Quality of life in children in a longitudinal perspective:

an exploratory review.

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Running head: Longitudinal quality of life in children.

Abstract

Objective: This paper explores the time variability of quality of life (QoL) in children between 0 to 12 years of age.

Design: A systematic review of original studies, with at least two QoL assessments, and published between 1966 and 1998. The publications were identified from medical and psychological sources by computerised searches followed by manual selection.

Data synthesis: The 32 selected publications were discussed according to their general characteristics, QoL assessment, longitudinal QoL research design and approaches to what changes QoL.

Main results: Only two publications met all QoL assessment requirements (multi-factorial, self-administered, subjective) as well as longitudinal requirements (clear description of assessment period, recall period, sample size at end of study, longitudinal statistics).

The approach to change that underlie the 32 publications can be described as: stable physical health gives stable QoL and changes in physical health change QoL. This mixed model can not be supported by current scientific knowledge.

Conclusions: More studies are needed that meet QoL assessment requirements as well as longitudinal requirements. It should be acknowledged that psychological, social and situational variables can change QoL as well. Discussion is necessary about what exactly changes QoL, as this influences the planning of the assessments and guides the interpretation of changes.

Key words: Quality of life, health-related quality of life, children, paediatric, literature review, longitudinal studies, follow-up.

Introduction

As medical successes in keeping children with serious diseases alive increase, the children's quality of life (QoL) receives growing attention. It is recognised that a certain disease or side effects of treatments can elicit quite different reactions in different children.[1] QoL accounts for these individual differences. As a result, QoL is increasingly used as one of the indicators of whether or not medical treatment is successful.[1,2] Although a widespread definition or theoretical framework is missing, there is a growing consensus on four aspects of QoL: it is multi-factorial (physical, psychological and social well-being), it is patient self-administered, it is subjective, and its value is variable over time.[1,3] We subscribe to the notion that these aspects of QoL are useful paradigms in adults' as well as children's QoL.

Concerning the aspect of patient self-administration, we add the comment that children cannot always be used as informants (too young or too ill) which makes a proxy respondent necessary. The closer the relationship between child and proxy, the higher the agreement is between them.[4] This makes the parent the most preferable proxy informant about the child's QoL. It is generally assumed that in childhood development is more rapid and important than at other stages in life. Given this, time variability is considered particularly relevant in children. In longitudinal research the time variability of QoL is the explicit objective of study. Therefore, the purpose of the present review is to explore children's QoL in a longitudinal perspective.

Approaching changes in children's QoL

The goal of a longitudinal study reveals implicit ideas of the investigators about the changeability of QoL. Two main approaches to change can be distinguished in advance: The first approach depends on a certain amount of invariability of QoL in time. This is expressed in

studies that are conducted for the following reasons: (a) To describe QoL in a particular group, for instance, to describe the impact of a disease on daily life or on the condition of a patient[5,6,7,8,9,10]; (b) To describe developmental processes; for instance, to describe age trends in a specific healthy sample or group of patients with a particular illness[10], or to assess patterns of QoL over time[8]; (c) to identify physical or psychological determinants of QoL[5,10] and predict future QoL from it[6,11]; (d) to predict morbidity and mortality using QoL as baseline data[5,7,8,10]; or (e) to evaluate the test-retest reliability or reproducability of new QoL instruments. Studies like these use a *predictability* approach to change, which is defined as the maintenance of a relative position on particular characteristics over time.[11] It can denote both stability (absolute levels of a characteristic remain stable over time), as well as continuity (consistency in relative rank over time on a characteristic).

The second approach emphasises the possibility of QoL to change over time. This is expressed in studies conducted (f) to evaluate the effect of an intervention or treatment on QoL[1,5,6,7,8,10]; or (g) to evaluate the responsiveness to change of a new QoL instrument. Studies like these use a *plasticity* approach to change, which is defined as describing the ability of an individual to change in characteristics over time. The plasticity approach is considered to be the changeable and time-variable aspect of development.[11]

Predictability (invariability) and plasticity (changeability) intuitively represent opposing characteristics. Therefore, the way change is approached needs to be further elaborated as we endeavour to study longitudinal QoL in children.

