (IRT methods applied)	+	Person Separation Index ≥0.70
	?	Person Separation Index not determined
	–	Person Separation Index <0.70
Measurement error	+	MIC > SDC OR MIC outside the LoA
	?	MIC not defined
	–	MIC ≤ SDC OR MIC equals or inside LoA
Reliability	+	ICC/weighted Kappa ≥0.70, OR Pearson's $r \geq 0.80$
	?	Neither ICC/weighted Kappa, nor Pearson's *r* determined
	–	ICC/weighted Kappa <0.70 OR Pearson's $r < 0.80$
Validity		
Content validity	+	All items are considered to be relevant for the construct to be measured, for the target population, and for the purpose of the measurement AND the questionnaire is considered to be comprehensive
	?	Not enough information available
	–	Not all items are considered to be relevant for the construct to be measured, for the target population, and for the purpose of the measurement OR the questionnaire is considered not to be comprehensive
Construct validity		
Structural validity (CTT methods applied)	+	Factors should explain at least 50 % of the variance
	?	Explained variance not mentioned
	–	Factors explain <50 % of the variance
Structural validity (IRT methods applied)	+	Residual correlations among the items after controlling for the dominant factor <0.20 OR Q3's <0.37, item scalability >0.30, IRT model fit: G^2 >0.01, no DIF for important subject characteristics (such as age, gender, education): McFadden's R^2 <0.02, OR no non-uniform DIF
	?	Important statistics not reported
	–	Residual correlations among the items after controlling for the dominant factor ≥0.20 OR Q3's ≥0.37, item scalability ≤0.30, IRT model fit: G^2 ≤0.01, important DIF for important subject characteristics (such as age, gender, education): McFadden's R^2 ≥0.02, OR non-uniform DIF
Hypothesis testing (convergent/divergent validity)	+	Correlations with instruments measuring the same construct ≥0.50 OR at least 75 % of the results are in accordance with the hypotheses AND correlation with related constructs is higher than with unrelated constructs
	?	Solely correlations determined with unrelated constructs
	–	Correlations with instruments measuring the same construct <0.50 OR <75 % of the results are in accordance with the hypotheses OR correlation with related constructs is lower than with unrelated constructs
Hypothesis testing (discriminative validity)	+	Differences in scores on the measurement instrument for all evaluated patient subgroups are statistically significant OR ≥75 % of results in accordance with hypotheses
	?	Some differences statistically significant, others not
	–	Differences in scores on the measurement instrument for all evaluated patient subgroups are not statistically significant OR <75 % of results in accordance with hypotheses
Cross-cultural validity	+	No differences in factor structure OR no important DIF between language versions
	?	Multiple group factor analysis not applied AND DIF not assessed

Table 3 Adequacy criteria for measurement properties adapted from [21] and [27] *(Continued)*

	–	Differences in factor structure OR important DIF between language versions
Responsiveness		
Responsiveness	+	Correlation with changes on instruments measuring the same construct ≥0.50 OR at least 75 % of the results are in accordance with the hypotheses OR AUC ≥0.70 AND correlations with changes in related constructs are higher than with unrelated constructs
	?	Solely correlations determined with unrelated constructs
	–	Correlations with changes on instruments measuring the same construct <0.50 OR <75 % of the results are in accordance with the hypotheses OR AUC <0.70 OR correlations with changes in related constructs are lower than with unrelated constructs

MIC minimal important change, *SDC* smallest detectable change, *LoA* limits of agreement, *ICC* intraclass correlation coefficient, *AUC* area under the curve, + positive rating, ? indeterminate rating, – negative rating

depending on the results of further validation studies.

C. QoL measure has low adequacy in at least one required adequacy criterion (≥1 rating of "minus") and therefore is not recommended to be used anymore.
D. QoL measure has (almost) not been validated. Its performance in all or most relevant adequacy items is unclear so that it is not recommended to be used until further validation studies clarify its adequacy.

Finally, we aim to identify one best (currently available) instrument to assess QoL in infants, one best (currently available) instrument to assess QoL in children, and one best (currently available) instrument to assess QoL in adolescents with eczema.

Differences between this review and previously suggested methodology

We refined our eligibility criteria and made clear that generic QoL instruments will not be eligible for this review [12]. As this review will focus on infants, children, and adolescents, proxy-reported instruments will also be included.

Because interpretability and feasibility of a QoL instrument are very important for researchers and clinicians, we emphasized that corresponding information will be collected where presented. We also decided to regard different language versions of the same QoL instrument separately; this approach was also used in our previous review on adult QoL instruments [13] but initially not specified in the pertaining protocol. Content comparison of the included instruments will be done on content domain level instead of item level because a comparison table on item level would become unclear and confusing due to the multitude of data shown. Moreover, we decided to use the term "adequacy of the measurement properties" instead of "quality of the measurement properties." For studies applying IRT methods, only internal consistency, construct validity, structural validity, and cross-cultural validity will be assessed, where applicable.

Important changes concern the adequacy criteria outlined in Table 3:

- For internal consistency, the indeterminate rating ("?") was changed from "Dimensionality not known OR Cronbach's alpha not determined" to "Cronbach's alpha not determined" in order to avoid an overlap between the adequacy criteria and the COSMIN criteria for methodological quality. Adequacy criteria for studies using IRT methods were added.
- The IRT criteria for structural validity were enhanced with criteria on differential item functioning (DIF) [25]. If a study shows that there is no non-uniform DIF, this can now also result in a positive rating. Non-uniform DIF will be rated negatively according to the new criteria.

Table 4 Levels of evidence for the overall adequacy of a measurement property adapted from [28]

Level	Rating	Criteria
Strong	+++, ? (strong) or −−−	Consistent findings in multiple studies of good methodological quality OR in one study of excellent methodological quality
Moderate	++, ? (moderate) or −−	Consistent findings in multiple studies of fair methodological quality OR in one study of good methodological quality
Limited	+, ? (limited) or −	One study of fair methodological quality
Conflicting	+/−	Conflicting findings
Unknown	?	Only studies of poor methodological quality

+ positive rating, ? indeterminate rating, – negative rating

Table 5 Adequacy criteria required for recommendation of QoL measures for eczema

Adequacy item (name)	Inclusion in OMERACT filter	Required rating for recommendation
Content validity	Truth	+
Structural validity	Truth	+
Hypotheses testing	Truth	+
Cross-cultural validity	Truth	+
Internal consistency	Discrimination	+
Reliability	Discrimination	+
Measurement error	Discrimination	+
Responsiveness	Discrimination	+

- Hypothesis testing was split into its two aspects convergent/divergent and discriminative validity, with separate criteria for each aspect, resulting in an overall rating for hypothesis testing in the end.
- The criteria developed by Terwee et al. for hypothesis testing will only be applied to convergent and divergent validity. For discriminative validity, another aspect of hypothesis testing, self-developed criteria were added. As the COSMIN initiative does not consider interpretability to be a formal measurement property, the adequacy criteria for interpretability were omitted [18].

An indeterminate rating for strong, moderate, and limited levels of evidence was added to the best evidence synthesis ratings each. This was done for scenarios where a QoL instrument would obtain an indeterminate rating for a certain measurement property. An indeterminate rating will be assigned to a measurement property if there is no clear evidence for either a positive or negative rating.

Discussion

The proposed systematic review will yield a comprehensive assessment of measurement properties of existing QoL instruments in infants, children, and adolescents with eczema. We aim to arrive at a recommendation of one best instrument for infants, one best instrument for children, and one best instrument for adolescents, respectively. Rigorous and appropriate methods are vital to obtain meaningful, scientifically acknowledged results that form the basis to put forward such recommendations [6]. With good reason, researchers and clinicians demand that the development of a COS for eczema must adhere to high standards. We have made various efforts to satisfy these expectations. Firstly, the processes underlying this systematic review are transparent and systematic. Secondly, the involvement of at least two reviewers at each stage will assure quality of and reduce variability in the assessments. Another strength of the proposed research is the use of well-established methods and criteria, such as the COSMIN checklist, that have been successfully applied in a considerable number of previous systematic reviews. Furthermore, the international coverage of the contributing reviewers will increase the credibility of any findings.

In addition to the results obtained by best evidence synthesis, the feasibility of a questionnaire, e.g., number of items and time needed for administration, is another essential requirement for recommendation. This is also reflected by the fact that all three criteria of the OMERACT filter, i.e., truth, discrimination, and feasibility, need to be met by an outcome measure to be recommended by the HOME initiative [9, 10]. Truth and discrimination are reflected by the results from best evidence synthesis. Although there are no adequacy criteria for feasibility, information on feasibility will be collected throughout the review process and will be considered for the conclusions of our systematic review. Sufficient feasibility of a questionnaire is important for its inclusion in the proposed COS and the widespread implementation in future eczema trials.

Moreover, we may consider the popularity of a QoL instrument as an additional parameter for recommendation if several instruments are placed in category A and a decision to recommend one of them based solely on best evidence synthesis is not possible. A potential benefit of well-known and frequently applied QoL instruments could be that more data on the questionnaire's feasibility and interpretability of its scores may be available compared to less popular instruments.

Whether or not we will be able to reach the goal of recommending one best instrument for each age group is unclear. It may well be that several instruments will meet the OMERACT filter criteria. If instruments lack important requirements, for instance, in relation to responsiveness or measurement error, they will not comply with the OMERACT filter criteria, and additional validation studies will need to be carried out before these instruments can be included in the COS. As a result, it could happen that our systematic review will only be able to identify priorities for further validation work

instead of putting forward a clear recommendation for a certain QoL measurement instrument. Nonetheless, the findings of this systematic review will inform a consensus-finding process at the fifth meeting of the HOME initiative (HOME V) that will take place in São Paulo, Brazil, in 2017. Based on the findings of this work, we hope to be able to inform group discussion and consensus voting with the ultimate goal to endorse one instrument for each age group to be included in the core set of outcome measurement instruments for eczema.

Additional files

Additional file 1: PRISMA-P 2015 checklist. The completed PRISMA-P checklist for this protocol.

Additional file 2: Search strings. The search strings for MEDLINE (via PubMed) and EMBASE.

Abbreviations

COS: core outcome set; COSMIN: COnsensus-based Standards for the selection of health Measurement INstruments; DIF: differential item functioning; HOME: Harmonising Outcome Measures for Eczema; HrQoL: health-related quality of life; IRT: item response theory; OMERACT: Outcome Measures in Rheumatology; PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols; PRO: patient-reported outcome; PROSPERO: International Prospective Register of Systematic Reviews; QoL: quality of life.

Competing interests

All authors are members of the HOME initiative. Christian Apfelbacher is a member of the HOME executive committee. Carsten Flohr is a member of the scientific advisory board of HOME. Aaron Drucker is involved with the development of a novel quality of life assessment instrument for atopic dermatitis that is as yet unpublished. The authors declare that they have no other competing interests.

Authors' contributions

DH and CA initiated the protocol, conceptualized the research plan for the proposed systematic review, wrote the manuscript, and reviewed it for important intellectual content. CP, TS, and AD critically reviewed the methodology, wrote the manuscript, and reviewed it for important intellectual content. RO, RH, and CF critically reviewed the methodology and reviewed the manuscript for important intellectual content. All authors read and approved the final manuscript.

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SYSTEMATIC REVIEW

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Measurement properties of quality-of-life measurement instruments for infants, children and adolescents with eczema: a systematic review

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Summary

Background Quality of life (QoL) is one of the core outcome domains identified by the Harmonising Outcome Measures for Eczema (HOME) initiative to be assessed in every eczema trial. There is uncertainty about the most appropriate QoL instrument to measure this domain in infants, children and adolescents.

Objectives To systematically evaluate the measurement properties of existing measurement instruments developed and/or validated for the measurement of QoL in infants, children and adolescents with eczema.

Methods A systematic literature search in PubMed and Embase, complemented by a thorough hand search of reference lists, retrieved studies on measurement properties of eczema QoL instruments for infants, children and adolescents. For all eligible studies, we judged the adequacy of the measurement properties and the methodological study quality with the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist. Results from different studies were summarized in a best-evidence synthesis and formed the basis to assign four degrees of recommendation.

Results Seventeen articles, three of which were found by hand search, were included. These 17 articles reported on 24 instruments. No instrument can be recommended for use in all eczema trials because none fulfilled all required adequacy criteria. With adequate internal consistency, reliability and hypothesis testing, the U.S. version of the Childhood Atopic Dermatitis Impact Scale (CADIS), a proxy-reported instrument, has the potential to be recommended depending on the results of further validation studies. All other instruments, including all self-reported ones, lacked significant validation data.

Conclusions Currently, no QoL instrument for infants, children and adolescents with eczema can be highly recommended. Future validation research should primarily focus on the CADIS, but also attempt to broaden the evidence base for the validity of self-reported instruments.

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Conflicts of interest
All authors are ordinary members of the Harmonising Outcome Measures for Eczema (HOME) initiative. C.A. is a member of the HOME Executive Committee. C.F. is a member of the Scientific Advisory Board of HOME. A.M.D. is involved with the development of a novel quality of life assessment instrument for atopic dermatitis that is as yet unpublished. The authors declare that they have no other competing interests.

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What's already known about this topic?

- Most eczema trials include the Infants' Dermatitis Quality of Life Index (IDQoL) or the Children's Dermatology Life Quality Index (CDLQI) as quality of life (QoL) measurement instruments.

- It is unclear which instruments are most appropriate to measure QoL in infants, children and adolescents with eczema.

What does this study add?

- Most QoL instruments for infants, children and adolescents with eczema are poorly validated, indicating a clear need for further validation work.

Affecting more than 10% of infants and children, eczema (synonyms: 'atopic eczema', 'atopic dermatitis') is one of the most common chronic diseases in children in many countries.[1–3] A high eczema prevalence is also observed in adolescence,[2] with a substantial risk of the disease persisting into adulthood.[4] Despite a multitude of treatment options, evidence-based decision-making based on systematic reviews and meta-analyses is hampered due to the heterogeneity of outcome measurement instruments used, particularly in randomized controlled trials.

Therefore, the Harmonising Outcome Measures for Eczema (HOME) initiative (www.homeforeczema.org) aims to develop a core outcome set (COS) for use in all future eczema trials. A COS is a minimum set of outcomes that should be measured and reported in all clinical trials of a specific disease or trial population.[5] The core outcome domains suggested by the HOME initiative are clinical signs, symptoms, long-term control of flares and quality of life (QoL).[6–8]

Following the HOME roadmap,[9] we performed a systematic review of the measurement properties of all instruments that were developed and validated to measure QoL in infants, children and adolescents with eczema. For adults, this step has already been completed.[10]

Material and methods

Protocol and registration

This systematic review was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[11] A completed PRISMA checklist is available as an online appendix to this publication (see Appendix SA1; Supporting Information). The study protocol was published[12] and registered in the International Prospective Register of Systematic Reviews (PROSPERO): CRD42015023483.

Literature search

A systematic literature search in PubMed and EMBASE was conducted on 18 June 2015. The entire search strategy is shown in detail in the study protocol.[12] Hand searching of the PROQOLID database (http://www.proqolid.org) and reference lists of included studies and key articles on QoL in infants, children and adolescents with eczema complemented the systematic search.

Eligible studies

We applied the eligibility criteria presented in the protocol.[12] Briefly, the study population of eligible development and validation studies of dermatology- or eczema-specific QoL instruments had to consist of at least 50% of patients with eczema younger than 16 years of age, or studies had to present subgroup analyses for this patient group.

Content comparison

The content of the included instruments was compared at the content domain level based on information from the original development paper.

Assessment of the methodological quality of included studies

We used the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist to judge the methodological quality of the included studies (www.cosmin.nl).[13–16] This checklist consists of 5–18 items per measurement property covering methodological standards; the compliance with these standards is rated on a four-point rating scale ('poor', 'fair', 'good', 'excellent'). The lowest rating for any item pertaining to a certain measurement property determines the overall rating for this measurement property.

Assessment of measurement properties and further characteristics of quality of life instruments

With the exception of criterion validity, all measurement properties from the COSMIN checklist were evaluated in this systematic review. Where available, interpretability and feasibility data were collected. Because we view them as distinct instruments, different language versions of the same questionnaire were considered separately throughout this review except for content comparison and instrument characteristics.

Assessment of the adequacy of the measurement properties

To evaluate the adequacy of the investigated measurement properties, we applied the corresponding predefined criteria

recommended by the COSMIN group in a slightly modified version (see Table SA1 in Appendix SA2; Supporting Information).[17,18] The specific changes we made to these criteria are explained in the protocol.[12] Where studies used item response theory (IRT) methods in the assessment of measurement properties instead of the development of measurement instruments, we assessed the adequacy and methodological quality of internal consistency, construct validity, structural validity and cross-cultural validity.

Best-evidence synthesis

Findings on the same instrument from multiple studies were synthesized if the characteristics of the included studies were sufficiently similar, the results did not show considerably different or conflicting findings and the methodological quality of the included studies was adequate.[19] Criteria for best-evidence synthesis are found in Table SA2 (in Appendix SA2; Supporting Information).[20]

Generating recommendations for the use of quality of life measurement instruments for eczema

Depending on the adequacy of each instrument and the methodological quality of the included studies, a standardized recommendation for usage and necessary future validation work was made for each investigated instrument.
Four categories of recommendation were made:[12]

A QoL measurement instrument meets all requirements and is recommended for use.
B QoL measure meets two or more adequacy criteria, but performance in all other required adequacy criteria is unclear, so that the outcome measure has the potential to be recommended in the future depending on the results of further validation studies.
C QoL measure has low adequacy in at least one required adequacy criterion (≥ 1 rating of 'minus') and therefore is not recommended to be used anymore.
D QoL measure has (almost) not been validated. Its performance in all or most relevant adequacy criteria is unclear so that it is not recommended to be used until further validation studies clarify its adequacy.

Finally, we aimed to identify one best (currently available) instrument to assess QoL in infants, one best (currently available) instrument to assess QoL in children, and one best (currently available) instrument to assess QoL in adolescents with eczema.

Results

Seventeen articles were included (Fig. 1).[21–37] One paper complying with the inclusion criteria presented only summary information, making analyses of the evaluated questionnaires and measurement properties impossible; the paper was consequently excluded.[38] Another paper containing data on the content validity of the Childhood Impact of Atopic Dermatitis (CIAD) did not formally meet the inclusion criteria and was thus excluded.[39] However, read in conjunction with the eligible development article of the CIAD,[34] information on content validity could be extracted from that excluded paper and was therefore considered for this review.

Most included studies reported on the Children's Dermatology Life Quality Index (CDLQI, n = 6)[22,29–31,33,36] and the Infants' Dermatitis Quality of Life Index (IDQoL, n = 6).[21,24,25,29,32,37] Three studies evaluated the Childhood Atopic Dermatitis Impact Scale (CADIS)[26,27,35] and two studies assessed the DISABKIDS Atopic Dermatitis Module (DISABKIDS-ADM).[23,28] Information on the CIAD was available from two studies,[34,39] but only one of them met the inclusion criteria.[34]

A comparison of the content covered by these five instruments is presented in Table SA3 (in Appendix SA2; Supporting Information). The CDLQI and the IDQoL are the most similar in content out of the five instruments. Table 1 shows other general characteristics of the included instruments. The CADIS, CIAD and IDQoL are proxy-reported, whereas the CDLQI is completed by the children themselves. The questionnaire DISABKIDS-ADM is available both in a self- and a proxy-reported version. Only the CDLQI is a dermatology-specific instrument; all others are eczema-specific. The lowest number of items in a questionnaire is seven, the highest 45. Four of the five questionnaires apply a 4- or 5-point Likert scale; only the CIAD uses a dichotomous response format.

Characteristics of the included studies

An overview of settings and study populations in the included studies is shown in Table 2. Most studies were conducted in secondary/tertiary care settings in Europe. Sample sizes ranged from eight to 370 patients.

Validity of the instruments and recommendations

In total, we were able to rate the methodological quality of 84 measurement properties. Two measurement properties (2%) had good, 18 (21%) had fair and 64 (76%) had poor methodological quality. Detailed results for every instrument and study investigated in this systematic review can be found in Supplementary Tables S1–S80 (found in the Detailed Results SR1; Supporting Information).

Proxy-reported instruments

Table SA4 (in Appendix SA2; Supporting Information) shows the number of studies assessing the different measurement properties of each included proxy-reported QoL instrument. The results of best-evidence synthesis and the degree of recommendation for each proxy-reported instrument are found in Table 3. There was no instrument for which all relevant measurement properties have been investigated. Hence, there was also no instrument that fulfilled all prespecified requirements of truth, discrimination and feasibility.

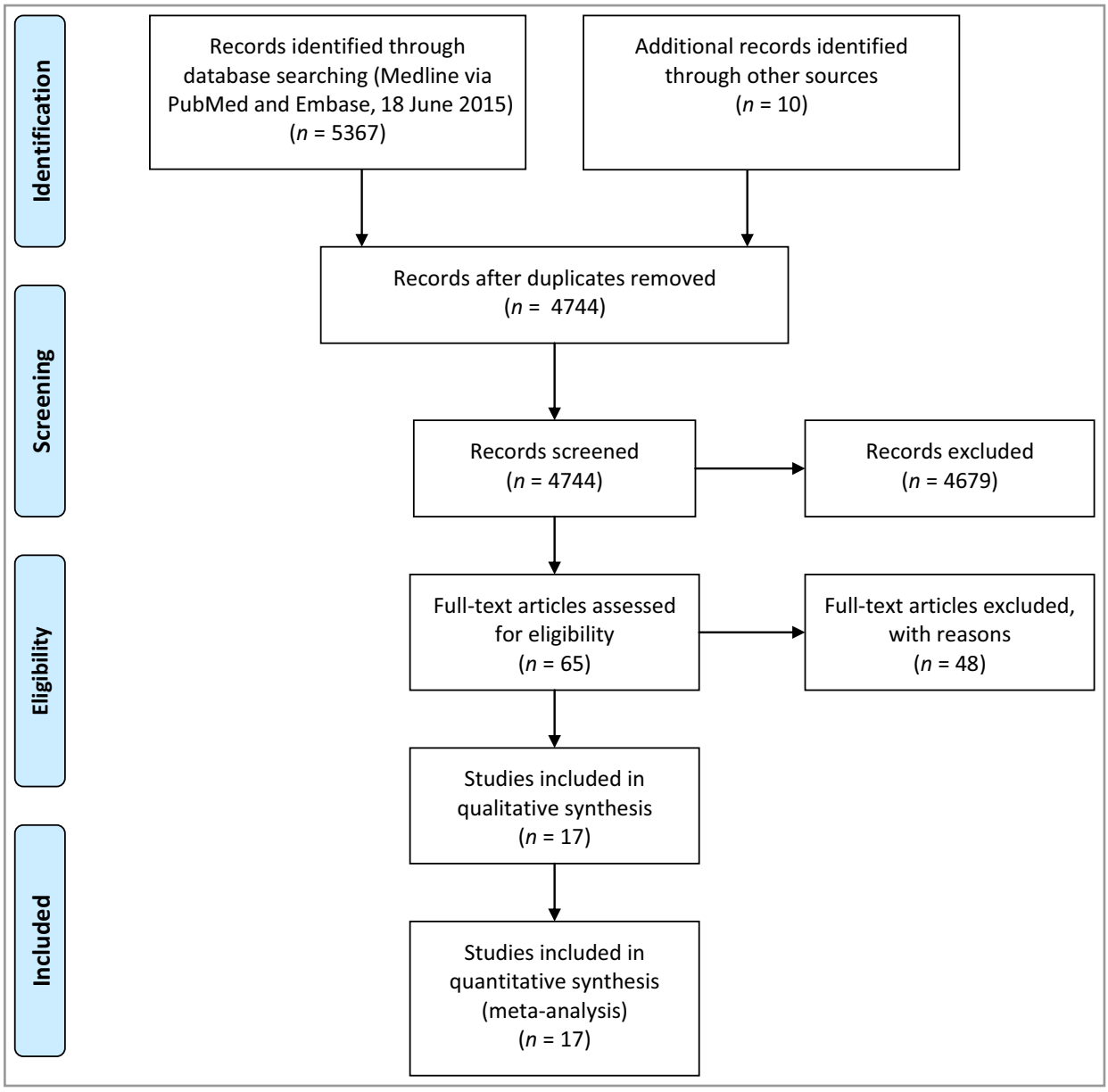

Fig 1. PRISMA 2009 flow diagram. From Moher D, Liberati A, Tetzlaff J, Altman DG; the PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* **6**:e1000097. For more information, visit www.prisma-statement.org.

With Cronbach's α ranging from 0·76 to 0·93 for its subscales, internal consistency of the U.S. version of the CADIS was found to be adequate.[26] Most language versions of the CIAD also demonstrated good internal consistency, with Cronbach's α values between 0·72 and 0·85.[34] For the other instruments, internal consistency assessment was either conducted methodologically poorly or was not done at all. Measurement error was not investigated for any of the proxy-reported instruments included. Good reliability was shown for the U.S. version of the CADIS, with intraclass correlation coefficients (ICC) of 0·89–0·95 for the domain scores and 0·96 for the total score between the two administrations.[27] An ICC of 0·89 was found for the Dutch IDQoL, proving this instrument to be adequately reliable.[37] While three language versions of the CIAD obtained an indeterminate rating for reliability, there was either no evidence or evidence only from methodologically poor studies for the other instruments.

Data on content validity could be extracted for the U.S. version of the CADIS, the U.K. version of the IDQoL and all language versions of the CIAD. However, all content validity assessments were conducted methodologically poorly. No clear rating could be assigned for the IRT methods used to investigate structural validity of the U.S. version of the CIAD.[34] Hypothesis testing was the measurement property most frequently evaluated, with information available for 14 of the 16 proxy-reported instruments. The two Italian CADIS versions correlated well with other QoL instruments; for instance, Spearman's correlation coefficients of 0·74 with the IDQoL

Table 1 Characteristics of the different instruments

Characteristic	CADIS	CDLQI	CIAD	DISABKIDS-ADM	IDQoL
Target population	Children with eczema aged 0–6 years (and their parents)	Children with skin disease aged 4–16 years	Children with eczema	Children and adolescents with eczema	Infants with eczema aged under 4 years
Mode of administration	Proxy-reported[a]	Self-reported[b]	Proxy-reported[a]	Self- or proxy-reported[b]	Proxy-reported[a]
Number of items	45/41/33[c]	10	9/7[d]	12	10
Number of subscales	5	6	ND	2	8
Number/type of response categories	5-point Likert scale	4-point Likert scale	Dichotomous (true/not true)	5-point Likert scale (and 'not applicable')	4-point Likert scale
Scoring algorithm	Calculation of domain scores by summing up item scores of all items in one domain; calculation of a total score by summing up scores of all items in the questionnaire	Calculation of a sum score, range 0–30	ND	Calculation of a mean standardized score for each dimension, range 0–100	Calculation of a sum score, range 0–30
Recall period in the items	4 weeks	1 week	None ('at the moment')	ND	1 week
Administration costs	No administration costs[43]	No charge for nonfunded studies; $11·50 per patient for pharmaceutical companies[51]	ND	ND	No charge for use in nonfunded studies and routine clinical practice; $11·50 per patient for pharmaceutical companies[52]
Available translations	English (U.S.), Italian, Japanese[43]	More than 50[51]	Dutch, English (U.K.), English (U.S.), French, German	Brazilian Portuguese, other languages[e]	More than 20[52]

CADIS, Childhood Atopic Dermatitis Impact Scale; CDLQI, Children's Dermatology Life Quality Index; CIAD, Childhood Impact of Atopic Dermatitis; DISABKIDS-ADM, DISABKIDS Atopic Dermatitis Module; IDQoL, Infants' Dermatitis Quality of Life Index; ND, not described. [a]'Proxy-reported' means that the (primary) caregiver of an infant fills in a questionnaire that assesses the quality of life of the infant. Proxy-reported instruments are often used with infants and younger children because they cannot report on their quality of life themselves due to their inability to read and a lack of understanding. [b]'Self-reported' instruments are used with older children and adolescents. These questionnaires are filled in by the children/adolescents themselves, not by their caregiver. [c]45 items in the original version, 41 items in the long Italian version, 33 items in the short Italian version (Italian versions include fewer items as some were found to misfit in factor analysis). [d]Nine items in each of the Dutch, English (U.K.), French and German versions; seven items in the English (U.S.) version. The European versions and the U.S. questionnaire have six items in common (of these, three are used as link items). [e]No description given regarding which language versions were tested in the European validation study.

and 0·68 with the Dermatitis Family Impact were found for the long-version Italian CADIS.[35] Discriminative validity of the U.S. version of the CADIS was proven adequate because the instrument could differentiate patients according to severity as measured by the SCORing Atopic Dermatitis (SCORAD) index.[27] Convergent validity of the U.K. version of the IDQoL was assessed in a study of fair methodological quality, but resulted in an indeterminate adequacy rating as only correlations with unrelated constructs were determined.[32] Evidence on hypothesis testing for the remaining questionnaires was available from methodologically poor studies only.[21,24,28,29,34,37] Likewise, we could not draw a conclusion on cross-cultural validity, which was assessed for the long version of the Italian CADIS and four language versions of the CIAD, due to poor methodological study quality.[34,35]

Responsiveness in patients with eczema was investigated for only three questionnaires, but these assessments were of poor methodological quality.[25,27,32,34]

Values for the minimal important change (MIC), the minimal important difference (MID) or validated banding systems are not available for the IDQoL.[40] Evidence from several included validation studies suggests that the IDQoL does not exhibit floor and ceiling effects (i.e. ≥ 15% of patients having the lowest/highest possible score).[24,29,32,37] We could not find information on the interpretability of the other proxy-reported questionnaires. Completion time of the CADIS amounted to approximately 6 min in one study.[26]

Table 2 Important characteristics of the included development and validation studies

QoL instrument	Number of studies	Geographic location(s)	Language(s)	Setting(s)	Study population: Number of participants per study	Study population: Age range
English CADIS (U.S.)	2[26,27]	U.S.A.	English (U.S.)	Secondary/tertiary care	270	1·5–71·4 months
Italian CADIS (long version)	1[35]	Italy	Italian	Secondary/tertiary care	135	2–72 months
Italian CADIS (short version)	1[35]	Italy	Italian	Secondary/tertiary care	135	2–72 months
Danish CDLQI	1[30]	Denmark	Danish	Secondary/tertiary care	35	ND
English CDLQI (U.K.)	1[31]	U.K.	English (U.K.)	Secondary/tertiary care	47	ND (mean ± SD: 9·2 ± 3·6 years)
Malay CDLQI	1[22]	Malaysia	Bahasa Malaysia	Secondary/tertiary care	33	ND (youngest: 7 years)
Serbian CDLQI	1[33]	Serbia	Serbian	Secondary/tertiary care	64	4–16 years
Spanish CDLQI (Mexico)	1[36]	Mexico	Mexican Spanish	Secondary/tertiary care	64	8–16 years
Swedish CDLQI	1[29]	Sweden	Swedish	Secondary/tertiary care	50	5–15 years
Dutch CIAD	1[34,39,a]	Netherlands	Dutch	Secondary/tertiary care and community[39]	15 (item generation)[39]	ND[39]
					20 (field testing)[39]	ND[39]
				Clinical trial[34,b]	48[34]	ND[34]
English CIAD (U.K.)	1[34,39,a]	U.K.	English (U.K.)	Secondary/tertiary care and community[39]	35 (item generation)[39]	ND[39]
					20 (field testing)[39]	ND[39]
				Clinical trial[34,b]	21[34]	ND[34]
English CIAD (U.S.)	1[34,39,a]	U.S.A.	English (U.S.)	Secondary/tertiary care and community[39]	20[39]	ND[39]
				Clinical trial[34,b]	243[34]	ND (mean ± SD: 48 ± 21·6 months)[34]
French CIAD	1[34,39,a]	France	French	Secondary/tertiary care and community[39]	19[39]	ND[39]
				Clinical trial[34,b]	52[34]	ND[34]
German CIAD	1[34,39,a]	Germany	German	Secondary/tertiary care and community[39]	19[39]	ND[39]
				Clinical trial[34,b]	87[34]	ND[34]
Italian CIAD	1[39,a]	Italy	Italian	Secondary/tertiary care and community	15 (item generation)	ND
					8 (field testing)	ND
Spanish CIAD	1[39,a]	Spain	Spanish	Secondary/tertiary care and community	20	ND
DISABKIDS-ADM (unknown language)	1[23]	ND (two European countries)	ND	ND	29	ND
Portuguese DISABKIDS-ADM (Brazil, proxy-reported version)	1[28]	Brazil	Brazilian Portuguese	Secondary/tertiary care	52	8–18 years
Portuguese DISABKIDS-ADM (Brazil, self-reported version)	1[28]	Brazil	Brazilian Portuguese	Secondary/tertiary care	52	8–18 years
Arabic IDQoL	1[21]	Saudi Arabia	Arabic	Secondary/tertiary care	370	ND (mean ± SD: 8·8 ± 9·9 months)

(continued)

Table 2 (continued)

QoL instrument	Number of studies	Geographic location(s)	Language(s)	Setting(s)	Study population: Number of participants per study	Study population: Age range
Dutch IDQoL	1[37]	Netherlands	Dutch	Primary care	66	0·5–83·5 months
English IDQoL (U.K.)	2[25,32]	U.K.	English (U.K.)	Secondary/tertiary care[25]	203[25]	1–53 months[25]
				Secondary/tertiary care and community[32]	89 (validation)[32]	ND (mean: 20·16 months)[32]
				Secondary/tertiary care[32]	92 (development)[32]	ND[32]
Italian IDQoL	1[24]	Italy	Italian	Secondary/tertiary care	21	12–48 months
Swedish IDQoL	1[29]	Sweden	Swedish	Secondary/tertiary care	28	24–48 months

CADIS, Childhood Atopic Dermatitis Impact Scale; CDLQI, Children's Dermatology Life Quality Index; CIAD, Childhood Impact of Atopic Dermatitis; DISABKIDS-ADM, DISABKIDS Atopic Dermatitis Module; IDQoL, Infants' Dermatitis Quality of Life Index; ND, not described; QoL, quality of life. [a]The study by McKenna *et al.*[39] from 2005 did not formally meet the inclusion criteria. However, read in conjunction with the eligible 2007 CIAD development article by McKenna *et al.*,[34] information on content validity of the CIAD could be extracted from the 2005 article. As a result, only the article by McKenna *et al.*[34] from 2007 was formally included, but information from the 2005 article was also taken into consideration for content validity assessment. [b]These studies were conducted in the context of a clinical trial. No further information on the participating health service providers was presented, which is why it was not possible to group these study populations into one of the three categories of community, primary care or secondary/tertiary care.

Self-reported instruments

Table SA5 (in Appendix SA2; Supporting Information) shows the number of studies assessing the different measurement properties of each included self-reported QoL instrument. The results of best evidence synthesis and the degree of recommendation for each self-reported instrument are found in Table 4. There was no instrument for which all relevant measurement properties have been investigated. Hence, there was also no instrument that fulfilled all prespecified requirements of truth, discrimination and feasibility.

Internal consistency assessments were available for four included self-reported QoL instruments, but all were conducted methodologically poorly. Measurement error was not evaluated for any self-reported instrument included. Both the Malay and the Mexican Spanish CDLQI were assigned an indeterminate rating for reliability, whereas this measurement property was not investigated for any other included self-reported instrument.

Content validity was investigated only for the unknown language version of the DISABKIDS-ADM, but the methodological study quality was poor.[23] Information on structural validity of the included self-reported instruments was not available. Data on hypothesis testing was available for all instruments except the unknown language version of the DISABKIDS-ADM. We found an intermediate rating for discriminative validity of the Swedish CDLQI because the instrument was able to differentiate patients according to age, but could not distinguish patients with eczema only from patients with eczema and another allergic comorbidity.[29] The assessments of construct validity of all other questionnaires were of poor methodological quality. Cross-cultural validity was not assessed for any self-reported QoL instrument included.

An investigation of responsiveness was available for the Danish CDLQI only, but was conducted methodologically poorly.[30]

Little information on interpretability is available for the self-reported QoL instruments. No floor and ceiling effects were found for the CDLQI in an analysis of 50 Swedish children with eczema.[29] Similarly, the CDLQI showed no floor and ceiling effects in the 47 children participating in its development study.[31] A recent meta-analysis provides an overview of CDLQI scores in different conditions, enabling comparisons of scores of patients with eczema with those of patients suffering from other diseases and helping to interpret patients' CDLQI scores.[41] Values for the MIC/MID for the CDLQI in patients with eczema, as well as interpretability data for the DISABKIDS-ADM, could not be found.

Discussion

This systematic review assessed the measurement properties of five different QoL instruments for use in infants, children and adolescents with eczema. None of these instruments complied with all prespecified filter criteria of truth, discrimination and feasibility, clearly indicating that more validation work is required.

The strengths of this systematic review include a registered and published protocol, the application of a validated, precise search filter[42] and of predefined eligibility criteria, and the use of the COSMIN checklist[13–16] to judge the methodological quality of the included studies. Every step of the review process was carried out by at least two reviewers. Furthermore, one reviewer (D.H.) was involved in every step of the review to ensure consistency among the participating reviewers. Discrepancies were resolved by frequent discussions within the whole team.

A limitation of this review is the fact that only PubMed and Embase were searched. A thorough hand search of reference lists of included studies, important reviews and the

Table 3 Summary of measurement properties of proxy-reported QoL instruments for infants, children and adolescents with eczema

Measurement property	English CADIS (U.S.)	Italian CADIS (long version)	Italian CADIS (short version)	Dutch CIAD	English CIAD (U.K.)	English CIAD (U.S.)	French CIAD	German CIAD	Italian CIAD	Spanish CIAD	Portuguese DISABKIDS-ADM (Brazil, proxy-reported version)	Arabic IDQoL	Dutch IDQoL	English IDQoL (U.K.)	Italian IDQoL	Swedish IDQoL
Internal consistency	+	Weak	Weak	+	Weak	+	+	+	/	/	Weak	Weak	/	/	Weak	/
Measurement error	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Reliability	+	Weak	Weak	Weak	Weak	? (limited)	? (limited)	? (limited)	/	/	/	/	+	Weak	Weak	/
Content validity	Weak	/	/	Weak	Weak	Weak	Weak	Weak	Weak	Weak	/	/	/	Weak	/	/
Structural validity	/	Weak	/	/	/	? (limited)	/	/	/	/	/	/	/	/	/	/
Hypothesis testing	+	+	+	Weak	Weak	Weak	Weak	Weak	/	/	Weak	Weak	Weak	? (limited)	Weak	Weak
Cross-cultural validity	/	Weak	/	Weak	Weak	/	Weak	Weak	/	/	/	/	/	/	/	/
Responsiveness	Weak	/	/	/	/	Weak	/	/	/	/	/	/	/	Weak	/	/
Recommendation	B	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D

CADIS, Childhood Atopic Dermatitis Impact Scale; CIAD, Childhood Impact of Atopic Dermatitis; DISABKIDS-ADM, DISABKIDS Atopic Dermatitis Module; IDQoL, Infants' Dermatitis Quality of Life Index; QoL, quality of life. Recommendations are defined as follows: A, QoL measurement instrument meets all requirements and is recommended for use; B, QoL measure meets two or more adequacy items, but performance in all other required adequacy items is unclear, so that the outcome measure has the potential to be recommended in the future depending on the results of further validation studies; C, QoL measure has low adequacy in at least one required adequacy criterion (≥ 1 rating of 'minus') and therefore is not recommended to be used anymore; D, QoL measure has (almost) not been validated. Its performance in all or most relevant adequacy items is unclear so that it is not recommended to be used until further validation studies clarify its adequacy. +, positive rating indicating adequate measurement property; ? (limited), intermediate rating indicating intermediate measurement property; Weak, measurement property was assessed only in studies of poor methodological quality (please refer to Table SA2 for further details in the Supporting Information);/, not assessed.

Table 4 Summary of measurement properties of self-reported QoL instruments for infants, children and adolescents with eczema

Measurement property	Danish CDLQI	English CDLQI (U.K.)	Malay CDLQI	Serbian CDLQI	Spanish CDLQI (Mexico)	Swedish CDLQI	DISABKIDS-ADM (unknown language)	Portuguese DISABKIDS-ADM (Brazil, self-reported version)
Internal consistency	/	/	Weak	Weak	Weak	/	/	Weak
Measurement error	/	/	/	/	/	/	/	/
Reliability	/	/	? (limited)	/	? (limited)	/	/	/
Content validity	/	/	/	/	/	/	Weak	/
Structural validity	/	/	/	/	/	/	/	/
Hypothesis testing	Weak	Weak	Weak	Weak	Weak	? (limited)	/	Weak
Cross-cultural validity	/	/	/	/	/	/	/	/
Responsiveness	Weak	/	/	/	/	/	/	/
Recommendation	D	D	D	D	D	D	D	D

CDLQI, Children's Dermatology Life Quality Index; DISABKIDS-ADM, DISABKIDS Atopic Dermatitis Module; QoL, quality of life. Recommendations are defined as follows: A, QoL measurement instrument meets all requirements and is recommended for use; B, QoL measure meets two or more adequacy items, but performance in all other required adequacy items is unclear, so that the outcome measure has the potential to be recommended in the future depending on the results of further validation studies; C, QoL measure has low adequacy in at least one required adequacy criterion (≥ 1 rating of 'minus') and therefore is not recommended to be used anymore; D, QoL measure has (almost) not been validated. Its performance in all or most relevant adequacy items is unclear so that it is not recommended to be used until further validation studies clarify its adequacy. ? (limited), intermediate rating indicating intermediate measurement property; Weak, measurement property was assessed only in studies of poor methodological quality (please refer to Table SA2 for further details in the Supporting Information);/, not assessed.

PROQOLID database retrieved 10 articles of interest not found in our initial systematic search, three of which were judged eligible and included. Another limitation may be that we could not consider responsiveness results of the CIAD obtained in the whole European sample because the paper provided no corresponding country-specific data. Also, information on discriminative validity of the CIAD could not be considered because the specific P-values were not presented by McKenna *et al.*[34]

Of all the instruments reviewed, only the U.S. version of the CADIS[26] reached category B, hence having the potential to be recommended in the future depending on the results of further validation studies. All other questionnaires were placed in category D; their future use cannot be endorsed until further validation data is available.