Questions to be answered in the review

In this systematic review the answers on the following questions were searched for.

a) How many QoL studies in children used a longitudinal perspective? In what area and in what age ranges were they performed?
b) Has QoL in these publications been defined and measured according to the current consensus?
c) Did the aim of the study have implications for the definition of QoL, the research design, or the approach to change?
d) Is it possible to draw general conclusions from these studies about QoL changes in children?
e)

Method

Criteria for Selecting Studies

1. Only original studies were included; reviews or theoretical papers without new data were excluded.
2. The majority of the subjects had to be between the ages of 0 and 12 years at the first QoL assessment.
3. At least two assessments of QoL had to be reported
4. The author(s) had to declare that their instruments assessed QoL
5. It had to be a prospective study
6. Studies with children with a mental retardation or with psychiatric patients were excluded.

Literature Base

We conducted a computer search using the following CD-ROM data bases: MEDLINE Express (1966-7/98), OVID-MEDLINE (1966-7/1998), PsycLIT (1967- 6/1998), PsycLIT Journal Articles (1991-12/1997), PsycLIT Chapters&Books (1974-12/1997), EMBASE (1979-1997), CC Search (1995-8/1998) and Pascal BioMed (1990-1997). To identify QoL studies the search terms Quality of life and Life Quality were used. In order to find studies in children between 0-12 years of age the following search terms were used: child, children , childhood, pediatr*, paediatr* or infant. To include longitudinal studies the following terms were used: longitudinal, longterm, long-term, long term, followup, follow-up, follow up, stability, stable, change, changes, increase, decrease, improve*, develop*. The position of the search terms in the records was not restricted, because longitudinal measurement of QoL in children was allowed to be an incidental or subsidiary aspect of a study. Search hits were captured into a computer database. Doubles were merged in a way that original CD-ROM data bases could be traced. The resulting references were all manually/visually studied to see if the selection criteria were met. If the publication language of the selected reference was English, a reprint of the paper was obtained from the university library. Available papers were studied in full in order to conclude whether they fitted the selection criteria.

Data synthesis

a) The numeric result of the computer search was presented.
b) General characteristics of the studies were listed using the following elements: year of publication, country in which the study was performed, years of children's birth, sample size, age at first assessment, description of subjects' characteristics, study aim, importance

of QoL in the study (main or subsidiary objective) and variables that were measured in addition to QoL.

c) The QoL assessment was given using the following elements: name of the QoL instrument(s), generic or disease specific instrument, type of instrument (utility, uni-dimensional or global, multi-dimensional, or battery approach), informant of QoL, objective or subjective evaluations, QoL domains (physical, psychological or social functioning), and QoL definition if provided by the authors.

d) The longitudinal QoL research design was evaluated using the following elements: research type (experimental, quasi-experimental or observational), an assessment diagram in which number of observations and time between observations were given, total period of assessments, instrument's recall period, sample size at the start of the study (both total size and group sizes), sample size at the end of the study, and longitudinal statistics used in the study to test the longitudinal changes.

e) An evaluation was made of the approaches to change that underlie the studies. The predictability approach was illustrated by the question: Was the QoL presumed to be stable (or continuous), and was this supported by the results of the study? The plasticity approach was illustrated by the question: What was presumed to elicit changes in QoL, and was this supported by the results of the study?

Results

The numeric result of the computer search

The search in the CD-ROM data-bases resulted in 4064 hits. After merging the doubles, 2573 references of publications remained. Seventy percent of the references would have been

found by solely using the MEDLINE Express data-base. None of the other databases could have given the remaining 30% on its own. Of the 2573 references only 115 met the selection criteria. In this selection, nine publications were non-English (French[12,13,14,15], Russian[16], Swedish[17], Italian[18], Spanish[19] or German[20]) and were therefore excluded. One publication was not available in the Netherlands.[21] It was decided that this publication probably was difficult to obtain in other countries as well, and could therefore be excluded. The remaining 105 publications were studied in full. Although these 105 publications all seemed to meet the selection criteria according to the information obtained from the data-base, only 32 fully met the selection criteria.[22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52, 53] The general characteristics of these publications will be presented in the next paragraph. If only MEDLINE Express would have been used, 27 publications (84%) from the final selection would have been found anyhow. In addition, four publications (12%) originated from the CC data-base. Although CC is specifically known for its up-to-date information, surprisingly these four were not the most recent publications in the selection.[23,27,28,35] The last article could have been found by using PsycLIT, PsycLIT Journal Articles or EMBASE.[46]

The search terms used resulted in many hits that appeared not to be useful in the end. For example, if somewhere in the reference the word ‘child’ was used, it was selected even if children were not the objective of the publication. Furthermore, in many references the abstract ended with recommending the study of QoL in future research, although QoL was not the objective of the publication. In other cases, the keyword QoL was given in the data bases to references that did not use the word QoL in the paper at all. Nevertheless, in retrospect it was not possible to use a better search term when conducting the computer search.