The CADIS, intended for use in patients with eczema 0–6 years of age, is an internally consistent, reliable questionnaire with adequate construct validity. Its conceptual framework is based on a literature review and directed focus sessions with experts and parents. Compared with the other included instruments, the CADIS is unique in that it assesses both the QoL of the affected infant or child and the QoL of their parents. Although the instrument provides a total score, separate scores for the domains relating to the child's QoL can also be calculated. Results from both the infant- or child-related domains and the parent-related domains were considered for this systematic review. The 45-item questionnaire was completed quickly. A disadvantage of the CADIS is that only three validated language versions of the instrument are currently available, with a validation study of a Spanish version being prepared for publication (personal communication; see reference list for details).[43] The validation article of the Japanese CADIS version, recently published,[44] was not investigated in this systematic review because it was not yet available when our systematic review was conducted. It will be taken into account in the first update to this systematic review. Measurement error and structural validity of the CADIS have not yet been investigated. Moreover, future studies of improved methodological quality should look at content validity, cross-cultural validity, responsiveness and interpretability of the CADIS.

The major finding of this systematic review is that nearly all existing QoL instruments for infants, children and adolescents with eczema are lacking significant validation data and were hence classified in category D. One reason for this is that 76% of the measurement properties were investigated in a methodologically poor manner, compared with 25% in our preceding systematic review assessing the measurement properties of adult eczema QoL instruments.[10] Part of this difference can be attributed to a stricter approach in judging whether hypotheses were formulated a priori when assessing hypothesis testing and responsiveness (item 4 in COSMIN box F, item 8 in COSMIN box I) in this review compared with the afore-mentioned review of adult eczema QoL instruments. However, only 16 of the 32 COSMIN boxes of hypothesis testing and responsiveness rated as 'poor' in this systematic review would obtain a better COSMIN rating if a less strict approach concerning hypotheses formulation were applied, still leaving 57% methodologically poorly investigated measurement properties in total. This result suggests that the methodological study quality is indeed worse than in the previous review on adult eczema QoL instruments.

In addition to insufficient or methodologically poor validation of most instruments included, interpretability data is also lacking. A MID of 2·5 points on the CDLQI has been found in

patients with psoriasis,[45] but corresponding data for patients with eczema do not exist. Similarly, a banding system to help in interpreting CDLQI scores has been developed,[46] but the study did not meet our eligibility criteria because it reported on general dermatology patients in abstract form only. Interpretability in patients with eczema is an important topic that future validation studies should address.

Only two of the five included instruments are self-reported by the affected children. While proxy-reported measures, including the CADIS, may be particularly useful in infants and younger children, they are not suitable for older children and adolescents. As both the CDLQI and the DISABKIDS-ADM were placed in category D, there is currently no self-reported QoL instrument for paediatric eczema that can be recommended for use. CDLQI and DISABKIDS-ADM are also intended for use in adolescents. However, it has been argued that factors influencing adolescents' QoL are fundamentally different from those observed in children and adults, leading to the development of the adolescent-specific Skindex-Teen.[47] The development study of this questionnaire was not eligible for this review, though. Future validation studies of self-reported QoL instruments should therefore investigate whether they are suitable for adolescents with eczema as well, or if separate instruments for this age group are needed.

Currently, only the CADIS has the potential to be recommended for use depending on the results of further validation studies. These validation studies should include all existing language versions of the CADIS and specifically examine measurement error, content validity, structural validity, cross-cultural validity, responsiveness and interpretability. If these studies find favourable measurement properties of the CADIS, it should be translated and validated in more languages to increase international applicability. As the IDQoL is the QoL instrument most often used in eczema trials involving infants,[48] it seems also advisable to undertake further validation work for this questionnaire. Additionally, future validation research should focus on self-reported QoL instruments for children and adolescents with eczema included in this review (CDLQI and DISABKIDS-ADM). For the time being, as none of the investigated QoL instruments can be highly recommended, we suggest using the proxy-reported CADIS for infants and younger children with eczema until formal consensus is reached by the HOME initiative. For older children and adolescents with eczema, there is currently no valid, reliable and feasible self-reported instrument. Trials in this age group should include the QoL instrument that in their authors' opinion is best suited for children and adolescents with eczema. In older adolescents, the two QoL instruments for adults with eczema placed in category B in a previous systematic review,[10] the Quality of Life Index for Atopic Dermatitis (QoLIAD)[49] and the Dermatology Life Quality Index (DLQI),[50] may be applicable.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix SA1. PRISMA 2009 checklist.

Appendix SA2. Supplementary Tables SA1–SA5 (outlined below) pertaining to this article, including supplementary references.

Table SA1. Adequacy criteria for measurement properties.

Table SA2. Levels of evidence for the overall adequacy of a measurement property.

Table SA3. Comparison of the content of the different QoL instruments on content domain level.

Table SA4. Number of studies assessing the measurement properties of proxy-reported QoL instruments for infants, children and adolescents with eczema.

Table SA5. Number of studies assessing the measurement properties of self-reported QoL instruments for infants, children and adolescents with eczema.

Detailed Results SR1. Rating of measurement properties of outcome instruments of quality of life for infants, children and adolescents, and assessment of the methodological quality of the included studies. Includes 80 Supplementary Tables (S1–S80).

9. Anhang

Nachfolgend finden sich unterstützende Materialien zu den von mir veröffentlichten Artikeln (z. B. Tabellen, Abbildungen), die von den jeweiligen Journals nicht gedruckt veröffentlicht, sondern als Online-Appendizes zur Verfügung gestellt wurden.

9.1 Anhang 1

zu Heinl D, Chalmers J, Nankervis H, Apfelbacher CJ. Eczema Trials: Quality of Life Instruments Used and Their Relation to Patient-Reported Outcomes. A Systematic Review. Acta Derm Venereol. 2016; 96: 596-601.

Inhaltsverzeichnis

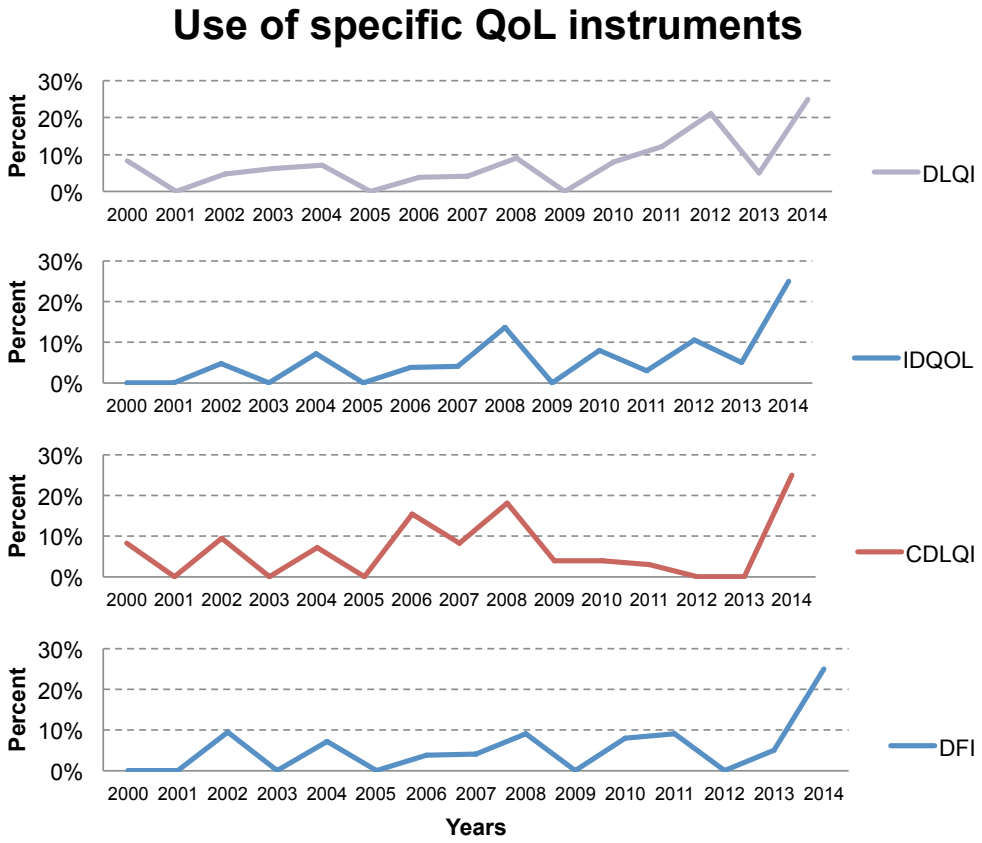

Fig. S1. Percentage of included full texts using one of the 4 most frequently applied quality of life (QoL) instruments over time. DLQI: Dermatology Life Quality Index; IDQOL: Infants' Dermatitis Quality of Life Index; CDLQI: Children's Dermatology Life Quality Index; DFI: Dermatitis Family Impact.

Appendix S1

This appendix contains references for all articles found in GREAT database for our systematic review.

Full text articles: E1-250;E251-287

Abstracts:E288-359

Excluded articles: protocol only (E360-368), no English or German abstract or full text available (E369-373), paper reported on a study already included (E374-377), paper was conference publication and not available as abstract or full text (E378)

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9.2 Anhang 2

zu Apfelbacher CJ, Heinl D, Prinsen CA, Deckert S, Chalmers J, Ofenloch R, Humphreys R, Sach T, Chamlin S, Schmitt J. Measurement properties of adult quality-of-life measurement instruments for eczema: protocol for a systematic review. Syst Rev. 2015;4(1):48. doi:10.1186/s13643-015-0041-3

Inhaltsverzeichnis

Search string **Medline** (via PubMed)

#1 (modified precision search terms by Terwee et al. 2009)

(instrumentation[sh] OR Validation Studies[pt] OR "reproducibility of results"[MeSH Terms] OR reproducib*[tiab] OR "psychometrics"[MeSH] OR psychometr*[tiab] OR clinimetr*[tiab] OR clinometr*[tiab] OR "observer variation"[MeSH] OR observer variation[tiab] OR "discriminant analysis" [MeSH] OR reliab*[tiab] OR valid*[tiab] OR coefficient[tiab] OR "internal consistency"[tiab] OR (cronbach*[tiab] AND (alpha[tiab] OR alphas[tiab])) OR "item correlation"[tiab] OR "item correlations"[tiab] OR "item selection"[tiab] OR "item selections"[tiab] OR "item reduction"[tiab] OR "item reductions"[tiab] OR agreement[tw] OR precision[tw] OR imprecision[tw] OR "precise values"[tw] OR test-retest[tiab] OR (test[tiab] AND retest[tiab]) OR (reliab*[tiab] AND (test[tiab] OR retest[tiab])) OR stability[tiab] OR interrater[tiab] OR inter-rater[tiab] OR intrarater[tiab] OR intra-rater[tiab] OR intertester[tiab] OR inter-tester[tiab] OR intratester[tiab] OR intra-tester[tiab] OR interobserver[tiab] OR inter-observer[tiab] OR intraobserver[tiab] OR intra-observer[tiab] OR intertechnician[tiab] OR intertechnician[tiab] OR intratechnician[tiab] OR intra-technician[tiab] OR interexaminer[tiab] OR inter-examiner[tiab] OR intraexaminer[tiab]) OR (intra-examiner[tiab] OR interassay[tiab] OR inter-assay[tiab] OR intraassay[tiab] OR intra-assay[tiab] OR interindividual[tiab] OR inter-individual[tiab] OR intraindividual[tiab] OR intra-individual[tiab] OR interparticipant[tiab] OR inter-participant[tiab] OR intraparticipant[tiab] OR intra-participant[tiab] OR kappa[tiab] OR kappa's[tiab] OR kappas[tiab] OR "coefficient of variation"[tiab] OR repeatab*[tw] OR ((replicab*[tw] OR repeated[tw]) AND (measure[tw] OR measures[tw] OR findings[tw] OR result[tw] OR results[tw] OR test[tw] OR tests[tw])) OR generaliza*[tiab] OR generalisa*[tiab] OR concordance[tiab] OR (intraclass[tiab] AND correlation*[tiab]) OR discriminative[tiab] OR "known group" [tiab] OR "factor analysis"[tiab] OR "factor analyses"[tiab] OR "factor structure"[tiab] OR "factor structures"[tiab] OR dimensionality[tiab] OR subscale*[tiab] OR "multitrait scaling analysis"[tiab] OR "multitrait scaling analyses"[tiab] OR "item discriminant"[tiab] OR "interscale correlation"[tiab] OR "interscale correlations"[tiab]) OR ((error[tiab] OR errors[tiab]) AND (measure*[tiab] OR correlat*[tiab] OR evaluat*[tiab] OR accuracy[tiab] OR accurate[tiab] OR precision[tiab] OR mean[tiab])) OR "individual variability"[tiab] OR "interval variability"[tiab] OR "rate variability"[tiab] OR "variability analysis"[tiab] OR (uncertainty[tiab] AND

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#2

(“addresses”[Publication Type] OR “biography”[Publication Type] OR “case reports”[Publication Type] OR “comment”[Publication Type] OR “directory”[Publication Type] OR “editorial”[Publication Type] OR “festschrift”[Publication Type] OR “interview”[Publication Type] OR “lectures”[Publication Type] OR “legal cases”[Publication Type] OR “legislation”[Publication Type] OR “letter”[Publication Type] OR “news”[Publication Type] OR “newspaper article”[Publication Type] OR “patient education handout”[Publication Type] OR “popular works”[Publication Type] OR “congresses”[Publication Type] OR “consensus development conference”[Publication Type] OR “consensus development conference, nih”[Publication Type] OR “practice guideline”[Publication Type]) NOT (“animals”[MeSH Terms] NOT “humans”[MeSH Terms])

#3: #1 NOT #2

#4

(quality of life[MH] OR quality of life[TW] OR health status[MH] OR health status[TW] OR "activities of daily living"[MH] OR activities of daily living[TW] OR life quality* OR daily life[TW]OR health level[TW] OR level of health[TW] OR patient reported outcome[TW] OR Skindex[TW] OR Eczema Disability Index[TW])

AND

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("dermatitis, atopic"[MeSH] OR atopic dermatitis[tiab] OR atopic eczema[tiab] OR eczema[MeSH] OR eczema[tiab] OR "neurodermatitis"[MeSH] OR Neurodermatitis[tiab] OR skin diseases[MH] OR skin disease*[tiab] OR dermatology[tiab])

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Search string **Embase**

#1

exp instrumentation/ or exp validation study/ or exp reproducibility/ or reproducib$.mp. or exp psychometry/ or psychometr$.mp. or clinimetr*.mp. or clinometr$.mp. or exp observer variation/ or observer variation.mp. or exp discriminant analysis/ or exp reliability/ or reliab$.mp. or exp Validity/ or valid$.mp. or coefficient.mp. or internal consistency.mp. or (cronbach$ and (alpha or alphas)).mp. or item correlation.mp. or item correlations.mp. or item selection.mp. or item selections.mp. or item reduction.mp. or item reductions.mp. or agreement.mp. or precision.mp. or imprecision.mp. or precise values.mp. or (test-retest or (test and retest) or (reliab$ and (test or retest)) or stability or interrater or inter-rater or intrarater or intra-rater or intertester or inter-tester or intratester or intra-tester or interobserver or inter-observer or intraobserver or intra-observer or intertechnician or intertechnician or intratechnician or intra-technician or interexaminer or inter-examiner or intraexaminer or intra-examiner or interassay or inter-assay or intraassay or intra-assay or interindividual or inter-individual or intraindividual or intra-individual or interparticipant or inter-participant or intraparticipant or intra-participant or kappa or kappa$ or coefficient of variation or repeatab$ or ((replicap$ or repeated) and (measure or measures or findings or result or results or test or tests))).mp. or (generaliza$ or generalisa$ or concordance or (intraclass and correlation$) or discriminative or known group or factor analysis or factor analyses or factor structure or factor structures or dimensionality or subscale$ or multitrait scaling analysis or multitrait scaling analyses or item discriminant or interscale correlation or interscale correlations or ((error or errors) and (measure$ or correlat$ or evaluat$ or accuracy or accurate or precision or mean)) or individual variability or interval variability or rate variability or variability analysis or (uncertainty and (measurement or measuring)) or standard error of measurement or sensitiv$ or responsive$ or (limit and detection) or minimal detectable concentration or interpretab$ or (small$ and (real or detectable) and (change or difference)) or meaningful change or minimal important change or minimal important difference or minimally important change or minimally important difference or minimal detectable change or minimal detectable difference or minimally detectable change or minimally detectable difference or minimal real change or minimal real difference or minimally real change or minimally real difference).mp. or (ceiling effect or floor effect or Item response model or IRT or Rasch or Differential item functioning or DIF or computer adaptive testing or item bank or cross-cultural equivalence or practica$ or feasib$).mp.

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quality of life/ or quality of life.mp. or health status/ or health status.mp. or daily life activity/ or activities of daily living.mp. or life quality$.mp. or daily life.mp. or health level.mp. or level of health.mp. or health status/ or patient reported outcome.mp. or Skindex.mp. or Eczema Disability Index.mp.

#5

exp Atopic Dermatitis/ or dermatitis, atopic.mp. or atopic dermatitis.mp. or exp eczema/ or atopic eczema.mp. or eczema, atopic.mp. or exp NEURODERMATITIS/ or neurodermatitis.mp. or skin disease/ or skin disease.mp. or dermatology/ or dermatology.mp.

9.3 Anhang 3

zu Heinl D, Prinsen CAC, Deckert S, Chalmers JR, Drucker AM, Ofenloch R, Humphreys R, Sach T, Chamlin SL, Schmitt J, Apfelbacher C. Measurement properties of adult quality-of-life measurement instruments for eczema: a systematic review. Allergy. 2016; 71: 358-370.

Inhaltsverzeichnis

Detailed results: Rating of measurement properties of outcomes instruments of quality of life of adult eczema patients and assessment of the methodological quality of the included studies

Table of contents

Abbreviations and symbols used

+ positive rating

? indeterminate rating

- negative rating

AD = atopic dermatitis; *AE* = atopic eczema; *ANOVA* = analysis of variance; *COSMIN* = COnsensus-based Standards for the selection of health status Measurement INstruments; *DIELH* = Deutsches Instrument zur Erfassung der Lebensqualität; *DIF* = Differential item functioning; *DLQI* = Dermatology Life Quality Index; *EASI* = Eczema Area and Severity Index; *GWBI* = General Well-Being Index; *INVAS* = Investigator overall assessment of disease severity; *QoL* = quality of life; *MCS* = Mental component score ; *NL* = Netherlands; *PCS* = Physical component score; *PGI* = Patient-Generated Index; *PGWB* = Psychological General Well-Being Index; *PRUVAS* = subjective measure of pruritus severity; *PTVAS* = subjective measure of eczema severity; *SCORAD* = SCORing Atopic Dermatitis; *SF-36* = Short form 36; *TCS* = topical corticosteroids; *UK* = United Kingdom; *US* = United States of America

1. Deutsches Instrument zur Erfassung der Lebensqualität bei Hauterkrankungen (DIELH)

Table E1: Structural validity of the DIELH

Author	Structural validity				
	Method	Result	Interpretation	Study base	COSMIN score
(E1)	Principal components analysis within the single diagnostic groups (including AE) performed; questions were included if they did not load >0.7 on more than one factor	Not given	?	Number of AE patients unknown	fair
Conclusion: One study assessed structural validity of the DIELH and indicated unclear structural validity as a QoL instrument for eczema ➔ Structural validity of the DIELH as a measurement of QoL: **unclear** ➔ Quality of evidence: **fair**					

Table E2: Discriminative validity of the DIELH

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E2)	Comparison of the sum scores of different diagnostic groups (Kruskal-Wallis test); hypothesis: Patients with chronic inflammatory dermatoses (like AE) have an higher impact on QoL	Median total score for AE 75.5 (highest value of all diagnostic groups); statistically significant ($p<0.0001$)	+	85 AE patients	fair
Conclusion: One study assessed discriminative validity of the DIELH and indicated adequate discriminative validity as a QoL instrument for eczema ➔ Discriminative validity of the DIELH as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

2. Dermatology Life Quality Index (DLQI) – Danish version

Table E3: Convergent/divergent validity of the Danish DLQI

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E3)	Spearman correlation coefficients between DLQI and 8 dimensions/PCS/MCS of the SF-36; Spearman correlation coefficients between DLQI, PRUVAS, PTVAS and INVAS; Wilcoxon rank scores between DLQI and SCORAD	The spearman correlation coefficients between DLQI and 8 dimensions/PCS/MCS of the SF-36 range between -0.54 (General health) and -0.11 (Bodily pain); most correlations <0.5 Spearman correlation coefficients for DLQI were 0.62 with PRUVAS, 0.81 with PTVAS and 0.82 with INVAS. DLQI was significantly (P < 0.0001) associated with objective SCORAD.	-	66 patients with eczema	poor
Conclusion: One study assessed convergent/divergent validity of the Danish DLQI, but due to poor methodological study quality no conclusion can be drawn ➔ Convergent/divergent validity of the Danish DLQI as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table E4: Discriminative validity of the Danish DLQI

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E3)	Discriminative was assessed (using Wilcoxon rank scores) by seeing how well the QOL measures could discriminate between groups of participants according to clinical assessed SCORAD	Differences in DLQI scores between patients with mild and moderate AD (according to objective SCORAD) were statistically significant (P<0.0001).	+	66 patients with eczema	poor
Conclusion: One study assessed discriminative validity of the Danish DLQI, but due to poor methodological study quality no conclusion can be drawn ➔ Discriminative validity of the Danish DLQI as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

3. Dermatology Life Quality Index (DLQI) – English version (UK)

Table E5: Internal consistency of the English DLQI (UK)