Closer inspection revealed that some papers were related to each other. It concerned Juniper et al.[38] with Guyatt et al.[26], and Cleary et al. [47] with Donadieu et al.[33] As they each had somewhat different study aims, they were not removed from the selection.

{insert Table 1. about here}

General characteristics

The general characteristics of the 32 publications are given in Table 1. As can be seen, the selected papers were published between 1981 and 1998. The distribution of the *publication years* is heavily skewed towards the more recent years, illustrating the flourishing development of children's QoL instruments since the nineties. Moreover, 12 of the publications had instrument development as their *aim of study*. Five of these papers tested reproducability (see aim (e) in the introduction)[30,37,39,44,45], five tested responsiveness to change (aim g)[22,26,27,35,38], and two papers tested both.[28,32] Seventeen studies aimed at treatment evaluation (aim f)[23,24,25,29,31,33,34,36,40,41,42,47,48,49,50,52,53], two at describing a particular group (aim a)[43,51], and one at identifying determinants of QoL (aim c).[46] None of the publications attempted to describe developmental processes (aim b), and none aimed at predicting morbidity and mortality by using QoL as baseline data (aim d). Seventeen publications had QoL as the *main objective* of the study[22,23,26,27,28,30,31,32,35,37,38,43,44,45,46,47,50], 14 considered QoL as subordinate objective.[24,25,29,33,34,36,39,40,41,42,48,49,51,52] One publication referred to QoL as a side issue according to the introduction, but as main objective according to the discussion.[53] Although QoL is considered to include physical, psychological as well as social functioning, most studies used separate instruments to measure one of these aspects apart from the QoL instrument. Twenty-eight papers included extra physical *variables* obtained from physicians or

parents.[22,23,24,26,27,28,29,31,32,33,35,36,37,38,39,40,41,42,43,44,45,46,48,49,50,51,52,53] Six papers included extra psychological variables[25,28,30,34,41,44], two studies included extra social variables[28,41], and two included no other assessments than QoL assessments.[45,47] Only four publications directly tested the relation between change in QoL and other variables.[22,26,27,38]

Some publications reported several studies or study phases.[22,37,44] The description of the study sample concerned the longitudinal parts of these publication only. The *sample size* ranged from 5 to 535 with a median of 75 children. All papers studied *children with a physical disorder,* although some of them included a healthy reference group in addition.[39,45,46,52] Twelve publications used several sub-groups[23,24,25,27,29,34,41,45,46,49,50,53], between group statistics were available in all but one.[53] In addition, four publications started with one group and ended up with two groups in retrospect, with children that changed or were stable.[22,28,32,38]

As a rule, management and treatment of disorders improves or changes during the years, and the conclusions drawn from certain populations could be outdated.[6,10] Therefore, it was considered important to report the *years of children's birth.* Unfortunately none of the publications reported these. To have at least some indication, the years of birth were estimated using the age of the children, the years of enrolment and the date the papers were received or accepted by the journals. As a result, the real years of birth could be earlier than given in the table, which is stressed by the '±'-sign. One of the selection criteria was that the subjects had to be primarily between the ages of 0 and 12 years. We had to interpret this criterion rather liberally because the cut-off points were rarely in this *age range* and the exact distribution of ages was not always completely clear. Some publications compared several age groups in their study.[26,30,38,42,45]