Author	Internal consistency				
	Method	Result	Interpretation	Study base	COSMIN score
(E4)	Person Separation Index (PSI)	0.63 for eczema patients (considered low by the author)	-	146 patients with eczema	good
Conclusion: One study assessed internal consistency of the UK version of the DLQI and indicated inadequate internal consistency as a QoL instrument for eczema ➔ Internal consistency of the English DLQI (UK) as a measurement of QoL: **inadequate** ➔ Quality of evidence: **good**					

Table E6: Content validity of the English DLQI (UK)

Author	Content validity				
	Method	Result	Interpretation	Study base	COSMIN score
(E5)	Comparison of the areas/activities in the DLQI and those that were mentioned by the patients in the PGI; hypothesis: patients would include a broader range of affected areas in their responses to the PGI than those included in the DLQI	36 patients (64%) mentioned areas or activities not part of the DLQI, 20 patients identified only areas included in the DLQI; DLQI item 1 not mentioned by any patient	-	56 patients with eczema	fair
Conclusion: One study assessed content validity of the UK version of the DLQI and indicated inadequate content validity as a QoL instrument for eczema ➔ Content validity of the English DLQI (UK) as a measurement of QoL: **inadequate** ➔ Quality of evidence: **fair**					

Table E7: Structural validity of the English DLQI (UK)

Author	Structural validity				
	Method	Result	Interpretation	Study base	COSMIN score
(E4)	Examination of overall fit to the Rasch model by reference to the overall item-trait interaction χ^2-fit value and via Item and Person interaction statistics; examination of DIF by ANOVA of standardized residuals.	DLQI does not fit a Rasch model for the overall sample, but fits a Rasch model for AD patients (item-trait interaction = 0.460); item residual statistics indicative of model misfit for the AD patients; 5/10 items showed DIF for different parameters (age and/or gender) in the AD sample. 5/10 items showed disease-specific DIF in the overall sample. A single item (item 4, P=0.048) showed misfit to the model. Items 4 (P=0.010) and 7 (P=0.043) showed uniform DIF by gender, and item 6 (P=0.012) exhibited nonuniform DIF by gender. Items 2 (P=0.010), 4 (P=0.020), 7 (P<0.001), and 10 (P=0.028) showed uniform DIF by age, and item 7 (p<0.001) showed nonuniform DIF by age.	-	292 patients (overall sample, 146 psoriasis, 146 eczema) 146 patients (eczema sample)	good
Conclusion: One study assessed structural validity of the UK version of the DLQI and indicated inadequate structural validity as a QoL instrument for eczema ➔ Structural validity of the English DLQI (UK) as a measurement of QoL: **inadequate** ➔ Quality of evidence: **good**					

Table E8: Convergent/divergent validity of the English DLQI (UK)

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E5)	Correlation between DLQI and PGI and individual DLQI questions were calculated. The mean PGI scores of those who scored 0 on items of the DLQI were compared, using a t-test, with the scores of those who scored 1-3 in each item of the DLQI. Calculation of correlations between the DLQI and the costs of eczema; hypothesis: patients with poor QoL incur high total costs, health service costs and personal costs	Total correlation between DLQI and PGI -0.52 ($p<0.001$) --> positive rating; Questions 1-5 of the DLQI were correlated with the PGI but only question 2 had a correlation of >0.5. Questions 6-10 were not statistically significant correlated. Correlations between DLQI and total costs -0.34 ($p<0.01$); correlation between DLQI and health service costs -0.47 ($p<0.001$); no correlation with personal costs Positive rating because correlation with a QoL measure (PGI) is higher than these correlations	+	56 patients with eczema	fair
Conclusion: One study assessed convergent/divergent validity of the UK version of the DLQI and indicated adequate convergent validity as QoL instrument for eczema ➔ Convergent/divergent validity of the English DLQI (UK) as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

Table E9: Discriminative validity of the English DLQI (UK)

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E6)	Comparison of DLQI scores between patients with atopic eczema, pruritus and psoriasis with patients with acne, basal cell carcinoma and viral warts	Scores for patients with atopic eczema, generalized pruritus and psoriasis were higher than for patients with acne, basal cell carcinoma and viral warts (P<0.001)	+	13 patients with eczema	poor
Conclusion: One study assessed discriminative validity of the UK version of the DLQI, but due to poor methodological study quality no conclusion can be drawn ➔ Discriminative validity of the English DLQI (UK) as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

4. Dermatology Life Quality Index (DLQI) – German version

Table E10: Discriminative validity of the German DLQI

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E7)	Discriminative validity: Comparison of mean and subscale scores between patients with psoriasis and AD; t-test to determine statistical significance	Differences in mean score statistically significant ($p<0.01$); Differences in all subscale scores statistically significant except for leisure/sport and relationships	?	80 patients with eczema	poor
Conclusion: One study assessed discriminative validity of the German DLQI, but due to poor methodological study quality no conclusion can be drawn ➔ Discriminative validity of the German DLQI as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

5. Dermatology Life Quality Index (DLQI) – Spanish version

Table E11: Reliability of the Spanish DLQI

Author	Reliability				
	Method	Result	Interpretation	Study base	COSMIN score
(E8)	Test retest using Intraclass Correlation Coefficient (ICC) between two administrations	ICC between the two administrations was 0.77 (95% CI) for eczema patients	+	45 patients with eczema	fair
Conclusion: One study assessed reliability of the Spanish DLQI and indicated adequate reliability as a QoL instrument for eczema ➔ Reliability of the Spanish DLQI as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

Table E12: Responsiveness of the Spanish DLQI

Author	Responsiveness				
	Method	Result	Interpretation	Study base	COSMIN score
(E8)	Change in scores over three visits after starting TCS	V1 = 4.53, V2 = 2.80, V3 = 1.64. Change between V1 and V3 was statistically significant (p=<0.001); change between V1 and V2 not statistically significant	?	69 patients with eczema	fair
(E8)	Sensitivity to change - effect size (ES) statistic	ES for change in overall DLQI score between visits 1 and 3 was 0.82.	+	69 patients with eczema	fair
Conclusion: One study assessed responsiveness of the Spanish DLQI and indicated adequate responsiveness as a QoL instrument for eczema ➔ Responsiveness of the Spanish DLQI as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

6. Freiburg Life Quality Assessment – core module (FLQA-c)

Table E13: Convergent/divergent validity of the FLQA-c

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E9)	FLQA scores compared to SCORAD severity scores using Pearson correlation coefficient	Low and moderate correlations between severity score and FLQA scales; between r = 14 and r = 34 in atopic dermatitis patients (p108, 2nd column)	?	253 patients with eczema	fair
Conclusion: One study assessed convergent/divergent validity of the FLQA-c and indicated unclear convergent validity as a QoL instrument for eczema ➔ Convergent/divergent validity of the FLQA-c as a measurement of QoL: **unclear** ➔ Quality of evidence: **fair**					

Table E14: Discriminative validity of the FLQA-c

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E9)	Comparison of scores between AD and psoriasis patients (ANOVA for independent samples)	Differences between AD and psoriasis patients statistically significant (p<0.001) for 5/6 subscales	?	253 patients with eczema	fair
Conclusion: One study assessed discriminative validity of the FLQA-c and indicated unclear discriminative validity as a QoL instrument for eczema ➔ Discriminative validity of the FLQA-c as a measurement of QoL: **unclear** ➔ Quality of evidence: **fair**					

Table E15: Responsiveness of the FLQA-c

Author	Responsiveness				
	Method	Result	Interpretation	Study base	COSMIN score
(E9)	Comparison of patient scores after 4 weeks of treatment (paired t-test)	Changes in scores on all subscales statistically significant (p<0.001) for AD patients	+	Number of AD patients unknown	poor
Conclusion: One study assessed responsiveness of the FLQA-c, but due to poor methodological study quality no conclusion can be drawn ➔ Responsiveness of the FLQA-c as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

7. Freiburg Life Quality Assessment for Dermatoses (FLQA-d)

Table E16: Discriminative validity of the FLQA-d

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E7)	Comparison of subscale scores between patients with psoriasis and AD; t-test to determine statistical significance	Differences in all subscale scores statistically significant ($p<0.01$) except for social life and treatment --> 4/6 statistically significant different --> indeterminate rating (in contrast to DLQI no data on mean scores)	?	80 patients with eczema	poor
Conclusion: One study assessed discriminative validity of the FLQA-d, but due to poor methodological study quality no conclusion can be drawn ➔ Discriminative validity of the FLQA-d as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

8. Impact of Chronic Skin Disease on Daily Life (ISDL)

Table E17: Internal consistency of the ISDL

Author	Internal consistency				
	Method	Result	Interpretation	Study base	COSMIN score
(E10)	Cronbach's alpha but poorly described	Ranged from 0.64 - 0.93	+	128 patients with eczema	poor
Conclusion: One study assessed internal consistency of the ISDL, but due to poor methodological study quality no conclusion can be drawn ➔ Internal consistency of the ISDL as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table E18: Content validity of the ISDL

Author	Content validity				
	Method	Result	Interpretation	Study base	COSMIN score
(E10)	Items based on literature had to be relevant for the construct to be measured; health professionals and patients with chronic skin diseases evaluated the initial item pool, resulting in 30 eligible items	Normal distributions of all items in pilot study	?	Item generation: unknown Pilot study: 65 psoriasis and 77 AD patients	poor
Conclusion: One study assessed content validity of the ISDL, but due to poor methodological study quality no conclusion can be drawn ➔ Content validity of the ISDL as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table E19: Convergent/divergent validity of the ISDL

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E10)	Convergent validity of ISDL assessed with patients rating of disease activity on a 4-point Likert scale (extent and severity of skin involvement of main disease characteristics for each body area), DLQI, anxiety scale (SCL), depression scale (SCL) and neuroticism scale (EPQ). Calculated Pearson's correlation coefficient.	Too many individual results to list. Moderate (0.30-0.50) to relatively high (>0.50) correlations in expected directions. More correlations <0.5 than above 0.5, see table 3 in paper.	-	128 patients with eczema	fair
Conclusion: One study assessed convergent/divergent validity of the ISDL and indicated inadequate convergent validity as a QoL instrument for eczema ➔ Convergent/divergent validity of the ISDL as a measurement of QoL: **inadequate** ➔ Quality of evidence: **fair**					

Table E20: Discriminative validity of the ISDL

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E10)	Comparison of scores of AD and psoriasis patients	AD patients had significantly higher scores for itch ($t=3.27$, $p<0.001$), scratch response (conscious $t=4.95$, $p<0.001$; automatic $t=6.40$, $p<0.001$) and daily-life impact ($t=4.14$, $p<0.001$); differences in scores on all other subscales not statistically significant	?	128 patients with eczema	poor
Conclusion: One study assessed discriminative validity of the ISDL, but due to poor methodological study quality no conclusion can be drawn ➔ Discriminative validity of the ISDL as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table E21: Responsiveness of the ISDL

Author	Responsiveness				
	Method	Result	Interpretation	Study base	COSMIN score
(E10)	Effect study of 5-session of cognitive behavioural group therapy programme where patients learn to cope with itch and reduce scratching to assess sensitivity to change.	Physical functioning: skin status (t=3.85), itch (t=5.07), conscious scratching (t=5.47), automatic scratching (t=4.80) - all p<0.001, pain (t=3.62, p<0.01), fatigue (t=1.89, p<0.07). Daily life impact: t=4.31, p<0.001, helplessness (t=2.70, p<0.01), acceptance (t= -3.52, p<0.01), perceived benefits (t= -3.59, p<0.01), anxiety (t=2.43, p=0.02). No significant changes for negative and positive mood, stigmatization and social support. So 11/16 showed some correlation.	?	49 patients with eczema	poor
Conclusion: One study assessed responsiveness of the ISDL, but due to poor methodological study quality no conclusion can be drawn ➔ Responsiveness of the ISDL as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

9. Quality of Life Index for Atopic Dermatitis (QoLIAD) – Dutch version

Table E22: Internal consistency of the Dutch QoLIAD

Author	Internal consistency				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Cronbach's coefficient	0.88 (time 1) and 0.89 (time 2)	+	39 patients with eczema	poor
Conclusion: One study assessed internal consistency of the Dutch QoLIAD, but due to poor methodological study quality no conclusion can be drawn ➔ Internal consistency of the Dutch QoLIAD as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table E23: Reliability of the Dutch QoLIAD

Author	Reliability				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Test-retest. Patients completed the QoLIAD twice, 2 weeks apart.	Spearman's correlation coefficient = 0.80	?	17 patients with eczema	poor
Conclusion: One study assessed reliability of the Dutch QoLIAD, but due to poor methodological study quality no conclusion can be drawn ➔ Reliability of the Dutch QoLIAD as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table E24: Content validity of the Dutch QoLIAD

Author	Content validity				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Interviews (15 NL, 65 total) to explore the effect AD has on the patient to generate wording for items. Tested for cultural applicability across countries. Patients completed questionnaire and interviewed to identify and remove problematic items. Field testing to further reduce items.	All needs affected by AD identified (not listed here) resulting in 76 item scale. 20 removed and 11 modified after cross cultural validation to yield a 56 item version for field testing. At the field testing stage 14 items were removed and two modified leaving 42. Final version had 25 items - fit to Rasch model. Local dependency between items was minimal - minimal item redundancy	+	Item generation and selection: 15 patients with eczema Field testing: 20 patients with eczema	good
Conclusion: One study assessed content validity of the Dutch QoLIAD and indicated adequate content validity as a QoL instrument for eczema ➔ Content validity of the Dutch QoLIAD as a measurement of QoL: **adequate** ➔ Quality of evidence: **good**					

Table E25: Convergent/divergent validity of the Dutch QoLIAD

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Patients completed the QoLIAD, DLQI and PGWB/GWBI (general) twice, 2 weeks apart. Assessed correlation between scales. Ranges predicted 0.6-0.8 for DLQI and 0.5-0.7 for PGWB/GWBI using Spearman's rank correlation coefficients	Correlations between QoLIAD and DLQI 0.79 (time 1) and 0.58 (time 2). Correlations between QoLIAD and PGWB/GWBI 0.63 (time 1) and 0.47 (time 2).	+	39 patients with eczema	fair
Conclusion: One study assessed convergent/divergent validity of the Dutch QoLIAD and indicated adequate convergent validity as a QoL instrument for eczema ➔ Convergent/divergent validity of the Dutch QoLIAD as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

Table E26: Discriminative validity of the Dutch QoLIAD

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Assessed ability of scale to discriminate between i) patient perceived severity (mild / moderate and quite/very severe AD, ii) flare or no flare and iii) patient perceived general health (excellent, good, fair or poor)	Dutch measure was not statistically significant for all 3 assessment groups. May be due to small sample size in Netherlands.	-	39 patients with eczema	fair
Conclusion: One study assessed discriminative validity of the Dutch QoLIAD and indicated inadequate discriminative validity as a QoL instrument for eczema ➔ Discriminative validity of the Dutch QoLIAD as a measurement of QoL: **inadequate** ➔ Quality of evidence: **fair**					

10. Quality of Life Index for Atopic Dermatitis (QoLIAD) – English version (UK)

Table E27: Internal consistency of the English QoLIAD (UK)

Author	Internal consistency				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Cronbach's coefficient	0.91 (time 1) and 0.94 (time 2)	+	269 patients with eczema	fair
(E12)	Internal consistency was assessed using Person Separation Index (PSI)	The PSI given in table 2 indicate there is a good level of internal reliability as they were greater than 0.7 (0.91 for initial fit of QoLIAD and 0.82 when 2 items removed).	+	146 patients with eczema	good
Conclusion: Two studies assessed internal consistency of the UK version of the QoLIAD and indicated adequate internal consistency as a QoL instrument for eczema ➔ Internal consistency of the English QoLIAD (UK) as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair** to **good**					

Table E28: Reliability of the English QoLIAD (UK)

Author	Reliability				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Test-retest. Patients completed the QoLIAD twice, 2 weeks apart.	Spearman's correlation coefficient = 0.86	?	269 patients with eczema	fair
Conclusion: One study assessed reliability of the UK version of the QoLIAD and indicated unclear reliability as a QoL instrument for eczema ➔ Reliability of the English QoLIAD (UK) as a measurement of QoL: **unclear** ➔ Quality of evidence: **fair**					

Table E29: Content validity of the English QoLIAD (UK)

Author	Content validity				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Interviews (36 UK, 65 total) to explore the effect AD has on the patient to generate wording for items. Tested for cultural applicability across countries. Patients completed questionnaire and interviewed to identify and remove problematic items. Field testing to further reduce items.	All needs affected by AD identified (not listed here) resulting in 76 item scale. 20 removed and 11 modified after cross cultural validation to yield a 56 item version for field testing. At the field testing stage 14 items were removed and two modified leaving 42 items. Final version had 25 items - fit to Rasch model. Local dependency between items was minimal - minimal item redundancy	+	Item generation and selection: 36 patients with eczema Field testing: 21 patients with eczema	good
Conclusion: One study assessed content validity of the UK version of the QoLIAD and indicated adequate content validity as a QoL instrument for eczema ➔ Content validity of the English QoLIAD (UK) as a measurement of QoL: **adequate** ➔ Quality of evidence: **good**					

Table E30: Structural validity of the English QoLIAD (UK)

Author	Structural validity				
	Method	Result	Interpretation	Study base	COSMIN score
(E12)	Examination of overall fit to the Rasch model by reference to the overall item-trait interaction χ^2-fit value and via Item and Person interaction statistics; examination of DIF by ANOVA of standardized residuals.	QoLIAD fits the Rasch model (item-trait interaction = 0.28), although there is evidence for marginal multidimensionality. No clear item misfit found. Authors do not refer to DIF in the results section (except for disease, but not statement whether DIF was uniform or non-uniform)	?	146 patients with eczema	good
Conclusion: One study assessed structural validity of the UK version of the QoLIAD and indicated unclear structural validity as a QoL instrument for eczema ➔ Structural validity of the English QoLIAD (UK) as a measurement of QoL: **unclear** ➔ Quality of evidence: **good**					

Table E31: Convergent/divergent validity of the English QoLIAD (UK)

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Patients completed the QoLIAD, DLQI and PGWB/GWBI (general) twice, 2 weeks apart. Assessed correlation between scales. Ranges predicted 0.6-0.8 for DLQI and 0.5-0.7 for PGWB/GWBI using Spearman's rank correlation coefficients	Correlations between QoLIAD and DLQI 0.69 (time 1) and 0.77 (time 2). Correlations between QoLIAD and PGWB/GWBI 0.55 (time 1) and 0.55 (time 2).	+	269 patients with eczema	fair
Conclusion: One study assessed convergent/divergent validity of the UK version of the QoLIAD and indicated adequate convergent validity as a QoL instrument for eczema ➔ Convergent/divergent validity of the English QoLIAD (UK) as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

Table E32: Discriminative validity of the English QoLIAD (UK)

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Assessed ability of scale to discriminate between i) patient perceived severity (mild / moderate and quite/very severe AD, ii) flare or no flare and iii) patient perceived general health (excellent, good, fair or poor)	Differences in scores for all 3 assessment groups statistically significant ($p<0.001$ for severity and general health, $p<0.01$ for flares)	+	269 patients with eczema	fair
Conclusion: One study assessed discriminative validity of the UK version of the QoLIAD and indicated adequate discriminative validity as a QoL instrument for eczema ➔ Discriminative validity of the English QoLIAD (UK) as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

11. Quality of Life Index for Atopic Dermatitis (QoLIAD) – English version (US)

Table E33: Internal consistency of the English QoLIAD (US)

Author	Internal consistency				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Cronbach's coefficient	0.93 (time 1) and 0.92 (time 2)	+	170 patients with eczema	fair
Conclusion: One study assessed internal consistency of the US version of the QoLIAD and indicated adequate internal consistency as a QoL instrument for eczema ➔ Internal consistency of the English QoLIAD (US) as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

Table E34: Reliability of the English QoLIAD (US)

Author	Reliability				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Test-retest. Patients completed the QoLIAD twice, 2 weeks apart.	Spearman's correlation coefficient = 0.90	?	170 patients with eczema	fair
Conclusion: One study assessed reliability of the US version of the QoLIAD and indicated unclear reliability as a QoL instrument for eczema ➔ Reliability of the English QoLIAD (US) as a measurement of QoL: **unclear** ➔ Quality of evidence: **fair**					

Table E35: Content validity of the English QoLIAD (US)

Author	Content validity				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Tested for cultural applicability across countries. Patients completed questionnaire and interviewed to identify and remove problematic items. Field testing to further reduce items.	All needs affected by AD identified (not listed here) resulting in 76 item scale. 20 removed and 11 modified after cross cultural validation to yield a 56 item version for field testing. At the field testing stage 14 items were removed and two modified leaving 42 items Final version had 25 items - fit to Rasch model. Local dependency between items was minimal - minimal item redundancy	+	Item generation and selection: not described Field testing: 20 patients with eczema	good
Conclusion: One study assessed content validity of the US version of the QoLIAD and indicated adequate content validity as a QoL instrument for eczema ➔ Content validity of the English QoLIAD (US) as a measurement of QoL: **adequate** ➔ Quality of evidence: **good**					

Table E36: Convergent/divergent validity of the English QoLIAD (US)

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Patients completed the QoLIAD, DLQI and PGWB/GWBI (general) twice, 2 weeks apart. Assessed correlation between scales. Ranges predicted 0.6-0.8 for DLQI and 0.5-0.7 for PGWB/GWBI using Spearman's rank correlation coefficients	Correlations between QoLIAD and DLQI 0.74 (time 1) and 0.75 (time 2). Correlations between QoLIAD and PGWB/GWBI 0.55 (time 1) and 0.67 (time 2).	+	170 patients with eczema	fair
Conclusion: One study assessed convergent/divergent validity of the US version of the QoLIAD and indicated adequate convergent validity as a QoL instrument for eczema ➔ Convergent/divergent validity of the English QoLIAD (US) as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

Table E37: Discriminative validity of the English QoLIAD (US)

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Assessed ability of scale to discriminate between i) patient perceived severity (mild / moderate and quite/very severe AD, ii) flare or no flare and iii) patient perceived general health (excellent, good, fair or poor)	Differences in scores for all 3 assessment groups statistically significant ($p<0.001$ for severity and general health, $p<0.01$ for flares)	+	170 patients with eczema	fair
Conclusion: One study assessed discriminative validity of the US version of the QoLIAD and indicated adequate discriminative validity as a QoL instrument for eczema ➔ Convergent validity of the English QoLIAD (US) as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

12. Quality of Life Index for Atopic Dermatitis (QoLIAD) – French version

Table E38: Internal consistency of the French QoLIAD

Author	Internal consistency				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Cronbach's coefficient	0.90 (time 1) and 0.92 (time 2)	+	200 patients with eczema	fair
Conclusion: One study assessed internal consistency of the French QoLIAD and indicated adequate internal consistency as a QoL instrument for eczema ➔ Internal consistency of the French QoLIAD as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

Table E39: Reliability of the French QoLIAD

Author	Reliability				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Test-retest. Patients completed the QoLIAD twice, 2 weeks apart.	Spearman's correlation coefficient = 0.89	?	200 patients with eczema	fair
Conclusion: One study assessed reliability of the French QoLIAD and indicated unclear reliability as a QoL instrument for eczema ➔ Reliability of the French QoLIAD as a measurement of QoL: **unclear** ➔ Quality of evidence: **fair**					

Table E40: Convergent/divergent validity of the French QoLIAD

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Patients completed the QoLIAD, DLQI and PGWB/GWBI (general) twice, 2 weeks apart. Assessed correlation between scales. Ranges predicted 0.6-0.8 for DLQI and 0.5-0.7 for PGWB/GWBI using Spearman's rank correlation coefficients	Correlations between QoLIAD and DLQI 0.65 (time 1) and 0.71 (time 2). Correlations between QoLIAD and PGWB/GWBI 0.63 (time 1) and 0.66 (time 2).	+	200 patients with eczema	fair
Conclusion: One study assessed convergent/divergent validity of the French QoLIAD and indicated adequate convergent validity as a QoL instrument for eczema ➔ Convergent/divergent validity of the French QoLIAD as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

Table E41: Discriminative validity of the French QoLIAD

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Assessed ability of scale to discriminate between i) patient perceived severity (mild / moderate and quite/very severe AD, ii) flare or no flare and iii) patient perceived general health (excellent, good, fair or poor)	Differences in scores for all 3 assessment groups statistically significant (p<0.001)	+	200 patients with eczema	fair
Conclusion: One study assessed discriminative validity of the French QoLIAD and indicated adequate discriminative validity as a QoL instrument for eczema ➔ Discriminative validity of the French QoLIAD as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

13. Quality of Life Index for Atopic Dermatitis (QoLIAD) – German version

Table E42: Internal consistency of the German QoLIAD

Author	Internal consistency				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Cronbach's coefficient	0.91 (time 1) and 0.92 (time 2)	+	178 patients with eczema	fair
Conclusion: One study assessed internal consistency of the German QoLIAD and indicated adequate internal consistency as a QoL instrument for eczema ➔ Internal consistency of the German QoLIAD as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

Table E43: Reliability of the German QoLIAD

Author	Reliability				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Test-retest. Patients completed the QoLIAD twice, 2 weeks apart.	Spearman's correlation coefficient = 0.86	?	178 patients with eczema	fair
Conclusion: One study assessed reliability of the German QoLIAD and indicated unclear reliability as a QoL instrument for eczema ➔ Reliability of the German QoLIAD as a measurement of QoL: **unclear** ➔ Quality of evidence: **fair**					

Table E44: Content validity of the German QoLIAD

Author	Content validity				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Tested for cultural applicability across countries. Patients completed questionnaire and interviewed to identify and remove problematic items. Field testing to further reduce items.	All needs affected by AD identified (not listed here) resulting in 76 item scale. 20 removed and 11 modified after cross cultural validation to yield a 56 item version for field testing. At the field testing stage 14 items were removed and two modified leaving 42 items. Final version had 25 items - fit to Rasch model. Local dependency between items was minimal - minimal item redundancy	+	Item generation and selection: not described Field testing: 17 patients with eczema	good
Conclusion: One study assessed content validity of the German QoLIAD and indicated adequate content validity as a QoL instrument for eczema ➔ Content validity of the German QoLIAD as a measurement of QoL: **adequate** ➔ Quality of evidence: **good**					

Table E45: Convergent/divergent validity of the German QoLIAD

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Patients completed the QoLIAD, DLQI and PGWB/GWBI (general) twice, 2 weeks apart. Assessed correlation between scales. Ranges predicted 0.6-0.8 for DLQI and 0.5-0.7 for PGWB/GWBI using Spearman's rank correlation coefficients	Correlations between QoLIAD and DLQI 0.70 (time 1) and 0.73 (time 2). Correlations between QoLIAD and PGWB/GWBI 0.64 (time 1) and 0.68 (time 2).	+	178 patients with eczema	fair
Conclusion: One study assessed convergent/divergent validity of the German QoLIAD and indicated adequate convergent validity as a QoL instrument for eczema ➔ Convergent/divergent validity of the German QoLIAD as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

Table E46: Discriminative validity of the German QoLIAD

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Assessed ability of scale to discriminate between i) patient perceived severity (mild / moderate and quite/very severe AD, ii) flare or no flare and iii) patient perceived general health (excellent, good, fair or poor)	Differences in scores for all 3 assessment groups statistically significant (p<0.001)	+	178 patients with eczema	fair
Conclusion: One study assessed discriminative validity of the German QoLIAD and indicated adequate discriminative validity as a QoL instrument for eczema ➔ Discriminative validity of the German QoLIAD as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

14. Quality of Life Index for Atopic Dermatitis (QoLIAD) – Italian version

Table E47: Content validity of the Italian QoLIAD

Author	Content validity				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Interviews (14 Italy, 65 total) to explore the effect AD has on the patient to generate wording for items. Tested for cultural applicability across countries. Patients completed questionnaire and interviewed to identify and remove problematic items. Field testing to further reduce items.	All needs affected by AD identified (not listed here) resulting in 76 item scale. 20 removed and 11 modified after cross cultural validation to yield a 56 item version for field testing. At the field testing stage 14 items were removed and two modified leaving 42 items.	+	Item generation and selection: 14 patients with eczema Field testing: 15 patients with eczema	excellent
Conclusion: One study assessed content validity of the Italian QoLIAD and indicated adequate content validity as a QoL instrument for eczema ➔ Content validity of the Italian QoLIAD as a measurement of QoL: **adequate** ➔ Quality of evidence: **excellent**					

15. Quality of Life Index for Atopic Dermatitis (QoLIAD) – Spanish version

Table E48: Internal consistency of the Spanish QoLIAD

Author	Internal consistency				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Cronbach's coefficient	0.88 (time 1) and 0.90 (time 2)	+	80 patients with eczema	poor
Conclusion: One study assessed internal consistency of the Spanish QoLIAD, but due to poor methodological study quality no conclusion can be drawn ➔ Internal consistency of the Spanish QoLIAD as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table E49: Reliability of the Spanish QoLIAD

Author	Reliability				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Test-retest. Patients completed the QoLIAD twice, 2 weeks apart.	Spearman's correlation coefficient = 0.88	?	80 patients with eczema	fair
Conclusion: One study assessed reliability of the Spanish QoLIAD and indicated unclear reliability as a QoL instrument for eczema ➔ Reliability of the Spanish QoLIAD as a measurement of QoL: **unclear** ➔ Quality of evidence: **fair**					

Table E50: Content validity of the Spanish QoLIAD

Author	Content validity				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Tested for cultural applicability across countries. Patients completed questionnaire and interviewed to identify and remove problematic items. Field testing to further reduce items.	All needs affected by AD identified (not listed here) resulting in 76 item scale. 20 removed and 11 modified after cross cultural validation to yield a 56 item version for field testing. At the field testing stage 14 items were removed and two modified leaving 42. Final version had 25 items - fit to Rasch model. Local dependency between items was minimal - minimal item redundancy	+	Item generation and selection: not described Field testing: 20 patients with eczema	good
Conclusion: One study assessed content validity of the Spanish QoLIAD and indicated adequate content validity as a QoL instrument for eczema ➔ Content validity of the Spanish QoLIAD as a measurement of QoL: **adequate** ➔ Quality of evidence: **good**					

Table E51: Convergent/divergent validity of the Spanish QoLIAD

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Patients completed the QoLIAD, DLQI and PGWB/GWBI (general) twice, 2 weeks apart. Assessed correlation between scales. Ranges predicted 0.6-0.8 for DLQI and 0.5-0.7 for PGWB/GWBI using Spearman's rank correlation coefficients	Correlations between QoLIAD and DLQI 0.76 (time 1) and 0.75 (time 2). Correlations between QoLIAD and PGWB/GWBI 0.79 (time 1) and 0.76 (time 2).	+	80 patients with eczema	fair
Conclusion: One study assessed convergent/divergent validity of the Spanish QoLIAD and indicated adequate convergent validity as a QoL instrument for eczema ➔ Convergent/divergent validity of the Spanish QoLIAD as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

Table E52: Discriminative validity of the Spanish QoLIAD

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E11)	Assessed ability of scale to discriminate between i) patient perceived severity (mild / moderate and quite/very severe AD, ii) flare or no flare and iii) patient perceived general health (excellent, good, fair or poor)	Spanish measure was not statistically significant for flare. Differences on scores between the two other assessment groups were statistically significant (p<0.001)	?	80 patients with eczema	fair
(E13)	Calculated differences in scores, compared QoLIAD and body parts affected (face/hands, face, hands), QoLIAD and treatment because of the symptoms; tested for statistical significance using Mann-Whitney-U and Kruskal-Wallis test; no hypotheses	QoLIAD and body parts: p=0.004 for face affected, p=0.114 for face/hands, p=0.052 for hands --> QoLIAD could distinguish patients whose face was affected QoLIAD and treatment: p=0.392 1/4 statistically significant	?	79 patients with eczema	poor
Conclusion: One study assessed discriminative validity of the Spanish QoLIAD and indicated unclear discriminative validity as a QoL instrument for eczema ➔ Discriminative validity of the Spanish QoLIAD as a measurement of QoL: **unclear** ➔ Quality of evidence: **fair**					

16. Skindex-29 – English version (US)

Table E53: Convergent/divergent validity of the English Skindex-29 (US)

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E14)	Determination of correlations between scores on the instrument and physician's judgment of severity of the skin disease using Pearson's correlation coefficients	Significant correlation with the emotion scale (r=0.29, P<0.01); correlations for the two other scales not statistically significant	?	102 patients with eczema	poor
Conclusion: One study assessed convergent/divergent validity of the English Skindex-29 (US), but due to poor methodological study quality no conclusion can be drawn ➔ Convergent/divergent validity of the English Skindex-29 (US) as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table E54: Discriminative validity of the English Skindex-29 (US)

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E14)	Comparison of scales scores of eczema patients with patients with isolated lesions (benign growths, nonmelanoma skin cancer) using the Wilcoxon rank-sum test Hypothesis: Patients with inflammatory dermatoses would have higher scale scores than patients with isolated lesions	Mean scores of patients with eczema were significantly higher than those with benign skin lesions or nonmelanoma skin cancer (P<0.001) for all 3 subscales	+	102 patients with eczema	good
Conclusion: One study assessed discriminative validity of the English Skindex-29 (US) and indicated adequate discriminative validity as a QoL instrument for eczema ➔ Discriminative validity of the English Skindex-29 (US) as a measurement of QoL: **adequate** ➔ Quality of evidence: **good**					

17. Skindex-29 – German version

Table E55: Discriminative validity of the German Skindex-29

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(E15)	Pearson correlation coefficients for each Skindex-29 subscale with EASI scores	Correlation between EASI/Skindex-29: functioning 0.73, emotion 0.61, symptoms 0.72 (all statistically significant)	?	13 patients with eczema	poor
(E15)	Pearson correlation coefficients for each Skindex-29 subscale with self-ratings of skin symptoms, itch and sleep disturbance	Correlation between patient ratings of severity and Skindex-29: functioning 0.54-0.59, emotion 0.35-0.40, symptoms 0.62-0.71 (all statistically significant)	?	63 patients with eczema	fair
Conclusion: One study assessed discriminative validity of the German Skindex-29 and indicated unclear discriminative validity as a QoL instrument for eczema ➔ Discriminative validity of the German Skindex-29 as a measurement of QoL: **unclear** ➔ Quality of evidence: **fair**					

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9.4 Anhang 4

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PRISMA-P 2015 Checklist

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ADMINISTRATIVE INFORMATION			
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Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration			
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number	3; 6
Authors			
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	3b	Describe contributions of protocol authors and identify the guarantor of the review	14-15
Amendments			
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	4-5; 11-12
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Sources	5a	Indicate sources of financial or other support for the review	15
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
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Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6; additional file

PRISMA-P 2015 Checklist

Section/topic	#	Checklist item	Reported on page(s) #
Study records			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-8
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7-8
METHODS			
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	8-9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5; 8-9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data			
Synthesis	15a	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	N/A
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	N/A
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
METHODS			
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	10-11

Abbreviations: N/A = not applicable.

From: Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, PRISMA-P Group (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 4:1. doi: 10.1186/2046-4053-4-1

Search string **Medline** (via PubMed)

#1 (modified precision search terms by Terwee et al. 2009)

(instrumentation[sh] OR Validation Studies[pt] OR "reproducibility of results"[MeSH Terms] OR reproducib*[tiab] OR "psychometrics"[MeSH] OR psychometr*[tiab] OR clinimetr*[tiab] OR clinometr*[tiab] OR "observer variation"[MeSH] OR observer variation[tiab] OR "discriminant analysis" [MeSH] OR reliab*[tiab] OR valid*[tiab] OR coefficient[tiab] OR "internal consistency"[tiab] OR (cronbach*[tiab] AND (alpha[tiab] OR alphas[tiab])) OR "item correlation"[tiab] OR "item correlations"[tiab] OR "item selection"[tiab] OR "item selections"[tiab] OR "item reduction"[tiab] OR "item reductions"[tiab] OR agreement[tw] OR precision[tw] OR imprecision[tw] OR "precise values"[tw] OR test-retest[tiab] OR (test[tiab] AND retest[tiab]) OR (reliab*[tiab] AND (test[tiab] OR retest[tiab])) OR stability[tiab] OR interrater[tiab] OR inter-rater[tiab] OR intrarater[tiab] OR intra-rater[tiab] OR intertester[tiab] OR inter-tester[tiab] OR intratester[tiab] OR intra-tester[tiab] OR interobserver[tiab] OR inter-observer[tiab] OR intraobserver[tiab] OR intra-observer[tiab] OR intertechnician[tiab] OR intertechnician[tiab] OR intratechnician[tiab] OR intra-technician[tiab] OR interexaminer[tiab] OR inter-examiner[tiab] OR intraexaminer[tiab]) OR (intra-examiner[tiab] OR interassay[tiab] OR inter-assay[tiab] OR intraassay[tiab] OR intra-assay[tiab] OR interindividual[tiab] OR inter-individual[tiab] OR intraindividual[tiab] OR intra-individual[tiab] OR interparticipant[tiab] OR inter-participant[tiab] OR intraparticipant[tiab] OR intra-participant[tiab] OR kappa[tiab] OR kappa's[tiab] OR kappas[tiab] OR "coefficient of variation"[tiab] OR repeatab*[tw] OR ((replicab*[tw] OR repeated[tw]) AND (measure[tw] OR measures[tw] OR findings[tw] OR result[tw] OR results[tw] OR test[tw] OR tests[tw])) OR generaliza*[tiab] OR generalisa*[tiab] OR concordance[tiab] OR (intraclass[tiab] AND correlation*[tiab]) OR discriminative[tiab] OR "known group" [tiab] OR "factor analysis"[tiab] OR "factor analyses"[tiab] OR "factor structure"[tiab] OR "factor structures"[tiab] OR dimensionality[tiab] OR subscale*[tiab] OR "multitrait scaling analysis"[tiab] OR "multitrait scaling analyses"[tiab] OR "item discriminant"[tiab] OR "interscale correlation"[tiab] OR "interscale correlations"[tiab]) OR ((error[tiab] OR errors[tiab]) AND (measure*[tiab] OR correlat*[tiab] OR evaluat*[tiab] OR accuracy[tiab] OR accurate[tiab] OR precision[tiab] OR mean[tiab])) OR "individual variability"[tiab] OR "interval variability"[tiab] OR "rate variability"[tiab] OR "variability analysis"[tiab] OR (uncertainty[tiab] AND

(measurement[tiab] OR measuring[tiab])) OR “standard error of measurement”[tiab] OR sensitiv*[tiab] OR responsive*[tiab] OR (limit[tiab] AND detection[tiab]) OR “minimal detectable concentration”[tiab] OR interpretab*[tiab] OR (small*[tiab] AND (real[tiab] OR detectable[tiab]) AND (change[tiab] OR difference[tiab])) OR “meaningful change”[tiab] OR “minimal important change”[tiab] OR “minimal important difference”[tiab]) OR (“minimally important change”[tiab] OR “minimally important difference”[tiab] OR “minimal detectable change”[tiab] OR “minimal detectable difference”[tiab] OR “minimally detectable change”[tiab] OR “minimally detectable difference”[tiab] OR “minimal real change”[tiab] OR “minimal real difference”[tiab] OR “minimally real change”[tiab] OR “minimally real difference”[tiab] OR “ceiling effect” [tiab] OR “floor effect”[tiab] OR “Item response model”[tiab] OR IRT[tiab] OR Rasch[tiab] OR “Differential item functioning”[tiab] OR DIF[tiab] OR “computer adaptive testing”[tiab] OR “item bank”[tiab] OR “cross-cultural equivalence”[tiab] OR accepta*[tiab] OR “ease of use”[tiab] OR practica*[tiab] OR feasib*[tiab])

#2

(“addresses”[Publication Type] OR “biography”[Publication Type] OR “case reports”[Publication Type] OR “comment”[Publication Type] OR “directory”[Publication Type] OR “editorial”[Publication Type] OR “festschrift”[Publication Type] OR “interview”[Publication Type] OR “lectures”[Publication Type] OR “legal cases”[Publication Type] OR “legislation”[Publication Type] OR “letter”[Publication Type] OR “news”[Publication Type] OR “newspaper article”[Publication Type] OR “patient education handout”[Publication Type] OR “popular works”[Publication Type] OR “congresses”[Publication Type] OR “consensus development conference”[Publication Type] OR “consensus development conference, nih”[Publication Type] OR “practice guideline”[Publication Type]) NOT (“animals”[MeSH Terms] NOT “humans”[MeSH Terms])

#3: #1 NOT #2

#4

(quality of life[MH] OR quality of life[TW] OR health status[MH] OR health status[TW] OR "activities of daily living"[MH] OR activities of daily living[TW] OR life quality* OR daily life[TW]OR health level[TW] OR level of health[TW] OR patient reported outcome[TW] OR CDLQI[TW] OR IDQOL[TW])

#5

("dermatitis, atopic"[MeSH] OR atopic dermatitis[tiab] OR atopic eczema[tiab] OR eczema[MeSH] OR eczema[tiab] OR "neurodermatitis"[MeSH] OR Neurodermatitis[tiab] OR skin diseases[MH] OR skin disease*[tiab] OR dermatology[tiab])

#3 AND #4 AND #5

Search string **Embase**

#1

exp instrumentation/ or exp validation study/ or exp reproducibility/ or reproducib$.mp. or exp psychometry/ or psychometr$.mp. or clinimetr*.mp. or clinometr$.mp. or exp observer variation/ or observer variation.mp. or exp discriminant analysis/ or exp reliability/ or reliab$.mp. or exp Validity/ or valid$.mp. or coefficient.mp. or internal consistency.mp. or (cronbach$ and (alpha or alphas)).mp. or item correlation.mp. or item correlations.mp. or item selection.mp. or item selections.mp. or item reduction.mp. or item reductions.mp. or agreement.mp. or precision.mp. or imprecision.mp. or precise values.mp. or (test-retest or (test and retest) or (reliab$ and (test or retest)) or stability or interrater or inter-rater or intrarater or intra-rater or intertester or inter-tester or intratester or intra-tester or interobserver or inter-observer or intraobserver or intra-observer or intertechnician or intertechnician or intratechnician or intra-technician or interexaminer or inter-examiner or intraexaminer or intra-examiner or interassay or inter-assay or intraassay or intra-assay or interindividual or inter-individual or intraindividual or intra-individual or interparticipant or inter-participant or intraparticipant or intra-participant or kappa or kappa$ or coefficient of variation or repeatab$ or ((replicap$ or repeated) and (measure or measures or findings or result or results or test or tests))).mp. or (generaliza$ or generalisa$ or concordance or (intraclass and correlation$) or discriminative or known group or factor analysis or factor analyses or factor structure or factor structures or dimensionality or subscale$ or multitrait scaling analysis or multitrait scaling analyses or item discriminant or interscale correlation or interscale correlations or ((error or errors) and (measure$ or correlat$ or evaluat$ or accuracy or accurate or precision or mean)) or individual variability or interval variability or rate variability or variability analysis or (uncertainty and (measurement or measuring)) or standard error of measurement or sensitiv$ or responsive$ or (limit and detection) or minimal detectable concentration or interpretab$ or (small$ and (real or detectable) and (change or difference)) or meaningful change or minimal important change or minimal important difference or minimally important change or minimally important difference or minimal detectable change or minimal detectable difference or minimally detectable change or minimally detectable difference or minimal real change or minimal real difference or minimally real change or minimally real difference).mp. or (ceiling effect or floor effect or Item response model or IRT or Rasch or Differential item

functioning or DIF or computer adaptive testing or item bank or cross-cultural equivalence or practica$ or feasib$).mp.