{insert Table 2. about here}

QoL assessment

In the next section the QoL assessment information in Table 2 is discussed in relation to the general characteristics in Table 1. As can be seen in Table 2, various instruments or techniques are used to measure QoL. Twenty publications presented the measurement properties of their main QoL instrument.[22,23,25,26,27,28,29,30,31,32,34,35,37,38,39,41,43,44,45,50] Obviously, all publications that had instrument testing as their aim, belonged to this category. Two studies provided very little information but suggested good measurement properties.[46,47] As many as 10 publications used instruments that had not been validated or tested at all.[24,33,36,40,42,48,49,51,52,53] These were not necessarily the oldest publications, although the oldest one was amongst them.[53] Instead, these were all publications that used QoL as a subordinate objective. Eleven publications used a generic instrument[25,27,31,35,39,43,46,48,49,50,51], 11 used a disorder specific instrument[22,24,26,29,33,34,36,37,41,44,53], seven used both[23,28,30,32,38,45,47] and in three publications it was unclear what was used.[40,42,52]

As stated before, QoL should be multi-factorial (physical, psychological and social well-being), patient self-administered or parent-administered, and subjective.[1,3] A multi-factorial measure could be obtained by multi-dimensional instruments as well as by utility instruments, although the last ones use often a final sum score instead of a profile.[9] A battery approach (a combination of instruments) could be multi-factorial but is less useful, because the instruments in the battery usually have different formats that are difficult to combine in a profile.[7] Ten publications used multi-factorial instruments measuring physical, psychological as well as social well-being[27,29,30,31,34,36,41,44,45,49] but only seven of these reported good measurement properties concerning reliability and validity as well.[27,29,31,34,41,44,45] Eleven publications used the child as informant[22,26,27,28,29,36,38,44,45,46,48]. Twenty-three publications used the parent or

caregiver as informant, [22,23,24,26,27,30,32,33,34,35,36,37,39,42,43,44,46,47,48,49,50,52,53] five used a clinician, teacher, nurse or psychologist as proxy.[22,23,35,42,50] Five publications compared a proxy informant like parents or clinician with the child.[22,26,36,44,46]. Six publications did not provide clear information about informants, since they did not report an informant,[40,41,51] or since they mentioned that parents 'helped if necessary'(in Table 2 referred to as 'child-or-parent').[25,27,31] In this way, however, it is not clear how much the parent provided the answers instead of the child. All but three publications[30,50,51] assessed subjective measurements of QoL. One publication stated, remarkably, that the concept of QoL is subjective and therefore unscientific.[42]

Preferably a QoL study covers physical, psychological as well as social well-being in one instrument and reports good measurement properties, assesses QoL by the children or parents and asks for their subjective opinion. Only five publications satisfied all QoL requirements.[29,30,34,44,45]

Finally, the column 'QoL definition' gives a nice illustration of the lack of consensus about a definition of QoL. Twelve publications used the term Health Related Quality of Life (HRQoL)[22,23,25,26,28,30,31,32,35,39,43,47], but the definitions of these studies did not substantially differ from the ones that used the term QoL. Eleven publications did not report a definition at all,[24,25,26,27,33,41,47,48,51,52,53] although three of them had QoL as their main study objective.[26,27,47] One paper administered an open question to explore the parental understanding of the concept QoL[39]: Eighty-seven percent of the parents thought that having a loving, caring family was most necessary in order for a child to have a good QoL. Good food, activity, health, and happiness were considered of lesser importance.

{insert Table 3 about here}

Longitudinal QoL research design

Table 3 starts with a schematic diagram of the research design focussing on quantity and timing of observations and interventions. As can be seen, in two publications the length of the period between assessments is not reported.[35(phase3.of 39)] The length of the total assessment period varies between 1 week (=0.25 months).[32,45,52] and 10 year (=120 months).[51] On average, publications that describe a particular group (aim a, see also Table 1) had the longest assessment periods, publications that aimed at reproducability (aim e), responsiveness to change (aim g) or both (aim e+g) had the shortest assessment periods, and the ones that aimed at treatment evaluation (aim f) or at identifying determinants (aim c) had assessment periods that fell between the two extremes.