#2 (Conference Abstract or Conference Paper or Conference Review or Editorial or Erratum or Letter or Note).pt.

#3: #1 NOT #2

#4

quality of life/ or quality of life.mp. or health status/ or health status.mp. or daily life activity/ or activities of daily living.mp. or life quality$.mp. or daily life.mp. or health level.mp. or level of health.mp. or health status/ or patient reported outcome.mp. or CDLQI.mp. or IDQOL.mp.

#5

exp Atopic Dermatitis/ or dermatitis, atopic.mp. or atopic dermatitis.mp. or exp eczema/ or atopic eczema.mp. or eczema, atopic.mp. or exp NEURODERMATITIS/ or neurodermatitis.mp. or skin disease/ or skin disease.mp. or dermatology/ or dermatology.mp.

#3 AND #4 AND #5

9.5 Anhang 5

zu Heinl D, Prinsen CAC, Sach T, Drucker AM, Ofenloch R, Flohr C, Apfelbacher C. Measurement properties of quality-of-life measurement instruments for infants, children and adolescents with eczema: a systematic review. Br J Dermatol. 2017; 176: 878-89.

Inhaltsverzeichnis

Online Appendix SA1: Tables pertaining to the *British Journal of Dermatology* publication "Measurement properties of quality-of-life measurement instruments for infants, children and adolescents with eczema: a systematic review"

Supplementary Table SA1. Adequacy criteria for measurement properties adapted from Terwee *et al*.[S1] and PROMIS Methodology[S2]

Property	Rating	Adequacy criteria
Reliability		
Internal consistency (CTT methods applied)	+ ? -	Cronbach's alpha(s) ≥ 0.70 Cronbach's alpha not determined Cronbach's alpha(s) < 0.70
Internal consistency (IRT methods applied)	+ ? -	Person Separation Index ≥ 0.70 Person Separation Index not determined Person Separation Index < 0.70
Measurement error	+ ? -	MIC > SDC OR MIC outside the LoA MIC not defined MIC <= SDC OR MIC equals or inside LoA
Reliability	+ ? -	ICC/weighted Kappa >=0.70, OR Pearson's r >= 0.80 Neither ICC/weighted Kappa, nor Pearson's r determined ICC/weighted Kappa < 0.70 OR Pearson's r < 0.80
Validity		
Content validity	+ ? -	All items are considered to be relevant for the construct to be measured, for the target population, and for the purpose of the measurement AND the questionnaire is considered to be comprehensive Not enough information available Not all items are considered to be relevant for the construct to be measured, for the target population, and for the purpose of the measurement OR the questionnaire is considered not to be comprehensive
Construct validity		
Structural validity (CTT methods applied)	+ ? -	Factors should explain at least 50% of the variance Explained variance not mentioned Factors explain < 50% of the variance
Structural validity (IRT methods applied)	+ ? -	Residual correlations among the items after controlling for the dominant factor < 0.20 OR Q3's < 0.37, item scalability >0.30, IRT model fit: G2 >0.01, no DIF for important subject characteristics (such as age, gender, education): McFadden's R2 < 0.02, OR no non-uniform DIF Important statistics not reported Residual correlations among the items after controlling for the dominant factor ≥ 0.20 OR Q3's ≥ 0.37, item

		scalability ≤0.30, IRT model fit: G2 ≤0.01, important DIF for important subject characteristics (such as age, gender, education): McFadden's R2 ≥0.02, OR non-uniform DIF
Hypothesis testing (convergent/divergent validity)	+ ? -	Correlations with instruments measuring the same construct >=0.50 OR at least 75% of the results are in accordance with the hypotheses AND correlation with related constructs is higher than with unrelated constructs Solely correlations determined with unrelated constructs Correlations with instruments measuring the same construct < 0.50 OR < 75% of the results are in accordance with the hypotheses OR correlation with related constructs is lower than with unrelated constructs
Hypothesis testing (discriminative validity)	+ ? -	Differences in scores on the measurement instrument for all evaluated patient subgroups are statistically significant OR ≥75% of results in accordance with hypotheses Some differences statistically significant, others not Differences in scores on the measurement instrument for all evaluated patient subgroups are not statistically significant OR <75% of results in accordance with hypotheses
Cross-cultural validity	+ ? -	No differences in factor structure OR no important DIF between language versions Multiple group factor analysis not applied AND DIF not assessed Differences in factor structure OR important DIF between language versions
Responsiveness		
Responsiveness	+ ? -	Correlation with changes on instruments measuring the same construct ≥ 0.50 OR at least 75% of the results are in accordance with the hypotheses OR AUC ≥ 0.70 AND correlations with changes in related constructs are higher than with unrelated constructs Solely correlations determined with unrelated constructs Correlations with changes on instruments measuring the same construct < 0.50 OR < 75% of the results are in accordance with the hypotheses OR AUC < 0.70 OR correlations with changes in related constructs are lower than with unrelated constructs

Abbreviations: *AUC,* area under the curve; *CTT,* classical test theory; *DIF,* differential item functioning; *ICC,* intraclass correlation coefficient; *LoA,* limits of agreement; *MIC,* minimal important change; *SDC,* smallest detectable change.

+ positive rating, ? indeterminate rating, - negative rating

Supplementary Table SA2. Levels of evidence for the overall adequacy of a measurement property adapted from Schellingerhout *et al*.[S3]

Level	Rating	Criteria
Strong	+++, ? (strong) or ---	Consistent findings in multiple studies of good methodological quality OR in one study of excellent methodological quality
Moderate	++, ? (moderate) or --	Consistent findings in multiple studies of fair methodological quality OR in one study of good methodological quality
Limited	+, ? (limited) or -	One study of fair methodological quality
Conflicting	+/-	Conflicting findings
Unknown	?	Only studies of poor methodological quality

+ positive rating, ? indeterminate rating, - negative rating

Supplementary Table SA3. Comparison of the content of the different QoL instruments on content domain level

Domain	CADIS[a]	CDLQI	CIAD[b]	DISABKIDS-ADM[c]	IDQoL
Symptoms	X	X			X
Emotions		X			
Difficulties with mood					X
Activities of daily living	X	X			X
Leisure		X			X
Sleep		X			X
Social/family life		X			X
Treatment		X			X
Behaviour	X				
Impact				X	
Stigmatization				X	

[a]The CADIS also contains the following content domains related to parental QoL: family and social function, sleep, emotions.

[b]No content domains for the CIAD were presented in the development article.

[c]Content comparison of DISABKIDS-ADM is based on dimensions empirically derived from factor analysis and not on content-related domains.

Abbreviations: *CADIS,* Childhood Atopic Dermatitis Impact Scale; *CDLQI,* Children's Dermatology Life Quality Index; *CIAD,* Childhood Impact of Atopic Dermatitis; *DISABKIDS-ADM,* DISABKIDS Atopic Dermatitis Module; *IDQoL,* Infants' Dermatitis Quality of Life Index; *QoL,* quality of life.

Supplementary Table SA4. Number of studies assessing the measurement properties of proxy-reported QoL instruments for infants, children and adolescents with eczema

Measurement property	English CADIS (US)	Italian CADIS (long version)	Italian CADIS (short version)	Dutch CIAD	English CIAD (UK)	English CIAD (US)	French CIAD	German CIAD	Italian CIAD	Spanish CIAD	Portuguese DISABKIDS-ADM (Brazil, proxy-reported version)	Arabic IDQoL	Dutch IDQoL	English IDQoL (UK)	Italian IDQoL	Swedish IDQoL
Internal consistency	1[S4]	1[S5]	1[S5]	1[S6]	1[S6]	1[S6]	1[S6]	1[S6]	/	/	1[S7]	1[S8]	/	/	1[S9]	/
Measurement error	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Reliability	1[S10]	1[S5]	1[S5]	1[S6]	1[S6]	1[S6]	1[S6]	1[S6]	/	/	/	/	1[S11]	1[S12]	1[S9]	/
Content validity	1[S4]	/	/	1[S13]	1[S13]	1[S13]	1[S13]	1[S13]	1[S13]	1[S13]	/	/	/	1[S12]	/	/
Structural validity	/	1[S5]	/	/	/	1[S6]	/	/	/	/	/	/	/	/	/	/
Hypothesis testing	1[S10]	1[S5]	1[S5]	1[S6]	1[S6]	1[S6]	1[S6]	1[S6]	/	/	1[S7]	1[S8]	1[S11]	2[S12,S14]	1[S9]	1[S15]
Cross-cultural validity	/	1[S5]	/	1[S6]	1[S6]	/	1[S6]	1[S6]	/	/	/	/	/	/	/	/
Responsiveness	1[S10]	/	/	/	/	1[S6]	/	/	/	/	/	/	/	2[S12,14]	/	/

Abbreviations: *CADIS,* Childhood Atopic Dermatitis Impact Scale; *CIAD,* Childhood Impact of Atopic Dermatitis; *DISABKIDS-ADM,* DISABKIDS Atopic Dermatitis Module; *IDQoL,* Infants' Dermatitis Quality of Life Index; *QoL,* quality of life; *UK,* United Kingdom; *US,* United States (of America).

Supplementary Table SA5. Number of studies assessing the measurement properties of self-reported QoL instruments for infants, children and adolescents with eczema

Measurement property	Danish CDLQI	English CDLQI (UK)	Malay CDLQI	Serbian CDLQI	Spanish CDLQI (Mexico)	Swedish CDLQI	DISABKIDS-ADM (unknown language)	Portuguese DISABKIDS-ADM (Brazil, self-reported version)
Internal consistency	/	/	1[S16]	1[S17]	1[S18]	/	/	1[S7]
Measurement error	/	/	/	/	/	/	/	/
Reliability	/	/	1[S16]	/	1[S18]	/	/	/
Content validity	/	/	/	/	/	/	1[S19]	/
Structural validity	/	/	/	/	/	/	/	/
Hypothesis testing	1[S20]	1[S21]	1[S16]	1[S17]	1[S18]	1[S15]	/	1[S7]
Cross-cultural validity	/	/	/	/	/	/	/	/
Responsiveness	1[S20]	/	/	/	/	/	/	/

Abbreviations: *CDLQI,* Children's Dermatology Life Quality Index; *DISABKIDS-ADM,* DISABKIDS Atopic Dermatitis Module; *QoL,* quality of life; *UK,* United Kingdom;

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Supplementary Detailed Results SR1

Rating of measurement properties of outcome instruments of quality of life for infants, children and adolescents, and assessment of the methodological quality of the included studies

Table of contents

Abbreviations and symbols used

+ positive rating

? indeterminate rating

- negative rating

AD = atopic dermatitis; *ANVOCA* = analysis of covariance; *ANOVA* = analysis of variance; *CADIS* = Childhood Atopic Dermatitis Impact Scale; *CDLQI* = Children's Dermatology Life Quality Index; *CIAD* = Childhood Impact of Atopic Dermatitis; *COSMIN* = COnsensus-based Standards for the selection of health Measurement INstruments; *DFI* = Dermatitis Family Impact; *DIF* = Differential item functioning; *DISABKIDS-ADM* = DISABKIDS Atopic Dermatitis Module; *EASI* = Eczema Area and Severity Index; *FDI* = Family Dermatitis Impact (identic with DFI); *ICC* = Intraclass Correlation Coefficient; *IDQoL* = Infants' Dermatitis Quality of Life Index; *INVAS* = Investigator overall assessment of disease severity; *QoL* = quality of life; *MCS* = Mental component score ; *NL* = Netherlands; *PAGS* = parental severity assessment; *PCS* = Physical component score; *PGWB* = Psychological General Well-Being Index; *PRUVAS* = subjective measure of pruritus severity; *PTVAS* = subjective measure of eczema severity; *R&L* = Rajka & Langeland; *SCORAD* = SCORing Atopic Dermatitis; *TIS* = Three Item Severity Score; *UK* = United Kingdom; *US* = United States of America

1. Childhood Atopic Dermatitis Impact Scale (CADIS) – English version (US)

Table S1: Internal consistency of the English version (US) of the CADIS

Author	Internal consistency				
	Method	Result	Interpretation	Study base	COSMIN score
(S1)	Calculation of Cronbach's alpha for every subscale	Cronbach's alpha ranged from 0.76-0.93 for the subscales	+	270 parents of children with eczema	fair
Conclusion: One study assessed internal consistency of the English version (US) of the CADIS and indicated adequate internal consistency as a QoL instrument for eczema ➔ Internal consistency of the English version (US) of the CADIS as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

Table S2: Reliability of the English version (US) of the CADIS

Author	Reliability				
	Method	Result	Interpretation	Study base	COSMIN score
(S2)	Completion of the CADIS at enrollment and 48 hours later; Calculation of the Intraclass Correlation Coefficient of Reliability for each domain score and for the total score	ICC total score: 0.96 ICC domain scores: 0.89-0.95	+	41 parents of children with AD	fair
Conclusion: One study assessed reliability of the English version (US) of the CADIS and indicated adequate reliability as a QoL instrument for eczema ➔ Reliability of the English version (US) of the CADIS as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

Table S3: Content validity of the English version (US) of the CADIS

Author	Reliability				
	Method	Result	Interpretation	Study base	COSMIN score
(S1)	Parents of young children with AD involved in construction of a conceptual framework (together with expert clinicians and published work); pilot test of initial version with 20 parents of AD children	Parents: 453 mentions of the ways that AD bothers their child and 410 mentions of the ways that AD bothers them; all mentions noted by more than 7% of the parents were included in the CADIS; removal of four items considered ambiguous, biased, or wordy (by the investigators)	?	Construction of conceptual framework: unknown Pilot study: 20 parents of children with AD	poor
Conclusion: One study assessed content validity of the English version (US) of the CADIS, but due to poor methodological study quality no conclusion can be drawn ➔ Content validity of the English version (US) of the CADIS as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S4: Convergent/divergent validity of the English version (US) of the CADIS

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S2)	Calculation of the correlation between CADIS scores and SCORAD total and objective scores and ratings of pruritus and sleep loss using Spearman's correlation coefficients	CADIS/total SCORAD: 0.48-0.65; CADIS/objective SCORAD: 0.42-0.53; subjective criteria (pruritus and sleep loss): 0.46-0.72	?	270 parents of children with AD	poor
Conclusion: One study assessed convergent/divergent validity of the English version (US) of the CADIS, but due to poor methodological study quality no conclusion can be drawn ➔ Convergent/divergent validity of the English version (US) of the CADIS as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S5: Discriminative validity of the English version (US) of the CADIS

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S2)	Comparison of CADIS scores between patients of three severity groups based on their objective SCORAD score using ANOVA	Scores from all 5 CADIS domains significantly differentiated patients at each clinical severity level (P<0.001); all pairwise comparisons significant (P<0.05)	+	270 parents of children with AD	fair
Conclusion: One study assessed discriminative validity of the English version (US) of the CADIS and indicated adequate discriminative validity as a QoL instrument for eczema ➔ Discriminative validity of the English version (US) of the CADIS as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

Table S6: Responsiveness of the English version (US) of the CADIS

Author	Responsiveness				
	Method	Result	Interpretation	Study base	COSMIN score
(S2)	Comparison of CADIS scores between patients that were improved, the same, or worsened after 4 weeks according to a global question about their skin condition; ANOVA	CADIS domains significantly differentiated patients from the three groups (P<0.001); improved subjects had significantly better scores than the other 2 groups on all domains (P<0.05); no significant difference between improved and worsened subjects (P>0.05)	?	228 parents of children with AD	poor
Conclusion: One study assessed responsiveness of the English version (US) of the CADIS, but due to poor methodological study quality no conclusion can be drawn ➔ Responsiveness of the English version (US) of the CADIS as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

2. Childhood Atopic Dermatitis Impact Scale (CADIS) – Italian long version

Table S7: Internal consistency of the Italian long version of the CADIS

Author	Internal consistency				
	Method	Result	Interpretation	Study base	COSMIN score
(S3)	Calculation of Cronbach's alpha	Italian long version: α for total score 0.95; α for subscales ranging from 0.77-0.95	+	135 parents of children with AD	poor
Conclusion: One study assessed internal consistency of the Italian long version of the CADIS, but due to poor methodological study quality no conclusion can be drawn ➔ Internal consistency of the Italian long version of the CADIS as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S8: Reliability of the Italian long version of the CADIS

Author	Reliability				
	Method	Result	Interpretation	Study base	COSMIN score
(S3)	Test-retest interval 48 hours; calculation of Spearman's correlation coefficients for each subscale and the total score	Italian long version: correlations for total scale 0.92; 0.90 for Child Symptoms; 0.80 for Child Activity Limitations and Behavior; 0.73 for Family and Social Function; 0.87 for Parent Emotion and Parent Sleep (for all: P≤0.001)	?	66 parents of children with AD	poor
Conclusion: One study assessed reliability of the Italian long version of the CADIS, but due to poor methodological study quality no conclusion can be drawn ➔ Reliability of the Italian long version of the CADIS as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S9: Structural validity of the Italian long version of the CADIS

Author	Structural validity				
	Method	Result	Interpretation	Study base	COSMIN score
(S3)	Two separate exploratory factor analysis (principal axis factoring) for child-related and parent-related scales, respectively; initial minimum loading for an item 0.32; later, for item reduction purposes, items with loadings below 0.50 were dropped	Child-related items: 2 factors accounted for 43.9% of the total variance Parent-related items: 3 factors accounted for 43.7% of the total variance Several items were eliminated (see cross-cultural validity for details).	-	135 parents of children with AD	poor
Conclusion: One study assessed structural validity of the Italian long version of the CADIS, but due to poor methodological study quality no conclusion can be drawn ➔ Structural validity of the Italian long version of the CADIS as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S10: Convergent/divergent validity of the Italian long version of the CADIS

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S3)	Calculation of Spearman's correlation coefficients between each CADIS domain score and objective, subjective and total SCORAD scores, total IDQoL, CDLQI and DFI scores; Hypothesis: higher correlations between CADIS and QoL instruments (IDQoL, CDLQI, DFI) than between CADIS and SCORAD	<u>Italian CADIS, long version (total score):</u> CADIS/oSCORAD 0.38, CADIS/subjective SCORAD 0.57, CADIS/total SCORAD 0.44, CADIS/IDQoL 0.74, CADIS/CDLQI 0.58, CADIS/DFI 0.68 <u>Italian CADIS, long version (domain scores):</u> CADIS/oSCORAD 0.27-0.37, CADIS/subjective SCORAD 0.31-0.58, CADIS/total SCORAD 0.32-0.44, CADIS/IDQoL 0.40-0.75, CADIS/CDLQI 0.38-0.60, CADIS/DFI 0.51-0.62	+	SCORAD: 135 parents of children with AD; IDQoL: 102 parents; CDLQI: 33 parents; DFI: 126 parents	fair
Conclusion: One study assessed convergent/divergent validity of the Italian long version of the CADIS and indicated adequate convergent validity as a QoL instrument for eczema ➔ Convergent/divergent validity of the Italian long version of the CADIS as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

Table S11: Discriminative validity of the Italian long version of the CADIS

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S3)	Comparison of CADIS scores of different patient severity groups according to SCORAD using ANOVA	Kruskal-Wallis test for difference between the different severity groups was significant for all CADIS domains (long and short version; P≤0.01); pairwise comparisons all significant except 4: moderate/severe AD in Child Activity Limitations and Behavior and in the Parent Emotions domain; mild/moderate in Family and Social Function and Parent Sleep Domains	?	135 parents of children with AD	poor
Conclusion: One study assessed discriminative validity of the Italian long version of the CADIS, but due to poor methodological study quality no conclusion can be drawn ➔ Discriminative validity of the Italian long version of the CADIS as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S12: Cross-cultural validity of the Italian long version of the CADIS

Author	Cross-cultural validity				
	Method	Result	Interpretation	Study base	COSMIN score
(S3)	Two separate exploratory factor analysis (principal axis factoring) for child-related and parent-related scales, respectively	Child-related items: 1 item from Child Symptoms loaded on both factors --> attributed to Activity Limitations and Behavior; 2 items from Activity Limitations and Behavior loaded on Child Symptoms, 1 loaded on both factors; 2 items from Activity Limitations and Behavior did not reach an acceptable loading on any factor and were excluded. Further 2 child-related items excluded after examination of the rotated factor matrix because of inadequate factor loadings. Parent-related items: 1 item from Parent Emotions scale loaded on Family and Social Function scale; 1 item from Parent Emotion scale eliminated (no acceptable loading on any factor). 1 item from Family and Social Function scale loaded on Parent sleep, 1 item loaded on both factors, and 1 was eliminated (no acceptable loading on any factor). Subsequent examination of the pattern matrix led to the elimination of 6 family-related items. Summary: 4 items loaded on factors different from the original version; 3 items loaded on two factors; 4 items reached no acceptable loading on any factor --> 11/45 items worked differently compared to the original version; 8 items eliminated in subsequent analysis	-	135 parents of children with AD	poor
Conclusion: One study assessed cross-cultural validity of the Italian long version of the CADIS, but due to poor methodological study quality no conclusion can be drawn ➔ Cross-cultural validity of the Italian long version of the CADIS as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

3. Childhood Atopic Dermatitis Impact Scale (CADIS) – Italian short version

Table S13: Internal consistency of the Italian short version of the CADIS

Author	Internal consistency				
	Method	Result	Interpretation	Study base	COSMIN score
(S3)	Calculation of Cronbach's alpha	Italian short version: α for total scale 0.90; α for subscales ranging from 0.72-0.89	+	135 parents of children with AD	poor
Conclusion: One study assessed internal consistency of the Italian short version of the CADIS, but due to poor methodological study quality no conclusion can be drawn ➔ Internal consistency of the Italian short version of the CADIS as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S14: Reliability of the Italian short version of the CADIS

Author	Reliability				
	Method	Result	Interpretation	Study base	COSMIN score
(S3)	Test-retest interval 48 hours; calculation of Spearman's correlation coefficients for each subscale and the total score	Italian short version: correlations for total scale 0.91; 0.91 for Child Symptoms; 0.78 for Child Activity Limitations and Behavior; 0.85 for Parent Emotions; 0.67 for Family and Social Function; 0.87 for Parent Sleep (for all: P≤0.001)	?	66 parents of children with AD	poor
Conclusion: One study assessed reliability of the Italian short version of the CADIS, but due to poor methodological study quality no conclusion can be drawn ➔ Reliability of the Italian short version of the CADIS as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S15: Convergent/divergent validity of the Italian short version of the CADIS

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S3)	Calculation of Spearman's correlation coefficients between each CADIS domain score and objective, subjective and total SCORAD scores, total IDQoL, CDLQI and DFI scores; Hypothesis: higher correlations between CADIS and QoL instruments (IDQoL, CDLQI, DFI) than between CADIS and SCORAD	Italian CADIS, short version (total score): CADIS/oSCORAD 0.38, CADIS/subjective SCORAD 0.56, CADIS/total SCORAD 0.44, CADIS/IDQoL 0.74, CADIS/CDLQI 0.56, CADIS/DFI 0.66 Italian CADIS, short version (domain scores): CADIS/oSCORAD 0.24-0.39, CADIS/subjective SCORAD 0.24-0.57, CADIS/total SCORAD 0.28-0.45, CADIS/IDQoL 0.32-0.74, CADIS/CDLQI 0.37-0.63, CADIS/DFI 0.46-0.61	+	SCORAD: 135 parents of children with AD; IDQoL: 102 parents; CDLQI: 33 parents; DFI: 126 parents	fair
Conclusion: One study assessed convergent/divergent validity of the Italian short version of the CADIS and indicated adequate convergent validity as a QoL instrument for eczema ➔ Convergent/divergent validity of the Italian short version of the CADIS as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

Table S16: Discriminative validity of the Italian short version of the CADIS

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S3)	Comparison of CADIS scores of different patient severity groups according to SCORAD using ANOVA	Kruskal-Wallis test for difference between the different severity groups was significant for all CADIS domains (long and short version; P≤0.01); pairwise comparisons all significant except 4: moderate/severe AD in Child Activity Limitations and Behavior and in the Parent Emotions domain; mild/moderate in Family and Social Function and Parent Sleep Domains	?	135 parents of children with AD	poor
Conclusion: One study assessed discriminative validity of the Italian short version of the CADIS, but due to poor methodological study quality no conclusion can be drawn ➔ Discriminative validity of the Italian short version of the CADIS as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

4. Children's Dermatology Life Quality Index (CDLQI) – Danish version

Table S17: Convergent/divergent validity of the Danish CDLQI

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S4)	Calculation of Spearman's correlation coefficient to determine the relationship between CDLQI and patient visual analogue scale for pruritus (PRUVAS), patient overall assessment visual analogue scale (PTVAS), investigator overall assessment visual analogue scale (INVAS) and physical component score (PCS) and mental component score (MCS) of SF-36	CDLQI/PCS: -0.90 (P<0.05) CDLQI/MCS: 0.52 (not significant) CDLQI/PRUVAS: 0.60 (P<0.0001) CDLQI/PTVAS: 0.75 (P<0.0001) CDLQI/INVAS: 0.71 (P<0.0001)	+	PCS/MCS: 6 children with AD aged 14-16 years PRUVAS/PTVAS/INVAS: 35 children with AD and 7 controls aged 3-14 years	poor
Conclusion: One study assessed convergent/divergent validity of the Danish CDLQI, but due to poor methodological study quality no conclusion can be drawn ➔ Convergent/divergent validity of the Danish CDLQI as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S18: Discriminative validity of the Danish CDLQI

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S4)	Comparison of scores of patients with mild and moderate AD according to SCORAD using Wilcoxon rank scores	Patients with moderate AD had significantly higher CDLQI scores than patients with mild eczema (P<0.0001)	+	35 children with eczema	poor
Conclusion: One study assessed discriminative validity of the Danish CDLQI, but due to poor methodological study quality no conclusion can be drawn ➔ Discriminative validity of the Danish CDLQI as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S19: Responsiveness of the Danish CDLQI

Author	Responsiveness				
	Method	Result	Interpretation	Study base	COSMIN score
(S4)	CDLQI compared at visit 1 and visit 2 (6 months later)	Visit 1: mean = 8; Visit 2: mean = 3. Statistical testing not reported.	?	35 children with eczema	poor
Conclusion: One study assessed responsiveness of the Danish CDLQI, but due to poor methodological study quality no conclusion can be drawn ➔ Responsiveness of the Danish CDLQI as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

5. Children's Dermatology Life Quality Index (CDLQI) – English version (UK)

Table S203: Discriminative validity of the English CDLQI (UK)

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S5)	Comparison of scores of patients with eczema, psoriasis and acne with those of patients with moles and naevi	Scores for eczema, psoriasis and acne all significantly higher than those for moles and naevi (P<0.002)	+	47 children with eczema	poor
Conclusion: One study assessed discriminative validity of the UK version of the CDLQI, but due to poor methodological study quality no conclusion can be drawn ➔ Discriminative validity of the English CDLQI (UK) as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

6. Children's Dermatology Life Quality Index (CDLQI) – Malay version

Table S21: Internal consistency of the Malay CDLQI

Author	Internal consistency				
	Method	Result	Interpretation	Study base	COSMIN score
(S6)	Calculation of Cronbach's alpha	α=0.92	+	33 children with AD	poor
Conclusion: One study assessed internal consistency of the Malay CDLQI, but due to poor methodological study quality no conclusion can be drawn ➔ Internal consistency of the Malay CDLQI as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S22: Reliability of the Malay CDLQI

Author	Reliability				
	Method	Result	Interpretation	Study base	COSMIN score
(S6)	Calculation of Spearman's correlation coefficient to determine relationship between mean scores on the CDLQI at administration 1 and 2; Kappa analysis of agreement (not mentioned if a weighted kappa value was calculated); Δt = 2 weeks	r=0.74; "average of moderate agreement" according to kappa (estimate not presented)	?	33 children with AD	fair
Conclusion: One study assessed reliability of the Malay CDLQI and indicated unclear reliability as a QoL instrument for eczema ➔ Reliability of the Malay CDLQI as a measurement of QoL: **unclear** ➔ Quality of evidence: **fair**					

Table S23: Discriminative validity of the Malay CDLQI

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S6)	Comparison of differences in CDLQI scores between patients with mild, moderate and severe AD using ANOVA	Difference between moderate/severe AD not significant (p=0.08); unclear whether differences between mild and moderate or severe were significant	?	33 children with AD	poor
Conclusion: One study assessed discriminative validity of the Malay CDLQI, but due to poor methodological study quality no conclusion can be drawn ➔ Discriminative validity of the Malay CDLQI as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

7. Children's Dermatology Life Quality Index (CDLQI) – Serbian version

Table S24: Internal consistency of the Serbian CDLQI

Author	Internal consistency				
	Method	Result	Interpretation	Study base	COSMIN score
(S7)	Calculation of Cronbach's alpha	α=0.92 (stated in discussion section)	+	64 children with AD	poor
Conclusion: One study assessed internal consistency of the Serbian CDLQI, but due to poor methodological study quality no conclusion can be drawn ➔ Internal consistency of the Serbian CDLQI as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S25: Convergent/divergent validity of the Serbian CDLQI

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S7)	Calculation of Spearman's correlation coefficient to determine the association between EASI and CDLQI subscales	Correlations ranged from 0.60 to 0.74	?	46 children above the age of 8 years	poor
Conclusion: One study assessed convergent/divergent validity of the Serbian CDLQI, but due to poor methodological study quality no conclusion can be drawn ➔ Convergent validity of the Serbian CDLQI as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S26: Discriminative validity of the Serbian CDLQI

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S7)	Comparison of CDLQI scores by disease severity levels (mild, moderate, severe) using ANOVA	All differences were statistically significant	+	64 children with AD	poor
Conclusion: One study assessed discriminative validity of the Serbian CDLQI, but due to poor methodological study quality no conclusion can be drawn ➔ Discriminative validity of the Serbian CDLQI as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

8. Children's Dermatology Life Quality Index (CDLQI) – Spanish version (Mexico)

Table S27: Internal consistency of the Mexican Spanish CDLQI

Author	Internal consistency				
	Method	Result	Interpretation	Study base	COSMIN score
(S8)	Cronbach's alpha	α=0.83	+	64 children with AD	poor
Conclusion: One study assessed internal consistency of the Mexican Spanish CDLQI, but due to poor methodological study quality no conclusion can be drawn ➔ Internal consistency of the Mexican Spanish CDLQI as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S28: Reliability of the Mexican Spanish CDLQI

Author	Reliability				
	Method	Result	Interpretation	Study base	COSMIN score
(S8)	Test-retest reliability by determining Spearman's correlation coefficient (second administration 1 week later)	Spearman's coefficient = 0.97, p<0.001	?	64 children with AD	fair
Conclusion: One study assessed reliability of the Mexican Spanish CDLQI and indicated unclear reliability as a QoL instrument for eczema ➔ Reliability of the Mexican Spanish CDLQI as a measurement of QoL: **unclear** ➔ Quality of evidence: **fair**					

Table S29: Convergent/divergent validity of the Mexican Spanish CDLQI

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S8)	Assessment of the correlation between CDLQI and SCORAD and of the correlation between CDLQI and COOP-Dartmouth by calculating Spearman's correlation coefficient	COOP-Dartmouth/CDLQI: 0.97, p<0.001 SCORAD/CDLQI: 0.53, p<0.001	+	64 children with AD	poor
Conclusion: One study assessed convergent/divergent validity of the Mexican Spanish CDLQI, but due to poor methodological study quality no conclusion can be drawn ➔ Convergent/divergent validity of the Mexican Spanish CDLQI as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

9. Children's Dermatology Life Quality Index (CDLQI) – Swedish version

Table S30: Convergent/divergent validity of the Swedish CDLQI

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S9)	Calculation of Spearman's correlation coefficient to determine the association between CDLQI and DFI, CDLQI and R&L score and CDLQI and objective SCORAD	CDLQI/DFI: 0.44 ($p<0.01$); CDLQI/R&L: 0.31 ($p<0.05$); CDLQI/oSCORAD: 0.18 ($p>0.05$)	?	50 children with eczema	poor
Conclusion: One study assessed convergent/divergent validity of the Swedish CDLQI, but due to poor methodological study quality no conclusion can be drawn ➔ Convergent/divergent validity of the Swedish CDLQI as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S31: Discriminative validity of the Swedish CDLQI

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S9)	Comparison of scores of children with eczema and children with eczema and asthma, allergic rhinoconjunctivitis, food allergy/intolerance or urticaria (AAFU) using ANOVA; Comparison of scores of younger and older children	No significant difference between children with eczema and children with eczema and AAFU Mean CDLQI score was significantly higher for younger children than for older ones ($p<0.05$)	?	50 children with eczema	fair
Conclusion: One study assessed discriminative validity of the Swedish CDLQI and indicated unclear discriminative validity as a QoL instrument for eczema ➔ Discriminative validity of the Swedish CDLQI as a measurement of QoL: **unclear** ➔ Quality of evidence: **fair**					

10. Childhood Impact of Atopic Dermatitis (CIAD) – Dutch version

Table S32: Internal consistency of the Dutch CIAD

Author	Internal consistency				
	Method	Result	Interpretation	Study base	COSMIN score
(S10)	Calculation of Cronbach's alpha	Cronbach's alpha ranged from 0.72 to 0.85 in all countries	+	48 parents of children with eczema	fair
Conclusion: One study assessed internal consistency of the Dutch CIAD and indicated adequate internal consistency as a QoL instrument for eczema ➔ Internal consistency of the Dutch CIAD as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

Table S33: Reliability of the Dutch CIAD

Author	Reliability				
	Method	Result	Interpretation	Study base	COSMIN score
(S10)	Calculation of test-retest correlations (type of correlation coefficient not described)	0.78 (Netherlands)	?	22 parents of children with eczema	poor
Conclusion: One study assessed reliability of the Dutch CIAD, but due to poor methodological study quality no conclusion can be drawn ➔ Reliability of the Dutch CIAD as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S34: Content validity of the Dutch CAD

Author	Content validity				
	Method	Result	Interpretation	Study base	COSMIN score
(S11)	Interviews (15 NL, 65 total) with parents to explore the effect AD has on their children to generate wording for items. Tested for cultural applicability across countries. Parents completed the draft questionnaire and were asked in field-test interviews to comment on its understandability, comprehensiveness, and relevance.	More than 150 items after item generation phase. Reduction to 55 items by researchers. Initial version relevant to parents. Removal of ten items and modification of three items based on field-test interviews. 12 of the final 45 items formed the basis for creation of the CIAD. No specific content validity tests, e.g. examining comprehensiveness and relevance, were conducted for these 12 items.	?	15 parents of children with AD (item generation) 20 parents of children with AD (field test)	poor
Conclusion: One study assessed content validity of the Dutch CIAD, but due to poor methodological study quality no conclusion can be drawn ➔ Content validity of the Dutch CIAD as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S35: Convergent/divergent validity of the Dutch CIAD

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S10)	Correlation of CIAD scores with scores on the Psychological General Well-Being Index (PGWB)	Correlations between 0.38 and 0.65	?	48 parents of children with eczema	poor
Conclusion: One study assessed convergent/divergent validity of the Dutch CIAD, but due to poor methodological study quality no conclusion can be drawn ➔ Convergent/divergent validity of the Dutch CIAD as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S36: Cross-cultural validity of the Dutch CIAD

Author	Cross-cultural validity				
	Method	Result	Interpretation	Study base	COSMIN score
(S10)	Assessment of country-specific DIF and splitting/removal of items exhibiting DIF	Europe: Four items exhibited significant DIF --> items were split by country; three misfitting items removed	+	48 parents of children with eczema	poor
Conclusion: One study assessed cross-cultural validity of the Dutch CIAD, but due to poor methodological study quality no conclusion can be drawn ➔ Cross-cultural validity of the Dutch CIAD as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

11. Childhood Impact of Atopic Dermatitis (CIAD) – English version (UK)

Table S37: Internal consistency of the English CIAD (UK)

Author	Internal consistency				
	Method	Result	Interpretation	Study base	COSMIN score
(S10)	Calculation of Cronbach's alpha	Cronbach's alpha ranged from 0.72 to 0.85 in all countries	+	21 parents of children with eczema	poor
Conclusion: One study assessed internal consistency of the UK version of the CIAD, but due to poor methodological study quality no conclusion can be drawn ➔ Internal consistency of the English CIAD (UK) as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S38: Reliability of the English CIAD (UK)

Author	Reliability				
	Method	Result	Interpretation	Study base	COSMIN score
(S10)	Calculation of test-retest correlations (type of correlation coefficient not described)	Correlations ranged from 0.78 in the Netherlands to 0.86 in the US	?	21 parents of children with eczema	poor
Conclusion: One study assessed reliability of the UK version of the CIAD, but due to poor methodological study quality no conclusion can be drawn ➔ Reliability of the English CIAD (UK) as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S39: Content validity of the English CIAD (UK)

Author	Content validity				
	Method	Result	Interpretation	Study base	COSMIN score
(S11)	Interviews (35 UK, 65 total) with parents to explore the effect AD has on their children to generate wording for items. Tested for cultural applicability across countries. Parents completed the draft questionnaire and were asked in field-test interviews to comment on its understandability, comprehensiveness, and relevance.	More than 150 items after item generation phase. Reduction to 55 items by researchers. Initial version relevant to parents. Removal of ten items and modification of three items based on field-test interviews. 12 of the final 45 items formed the basis for creation of the CIAD. No specific content validity tests, e.g. examining comprehensiveness and relevance, were conducted for these 12 items.	?	35 parents of children with AD (item generation) 20 parents of children with AD (field test)	poor
Conclusion: One study assessed content validity of the UK version of the CIAD, but due to poor methodological study quality no conclusion can be drawn ➔ Content validity of the English CIAD (UK) as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S40: Convergent/divergent validity of the English CIAD (UK)

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S10)	Correlation of CIAD scores with scores on the Psychological General Well-Being Index (PGWB)	Correlations between 0.38 and 0.65	?	21 parents of children with eczema	poor
Conclusion: One study assessed convergent/divergent validity of the UK version of the CIAD, but due to poor methodological study quality no conclusion can be drawn ➔ Convergent/divergent validity of the English CIAD (UK) as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S41: Cross-cultural validity of the English CIAD (UK)

Author	Cross-cultural validity				
	Method	Result	Interpretation	Study base	COSMIN score
(S10)	Assessment of country-specific DIF and splitting/removal of items exhibiting DIF	Europe: Four items exhibited significant DIF --> items were split by country; three misfitting items removed	+	21 parents of children with eczema	poor
Conclusion: One study assessed cross-cultural validity of the UK version of the CIAD, but due to poor methodological study quality no conclusion can be drawn ➔ Cross-cultural validity of the English CIAD (UK) as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

12. Childhood Impact of Atopic Dermatitis (CIAD) – English version (US)

Table S42: Internal consistency of the English CIAD (US)

Author	Internal consistency				
	Method	Result	Interpretation	Study base	COSMIN score
(S10)	Calculation of Cronbach's alpha	Cronbach's alpha ranged from 0.72 to 0.85 in all countries	+	243 parents of children with eczema	fair
Conclusion: One study assessed internal consistency of the US version of the CIAD and indicated adequate internal consistency as a QoL instrument for eczema ➔ Internal consistency of the English CIAD (US) as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

Table S43: Reliability of the English CIAD (US)

Author	Reliability				
	Method	Result	Interpretation	Study base	COSMIN score
(S10)	Calculation of test-retest correlations (type of correlation coefficient not described)	0.86 (US)	?	243 parents of children with eczema	fair
Conclusion: One study assessed reliability of the US version of the CIAD and indicated unclear reliability as a QoL instrument for eczema ➔ Reliability of the English CIAD (US) as a measurement of QoL: **unclear** ➔ Quality of evidence: **fair**					

Table S44: Content validity of the English CIAD (US)

Author	Content validity				
	Method	Result	Interpretation	Study base	COSMIN score
(S11)	Tested items for cultural applicability across countries. Parents completed the draft questionnaire and were asked in field-test interviews to comment on its understandability, comprehensiveness, and relevance.	Reduction of initial item pool to 55 items by researchers. Initial version relevant to parents. Removal of ten items and modification of three items based on field-test interviews. 12 of the final 45 items formed the basis for creation of the CIAD. No specific content validity tests, e.g. examining comprehensiveness and relevance, were conducted for these 12 items.	?	20 parents of children with AD	poor
Conclusion: One study assessed content validity of the US version of the CIAD, but due to poor methodological study quality no conclusion can be drawn ➔ Content validity of the English CIAD (US) as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S45: Structural validity of the English CIAD (US)

Author	Structural validity				
	Method	Result	Interpretation	Study base	COSMIN score
(S10)	Assessment of overall fit to the Rasch model using Chi-square-statistics	Chi² statistics significant at 5% level both for Europe and the USA ($p<0.002$ and $p<0.004$, respectively); however, they used Bonferroni correction, so these p values may in fact be not significant (corrected alpha level not reported)	?	243 parents of children with eczema	fair
Conclusion: One study assessed structural validity of the US version of the CIAD and indicated unclear structural validity as a QoL instrument for eczema ➔ Structural validity of the English CIAD (US) as a measurement of QoL: **unclear** ➔ Quality of evidence: **fair**					

Table S46: Convergent/divergent validity of the English CIAD (US)

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S10)	Correlation of CIAD scores with scores on the Psychological General Well-Being Index (PGWB)	Correlations between 0.38 and 0.65	?	243 parents of children with eczema	poor
Conclusion: One study assessed convergent/divergent validity of the US version of the CIAD, but due to poor methodological study quality no conclusion can be drawn ➔ Convergent/divergent validity of the English CIAD (US) as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S47: Responsiveness of the English CIAD (US)

Author	Responsiveness				
	Method	Result	Interpretation	Study base	COSMIN score
(S10)	ANCOVA to test for differences in change scores between elidel and placebo group	USA: no significant differences	-	243 parents of children with eczema	poor
Conclusion: One study assessed responsiveness of the US version of the CIAD, but due to poor methodological study quality no conclusion can be drawn ➔ Responsiveness of the English CIAD (US) as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