Thirteen publications reported the instrument's recall period[22,23,24,27,28,30,32,34,35,38,43,44,47], that varied between the 'previous three months'[43] and 'at that point of time'.[23,35,44] In one publication the recall period of the instrument coincides with the period between assessments.[32] Ten publications did not report the sample size at the end of the study.[24,29,31,34,35,41,42,45,49,53] Eight publications did not report a longitudinal statistic to test the change in QoL[24,26,29,40,42,46,51,52], although some had QoL as their main objective.[26,46]

Of the five publications that satisfied all requirements for QoL assessment in Table 2 [29,30,34,44,45], all had clear assessment descriptions[29,30,34,45,44], some reported a recall period[30,34,44], some had good description of the sample size at the end of the study[30,44], and some used longitudinal statistics[30,34,44,45], leaving two studies that met QoL assessment as well as longitudinal requirements.[30,44] Both had a rather large age range : between 8-20[44] and between 5-20[30], but one presented separate results for the 5-12 and 13 to 20 year olds.[30] This is a rather small basis for making generalisations about QoL changes in children.

{insert Figure 1. about here}

Approaching change: prediction or plasticity

When considering the approach to change by the aim of the study, eight publications covered predictability (aim a:[43,51], aim c:[46], aim e:[30,37,39,44,45]), 22 covered plasticity (aim f:[23,24,25,29,31,33,34,36,40,41,42,47,48,49,50,52,53]; aim g:[22,26,27,35,38]) and two studies covered both (aim e+g:[28,32]). At first sight, the plasticity approach to change in QoL appeared far more popular. The picture changes when additional information is considered, collected by means of the two questions that illustrate the approach to change: 1) Was the QoL presumed to be stable (or continuous), and was this supported by the results of the study? (predictability); 2) What was presumed to elicit changes in QoL, and was this supported by the results of the study? (plasticity). Half of the publications appeared to use a mixed approach which might be summarised as: Predictability has to be tested in children whose physical condition has not changed, and plasticity in children whose physical condition did change.[22,25,27,28,29,30,32,37,38,39,44,45,47,49,50,51,53] Two publications presumed that changes in physical and psychological status would change QoL.[34,44] One of these found that regardless of physical status the QoL improved during the six months period, which points to continuity or consistency in relative ranks. In other words, they presumed plasticity but found predictability.[34] The publication with study aim c (identifying a determinant)[46] measured a combination of predictability and plasticity rather than predictability alone: these investigators studied if changes in physical status could predict changes in QoL.

The presumption about changing QoL by changing physical status was tested in 14 publications, either by testing between groups with or without changing physical

status[22,24,28,32,34,36,38,41,49], between disorder and healthy groups[27,45,46,50], or by testing the influence of other variables on changes in QoL.[22,26,27,28,38]

Discussion

The discussion is organised around the approaches of change in QoL as found in the reviewed publications, supplemented with the methodological requirements that are needed to consider these approaches in full. Although predictability (invariability) and plasticity (changeability) intuitively represent opposing characteristics, half of the publications used a mixed approach. As stated before this might be summarized as: predictability has to be tested in children whose physical condition has not changed, and plasticity in children whose physical condition did change. In the next paragraph it is explored if this assumption can be supported by current scientific knowledge.

Predictability

About 50% of the publications presumed the QoL to be stable or continuous, at least when the physical status is stable. Evidence obtained from studies on adults, suggests that QoL is quite stable anyway, and often does not reflect changes in life circumstances.[54] *Stability* in QoL is mainly influenced by personality traits.[54] Temperament or dispositional mood influences the QoL judgement of the individual.[54,55] and determines individual differences in the tendency to give socially desirable responses. Temperament shapes the pattern of experiences that individuals are exposed to, leading to a stable set of life circumstances[54], guides the individual in how the experiences are interpreted, or which circumstances are noticed.[56] Another stabilising factor is adaptation and adjusting to changes in life circumstances. As a result the impact of changes in circumstances can be detected in the short term, but in the medium term QoL

perceptions return to a stable baseline.[54] Adaptation can be influenced by social comparisons: seriously handicapped patients evaluate their QoL as high because they compare themselves to patients with similar problems rather than to healthy individuals.[54,57] These findings contradicts the assumption that only children with stable health would have stable QoL.