13. Childhood Impact of Atopic Dermatitis (CIAD) – French version

Table S48: Internal consistency of the French CIAD

Author	Internal consistency				
	Method	Result	Interpretation	Study base	COSMIN score
(S10)	Calculation of Cronbach's alpha	Cronbach's alpha ranged from 0.72 to 0.85 in all countries	+	52 parents of children with eczema	fair
Conclusion: One study assessed internal consistency of the French CIAD and indicated adequate internal consistency as a QoL instrument for eczema ➔ Internal consistency of the French CIAD as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

Table S49: Reliability of the French CIAD

Author	Reliability				
	Method	Result	Interpretation	Study base	COSMIN score
(S10)	Calculation of test-retest correlations (type of correlation coefficient not described)	Correlations ranged from 0.78 in the Netherlands to 0.86 in the US	?	52 parents of children with eczema	fair
Conclusion: One study assessed reliability of the French CIAD and indicated unclear reliability as a QoL instrument for eczema ➔ Reliability of the French CIAD as a measurement of QoL: **unclear** ➔ Quality of evidence: **fair**					

Table S50: Content validity of the French CIAD

Author	Content validity				
	Method	Result	Interpretation	Study base	COSMIN score
(S11)	Tested items for cultural applicability across countries. Parents completed the draft questionnaire and were asked in field-test interviews to comment on its understandability, comprehensiveness, and relevance.	Reduction of initial item pool to 55 items by researchers. Initial version relevant to parents. 12 of the final 45 items formed the basis for creation of the CIAD. No specific content validity tests, e.g. examining comprehensiveness and relevance, were conducted for these 12 items.	?	19 parents of children with AD	poor
Conclusion: One study assessed content validity of the French CIAD, but due to poor methodological study quality no conclusion can be drawn ➔ Content validity of the French CIAD as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S51: Convergent/divergent validity of the French CIAD

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S10)	Correlation of CIAD scores with scores on the Psychological General Well-Being Index (PGWB)	Correlations between 0.38 and 0.65	?	52 parents of children with eczema	poor
Conclusion: One study assessed convergent/divergent validity of the French CIAD, but due to poor methodological study quality no conclusion can be drawn ➔ Convergent/divergent validity of the French CIAD as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S52: Cross-cultural validity of the French CIAD

Author	Cross-cultural validity				
	Method	Result	Interpretation	Study base	COSMIN score
(S10)	Assessment of country-specific DIF and splitting/removal of items exhibiting DIF	Europe: Four items exhibited significant DIF --> items were split by country; three misfitting items removed	+	52 parents of children with eczema	poor
Conclusion: One study assessed cross-cultural validity of the French CIAD, but due to poor methodological study quality no conclusion can be drawn ➔ Cross-cultural validity of the French CIAD as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

14. Childhood Impact of Atopic Dermatitis (CIAD) – German version

Table S53: Internal consistency of the German CIAD

Author	Internal consistency				
	Method	Result	Interpretation	Study base	COSMIN score
(S10)	Calculation of Cronbach's alpha	Cronbach's alpha ranged from 0.72 to 0.85 in all countries	+	87 parents of children with eczema	fair
Conclusion: One study assessed internal consistency of the German CIAD and indicated adequate internal consistency as a QoL instrument for eczema ➔ Internal consistency of the German CIAD as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

Table S54: Reliability of the German CIAD

Author	Reliability				
	Method	Result	Interpretation	Study base	COSMIN score
(S10)	Calculation of test-retest correlations (type of correlation coefficient not described)	Correlations ranged from 0.78 in the Netherlands to 0.86 in the US	?	87 parents of children with eczema	fair
Conclusion: One study assessed reliability of the German CIAD and indicated unclear reliability as a QoL instrument for eczema ➔ Reliability of the German CIAD as a measurement of QoL: **unclear** ➔ Quality of evidence: **fair**					

Table S55: Content validity of the German CIAD

Author	Content validity				
	Method	Result	Interpretation	Study base	COSMIN score
(S11)	Tested items for cultural applicability across countries. Parents completed the draft questionnaire and were asked in field-test interviews to comment on its understandability, comprehensiveness, and relevance.	Reduction of initial item pool to 55 items by researchers. Initial version relevant to parents. Removal of ten items and modification of three items based on field-test interviews. 12 of the final 45 items formed the basis for creation of the CIAD. No specific content validity tests, e.g. examining comprehensiveness and relevance, were conducted for these 12 items.	?	19 parents of children with AD	poor
Conclusion: One study assessed content validity of the German CIAD, but due to poor methodological study quality no conclusion can be drawn ➔ Content validity of the German CIAD as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S56: Convergent/divergent validity of the German CIAD

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S10)	Correlation of CIAD scores with scores on the Psychological General Well-Being Index (PGWB)	Correlations between 0.38 and 0.65	?	87 parents of children with eczema	poor
Conclusion: One study assessed convergent/divergent validity of the German CIAD, but due to poor methodological study quality no conclusion can be drawn ➔ Convergent/divergent validity of the German CIAD as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S57: Cross-cultural validity of the German CIAD

Author	Cross-cultural validity				
	Method	Result	Interpretation	Study base	COSMIN score
(S10)	Assessment of country-specific DIF and splitting/removal of items exhibiting DIF	Europe: Four items exhibited significant DIF --> items were split by country; three misfitting items removed	+	87 parents of children with eczema	poor
Conclusion: One study assessed cross-cultural validity of the German CIAD, but due to poor methodological study quality no conclusion can be drawn ➔ Cross-cultural validity of the German CIAD as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

15. Childhood Impact of Atopic Dermatitis (CIAD) – Italian version

Table S58: Content validity of the Italian CIAD

Author	Content validity				
	Method	Result	Interpretation	Study base	COSMIN score
(S11)	Interviews (15 Italy, 65 total) with parents to explore the effect AD has on their children to generate wording for items. Tested for cultural applicability across countries. Parents completed the draft questionnaire and were asked in field-test interviews to comment on its understandability, comprehensiveness, and relevance.	More than 150 items after item generation phase. Reduction to 55 items by researchers. Initial version relevant to parents. Removal of ten items and modification of three items based on field-test interviews. 12 of the final 45 items formed the basis for creation of the CIAD. No specific content validity tests, e.g. examining comprehensiveness and relevance, were conducted for these 12 items.	?	15 parents of children with AD (item generation) 8 parents of children with AD (field test)	poor
Conclusion: One study assessed content validity of the Italian CIAD, but due to poor methodological study quality no conclusion can be drawn ➔ Content validity of the Italian CIAD as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

16. Childhood Impact of Atopic Dermatitis (CIAD) – Spanish version

Table S59: Content validity of the Spanish CIAD

Author	Content validity				
	Method	Result	Interpretation	Study base	COSMIN score
(S11)	Tested items for cultural applicability across countries. Parents completed the draft questionnaire and were asked in field-test interviews to comment on its understandability, comprehensiveness, and relevance.	Reduction of initial item pool to 55 items by researchers. Initial version relevant to parents. 12 of the final 45 items formed the basis for creation of the CIAD. No specific content validity tests, e.g. examining comprehensiveness and relevance, were conducted for these 12 items.	?	20 parents of children with AD	poor
Conclusion: One study assessed content validity of the Spanish CIAD, but due to poor methodological study quality no conclusion can be drawn ➔ Content validity of the Spanish CIAD as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

17. DISABKIDS Atopic Dermatitis Module (DISABKIDS-ADM) – proxy-reported Portuguese version (Brazil)

Table S60: Internal consistency of the proxy-reported Brazilian Portuguese version of DISABKIDS-ADM

Author	Internal consistency				
	Method	Result	Interpretation	Study base	COSMIN score
(S12)	Calculation of Cronbach's alpha (proxy-reported version)	Cronbach's alpha was 0.7239 for impact dimension and 0.8604 for stigma dimension	+	52 parents of children and adolescents with eczema	poor
Conclusion: One study assessed internal consistency of the proxy-reported Brazilian Portuguese version of DISABKIDS-ADM, but due to poor methodological study quality no conclusion can be drawn ➔ Internal consistency of the proxy-reported Brazilian Portuguese version of DISABKIDS-ADM as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S61: Convergent/divergent validity of the proxy-reported Brazilian Portuguese version of DISABKIDS-ADM

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S12)	Correlation of scores with parent-evaluated disease severity by calculation of Pearson's correlation coefficient (proxy-reported version)	Impact dimension: r=-0.401 to -0,695 (p≤0.003); stigma dimension: r=-0.346 to -0.642 (p≤0.012)	?	52 parents of children and adolescents with eczema	poor
Conclusion: One study assessed convergent/divergent validity of the proxy-reported Brazilian Portuguese version of DISABKIDS-ADM, but due to poor methodological study quality no conclusion can be drawn ➔ Convergent/divergent validity of the proxy-reported Brazilian Portuguese version of DISABKIDS-ADM as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S62: Discriminative validity of the proxy-reported Brazilian Portuguese version of DISABKIDS-ADM

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S12)	Comparison of scores of different severity groups using ANOVA (proxy-reported version)	Statistically significant differences in both dimensions between mild, moderate and severe disease (P<0.001), but no statistically significant differences between moderate and severe disease in both dimensions	?	52 parents of children and adolescents with eczema	poor
Conclusion: One study assessed discriminative validity of the proxy-reported Brazilian Portuguese version of DISABKIDS-ADM, but due to poor methodological study quality no conclusion can be drawn ➔ Discriminative validity of the proxy-reported Brazilian Portuguese version of DISABKIDS-ADM as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

18. DISABKIDS Atopic Dermatitis Module (DISABKIDS-ADM) – self-reported Portuguese version (Brazil)

Table S63: Internal consistency of the self-reported Brazilian Portuguese version of DISABKIDS-ADM

Author	Internal consistency				
	Method	Result	Interpretation	Study base	COSMIN score
(S12)	Calculation of Cronbach's alpha (self-reported version)	Cronbach's alpha was 0.7024 for impact dimension and 0.8124 for stigma dimension	+	52 children and adolescents with eczema	poor
Conclusion: One study assessed internal consistency of the self-reported Brazilian Portuguese version of DISABKIDS-ADM, but due to poor methodological study quality no conclusion can be drawn ➔ Internal consistency of the self-reported Brazilian Portuguese version of DISABKIDS-ADM as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S64: Convergent/divergent validity of the self-reported Brazilian Portuguese version of DISABKIDS-ADM

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S12)	Correlation of scores with patient-evaluated disease severity by calculation of Pearson's correlation coefficient (self-reported version)	Impact dimension: r=-0.465 to -0.609 (p≤0.001); stigma dimension: r=0.417 to -0.555 (p≤0.002)	?	52 children and adolescents with eczema and their parents	poor
Conclusion: One study assessed convergent/divergent validity of the self-reported Brazilian Portuguese version of DISABKIDS-ADM, but due to poor methodological study quality no conclusion can be drawn ➔ Convergent/divergent validity of the self-reported Brazilian Portuguese version of DISABKIDS-ADM as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S65: Discriminative validity of the self-reported Brazilian Portuguese version of DISABKIDS-ADM

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S12)	Comparison of scores of different severity groups using ANOVA (self-reported version)	Statistically significant differences in both dimensions across all disease severity categories (P<0.001)	+	52 children and adolescents with eczema and their parents	poor
Conclusion: One study assessed discriminative validity of the self-reported Brazilian Portuguese version of DISABKIDS-ADM, but due to poor methodological study quality no conclusion can be drawn ➔ Discriminative validity of the self-reported Brazilian Portuguese version of DISABKIDS-ADM as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

19. DISABKIDS Atopic Dermatitis Module (DISABKIDS-ADM) – unknown language version

Table S66: Content validity of DISABKIDS-ADM (unknown language version)

Author	Content validity				
	Method	Result	Interpretation	Study base	COSMIN score
(S13)	Item selection from focus groups and semi-structured interviews; pilot study: item reduction by calculation of percentages of 'never' or 'not applicable' responses, cognitive interviews with affected children and adolescents, and clinical judgment of clinicians and investigators	?	?	Item selection: unknown Pilot study: 29 AD patients	poor
Conclusion: One study assessed content validity of DISABKIDS-ADM (unknown language version), but due to poor methodological study quality no conclusion can be drawn ➔ Content validity of DISABKIDS-ADM (unknown language version) as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

20. Infants' Dermatitis Quality of Life Index (IDQoL) – Arabic version

Table S67: Internal consistency of the Arabic IDQoL

Author	Internal consistency				
	Method	Result	Interpretation	Study base	COSMIN score
(S14)	Cronbach's alpha	α=0.87	+	370 AD patients + 120 controls	poor
Conclusion: One study assessed internal consistency of the Arabic IDQoL, but due to poor methodological study quality no conclusion can be drawn ➔ Internal consistency of the Arabic IDQoL as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S48: Convergent/divergent validity of the Arabic IDQoL

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S14)	Correlation of items and severity (not described which correlation coefficient was calculated)	Correlations range from 0.51-0.72	?	370 AD patients	poor
Conclusion: One study assessed convergent/divergent validity of the Arabic IDQoL, but due to poor methodological study quality no conclusion can be drawn ➔ Convergent/divergent validity of the Arabic IDQoL as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S69: Discriminative validity of the Arabic IDQoL

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S14)	Calculation of p value for item and total IDQoL scores for patients with mild, moderate and severe AD according to SCORAD	Statistically significant for mild vs. moderate, mild vs. severe, moderate vs. severe ($p<0.000$ for all items and for the total score)	+	370 cases with AD	poor
Conclusion: One study assessed discriminative validity of the Arabic IDQoL, but due to poor methodological study quality no conclusion can be drawn ➔ Discriminative validity of the Arabic IDQoL as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

21. Infants' Dermatitis Quality of Life Index (IDQoL) – Dutch version

Table S70: Reliability of the Dutch IDQoL

Author	Internal consistency				
	Method	Result	Interpretation	Study base	COSMIN score
(S15)	Calculation of the Intraclass Correlation Coefficient between administration 1 and 2 (Δt=24h)	ICC for overall scale = 0.89; ICC for individual questions ranged from 0.485 to 0.941	+	58 parents of children with AD	fair
Conclusion: One study assessed reliability of the Dutch IDQoL and indicated adequate reliability as a QoL instrument for eczema ➔ Reliability of the Dutch IDQoL as a measurement of QoL: **adequate** ➔ Quality of evidence: **fair**					

Table S71: Convergent/divergent validity of the Dutch IDQoL

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S15)	Calculation of Spearman's correlation coefficient to determine relationship between IDQoL and parent-assessed severity, Three Item Severity Score (TIS) and oSCORAD	IDQoL/parent-assessed severity: 0.728 (first visit), 0.662 (second visit) IDQoL/TIS: 0.134 (first visit), 0.356 (second visit) IDQoL/oSCORAD: 0.080 (first visit), 0.248 (second visit)	?	66 parents of children with AD (first visit) 65 parents of children with AD (second visit)	poor
Conclusion: One study assessed convergent/divergent validity of the Dutch IDQoL, but due to poor methodological study quality no conclusion can be drawn ➔ Convergent/divergent validity of the Dutch IDQoL as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

22. Infants' Dermatitis Quality of Life Index (IDQoL) – English version (UK)

Table S72: Reliability of the English IDQoL (UK)

Author	Reliability				
	Method	Result	Interpretation	Study base	COSMIN score
(S16)	Calculation of Spearman's correlation coefficients between the two assessments	r=0.91	?	72/102 24 hour delayed questionaires received	poor
Conclusion: One study assessed reliability of the UK version of the IDQoL, but due to poor methodological study quality no conclusion can be drawn ➔ Reliability of the UK version of the IDQoL as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S73: Content validity of the English IDQoL (UK)

Author	Content validity				
	Method	Result	Interpretation	Study base	COSMIN score
(S16)	92 parents of infants aged under 4 years with AD attending a Paediatric Dermatology outpatient department were asked to write down all the ways that the AD affected their child	70 responses collected; construction of an initial nine item questionnaire (IELQI); a tenth question was added after a pilot study	?	92 parents of infants with AD	poor
Conclusion: One study assessed content validity of the UK version of the IDQoL, but due to poor methodological study quality no conclusion can be drawn ➔ Content validity of the UK version of the IDQoL as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S74: Convergent/divergent validity of the English IDQoL (UK)

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S16)	Calculation of the correlation between IDQoL and FDI and between IDQoL and parent-rated severity using Spearman's correlation coefficient	IDQoL/FDI: r=0.87 IDQoL/severity: r=0.58	?	89 parents of infants with AD	fair
(S17)	Calculation of Spearman's correlation coefficient to compare scores of IDQOL/DFI and IDQOL/parental severity assessment (PAGS)	IDQOL/DFI: 0.776 (P<0.0001); IDQOL/PAGS 0.636 (P<0.0001) Correlations of individual IDQOL items with PAGS range from 0.26-0.59	?	203 parents of children with AD	poor
Conclusion: Two studies assessed convergent/divergent validity of the UK version of the IDQoL and indicated unclear convergent validity as a QoL instrument for eczema ➔ Convergent validity of the UK version of the IDQoL as a measurement of QoL: **unclear** ➔ Quality of evidence: **fair**					

Table S75: Responsiveness of the English IDQoL (UK)

Author	Responsiveness				
	Method	Result	Interpretation	Study base	COSMIN score
(S16)	Comparison of IDQoL scores before and after treatment using Wilcoxon's signed rank test. They also plot Change in IDQOL vs. change in clinical severity, but don't say whether their correlation is significant. Also, they don't say what treatment was and the time between assessments.	Difference in scores was statistically significant (p=0.0473)	?	25 parents of infants with AD	poor
(S17)	Comparison of scores before and after intervention using ANOVA	Median IDQOL score fell from 8 before treatment to 5.5 after treatment (P<0.0001); p values for analysis of different severity subgroups not given. Didn't assess correlation between change in severity or DFI with IDQOL.	?	50 parents of children with AD	poor
Conclusion: Two studies assessed responsiveness of the UK version of the IDQoL, but due to poor methodological study quality no conclusion can be drawn ➔ Responsiveness of the UK version of the IDQoL as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

23. Infants' Dermatitis Quality of Life Index (IDQoL) – Italian version

Table S76: Internal consistency of the Italian IDQoL

Author	Internal consistency				
	Method	Result	Interpretation	Study base	COSMIN score
(S18)	Cronbach's alpha	α=0.743 (first test); α=0.740 (second test)	+	21 children with AD	poor
Conclusion: One study assessed internal consistency of the Italian IDQoL, but due to poor methodological study quality no conclusion can be drawn ➔ Internal consistency of the Italian IDQoL as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S77: Reliability of the Italian IDQoL

Author	Reliability				
	Method	Result	Interpretation	Study base	COSMIN score
(S18)	Intraclass Correlation Coefficient (ICC) for the total score	ICC=0.950 (P<0.0001)	+	21 children with AD	poor
(S18)	Weighted Kappa for scores of individual questions	Weighted Kappa ranged from 0.632-1.000	?	21 children with AD	poor
(S18)	Comparison of scores of tests 1 and 2 using Wilcoxon rank scores	No significant differences between the two administrations according to Wilcoxon test	+	21 children with AD	poor
Conclusion: One study assessed reliability of the Italian IDQoL, but due to poor methodological study quality no conclusion can be drawn ➔ Reliability of the Italian IDQoL as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S78: Convergent/divergent validity of the Italian IDQoL

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S18)	Calculation of Spearman's correlation coefficient to determine the relationship between IDQoL and FDI, IDQoL and parent-reported severity, and IDQoL and SCORAD	First administration: IDQoL/FDI 0.763, IDQoL/parent-reported severity 0.486, IDQoL/SCORAD 0.764 Second administration: IDQoL/FDI 0.828, IDQoL/parent-reported severity 0.591	?	21 children with AD	poor
Conclusion: One study assessed convergent/divergent validity of the Italian IDQoL, but due to poor methodological study quality no conclusion can be drawn ➔ Convergent validity of the Italian IDQoL as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

24. Infants' Dermatitis Quality of Life Index (IDQoL) – Swedish version

Table S79: Convergent/divergent validity of the Swedish IDQoL

Author	Hypothesis testing (convergent/divergent validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S9)	Calculation of Spearman's correlation coefficient to determine the association between IDQoL and DFI, IDQoL and R&L score and IDQoL and objective SCORAD	IDQoL/DFI: 0.78 ($p<0.01$); IDQoL/R&L: 0.48 ($p<0.05$); IDQoL/oSCORAD 0.30 ($p>0.05$)	?	28 infants with eczema	poor
Conclusion: One study assessed convergent/divergent validity of the Swedish IDQoL, but due to poor methodological study quality no conclusion can be drawn ➔ Convergent/divergent validity of the Swedish IDQoL as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

Table S80: Discriminative validity of the Swedish IDQoL

Author	Hypothesis testing (discriminative validity)				
	Method	Result	Interpretation	Study base	COSMIN score
(S9)	Comparison of scores of infants with eczema and infants with eczema and asthma, allergic rhinoconjunctivitis, food allergy/intolerance or urticaria (AAFU) using ANOVA	No significant difference between infants with eczema and infants with eczema and AAFU	-	28 infants with eczema	poor
Conclusion: One study assessed discriminative validity of the Swedish IDQoL, but due to poor methodological study quality no conclusion can be drawn ➔ Discriminative validity of the Swedish IDQoL as a measurement of QoL: **unclear** ➔ Quality of evidence: **poor**					

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