The effects of the child's age and level of development probably interfere with stability but can still imply *continuity*, the consistency in relative rank over time. One of the factors that influences predictions of QoL is the cognitive development of the child. The level of cognitive development influences the child's concepts of health and illness.[58] It influences the ability of the child to read and understand the QoL questions, to recall the relevant information and to formulate the answer.[6,7,59] A publication from our selection reported that if the statistics between scores of younger children and adults are worse than the statistics between scores of older children and adults, then this would be a strong indication that the younger children did not fully understand the ratings.[22] However, another publication from our selection studied the minimum skills required by children to complete various QoL instruments.[28] The Standard Gamble method, for instance, required better than grade 6 reading skills. Children are not able to consider whether they would prefer to remain in a certain health state or take a chance with a new (imaginary) treatment. The children did not have problems with the other three questionnaires in that publication. Another selected publication stated that from 4 or 5 years upwards children are able to introspect and report upon their QoL.[45] Furthermore, in a previous publication we showed that children, like their parents, can give valid information about the child's QoL, although the information can be somewhat different.[4]

It should be noted, that individual continuity does not imply a certain shape of the developmental functioning, nor does it imply that all children necessarily exhibit the same pattern of development.[11] Therefore, variance between children can increase when they become

older, but a temporary increase in variance will occur too if individual differences in timing of universal developmental events are important.[60] Some of the publications in our selection provided a comparison between two or more age groups.[26,30,38,42,45], but they did not provide variances that could support this assumption.

It may be that the levels of function in various dimensions change with age like the relative weightings of QoL domains do.[3,61] The specific impact of a medical situation also varies with age. For example, hair loss associated with chemotherapy of childhood cancer, may be especially disturbing during adolescence and less during childhood.[7] A publication from our selection[38] accounted for this by individualising items from the activity domain, which was regarded most likely to show heterogeneity across age. Furthermore, they reported that in younger children fewer domains of QoL could be distinguished than in older children. As a result it is better to use a limited age range: changes in children's QoL are probably different from changes in adolescents or adults, and most instruments are age-related.It is therefore regrettable that twenty of the selected studies used age ranges of ten years or more.

Given the above, it may be inferred that children with stable health can have changes in their QoL, although these changes might be a (developmentally guided) continuity effect rather than resulting from changes in health. Before, it was described that stability in QoL can be caused by other factors than merely a stable health (e.g. disposition or adaptation). In conclusion, the assumption that QoL will be stable in children whose physical condition has not changed, can not be supported.

Plasticity

All studies presumed QoL to be changeable, at least when the physical status has changed. Since this presumption was tested in only 14 publications, we conclude that this presumption is so strong that most researchers do not feel the need to prove it.

Nowadays, in defining QoL, a strictly "biomedical model of health" is replaced by a broader model in which QoL contains the three factors, physical, psychological and social functioning.[9] In approaching change, however, a biomedical model is still in use, suggesting that the only change of importance is a change in physical functioning. This approach is supported by the publications in our selection. The use of a biomedical model on QoL change is considered a *restricted view* because it ignores the possible influence of psychological or social factors on QoL. Probably the physician's interest in the influence of physical changes on QoL is related to the fact that these changes can be modified by medical treatment.[62] This means that the restriction to physical variables represents a choice, which is sometimes stressed by using the term 'Health Related' QoL. In studies using the restricted view, only clinical variables were collected, and assessment of QoL was planned in relation to the medical intervention process only.[3,8,9] In our selection, 28 papers included extra physical variables in addition to the QoL data, but only eight papers included psychological[25,28,30,34,41,44], or social variables.[28,41] Nineteen studies planned there assessments in relation to a medical intervention. The restricted view furthermore implies a linear model in that it assumes that treatment A leads to physical change B which leads to QoL outcome C.[9]

Plasticity could alternatively be viewed according to a more comprehensive biopsychosocial model. This model recognises that health and QoL are determined by psychological and social as well as physical factors, all of which interact to produce the current QoL.[9] In studies using

this *broad view,* psychological and social variables were collected together with clinical variables[8,3], as was done by two papers in our selection.[30,41] Furthermore, in a broad view, medical treatments as well as psychological interventions could be beneficial in changing QoL. In three publications psychological[25,34], or social interventions were performed[41] One paper[46] studied a 'time-delay' model, which predicts that psychosocial complications may follow the development of disease symptoms, however with a considerable time delay. Consequently psychosocial reactions may persist after normalisation of physical symptoms. The parents in this study continued to report disease-related problems and remained worried although the children were considered cured. The children however showed an abrupt adaptation to news of being cured and even showed a super-positive QoL evaluation.[46] The QoL changes could be the result of changing priorities and goals of the individual. Calman[63] defined QoL as the gap between the patient's expectations and achievements. The priorities and goals of an individual must be realistic and would therefore be expected to change with time and be modified by age and experience.[63,3] Changing priorities and goals could result in changing internal standards about what is important in QoL. This change of internal standards is also called 'response shift'. Response shift is the result of a psychological process that includes adaptation to the current physical situation. However, originally response shift is approached as a purely methodological problem. It is interpreted as a systematic bias, because the 'real' QoL changes as a result of a physical condition will be overshadowed.[64] Probably in order to meet with this bias, in some publications from our selection, the QoL informants were allowed to see their previous assessments.[38,49] This reasoning seems to express a restricted view on plasticity, in which psychosocial processes are interpreted as confounders. In a broad view, response shift is the result of a combination of physical and psychological changes and not merely a measurement bias. These findings contradicts the assumption that a change in health is

necessary to generate changes in QoL. In few of the selected studies it was acknowledged that along with changes in physical status, changes in psychological or sociological status could alter QoL.

Measuring QoL plasticity is furthermore complicated by *situational variables* at the time of assessment. A certain mood may increase access to memories with congruent information.[54,65] Therefore, mood, diet, sleep, current level of stress, the setting (clinic, home or laboratory), all may influence the judgement of QoL.[8,9] Under time pressure or threat, adults as well as children will not consider all domains of one's life when giving an overall judgement of their QoL. Instead they will choose a simpler strategy in which the emotional state at the time of assessment will be used to base their QoL judgement upon.[1,54,59] This was even promoted, though unintentionally, by one of the selected publications, in which the investigators explained the recall period of 'last week' to the children by referring to something that happened a week ago.[28] Therefore, retrospective estimates of former QoL are highly correlated with the present state.[32] The information from a questionnaire with a very long recall period may therefore hardly differ from that assessed with a short recall period. Thus, situational variables can take away the visibility of changes in QoL. In conclusion, the assumption that QoL scores will change in children whose physical condition changed, can not be supported.

Interaction between predictability and plasticity

The relation between change and health is even more complicated because factors which influence predictability in turn influence plasticity. Predictability factors like personality and cognitive development are potential moderators of QoL plasticity, both directly or through experience. Experiences influence the way the child judges his or her QoL.[6,9]

Methodological considerations

The interrelation between predictability and plasticity implies that longitudinal research should contain both approaches, which has implications for the planning of the QoL assessments.[1,3,55,66] Therefore, the following aspects are recommend: Measure factors like disposition or adaptation since they influence stability of QoL. Use limited age ranges and use age appropriate control groups to rule out continuity effects. Measure the medical, psychological as well as sociological status of the children to approach change of QoL in a broad view. Control for situational variables that might take away the visibility of changes in QoL.

It is somewhat worrying that only two publications met all QoL assessment requirements as well as longitudinal requirements. Several publications discuss the basic necessities for conducting QoL studies in general[8,9,10,55,67,68] and longitudinal QoL studies in particular[3,11,69,70], or give good suggestions for presentation.[71] Instead of repeating all requirements that are needed for a good longitudinal QoL design, we refer to these publications and to the results and discussion in this paper. In addition, the following aspects are considered important: Firstly, the *sample size* should be big enough to avoid type 2 errors (concluding that there is no difference between groups when there really is a difference) although repeated measures designs have an increased power to detect between group differences. Secondly, QoL assessed prospectively (e.g. 'How did you feel today ') differs from QoL obtained in retrospect (e.g. 'How did you feel on a certain day one year ago'). Therefore, QoL is not recoverable once lost. Careful attention to the timing of measurement and consistency of measurement across treatment arms is important.[3,8] Thirdly, As the choice of informant influences the QoL judgements[9,4,72,73], the same informant should be used at all points of measurement. If, for

instance, at start a proxy is used because the child is to young to fill in questionnaires, maintain the proxy as informant even when the child can read at a later time. Do not mix scores of various informants. Fourthly, some of the selected publications used an instrument without limited measurement properties, and most instruments did not meet the basic requirements for measuring QoL. At present many QoL instruments for children are being developed and it must be possible to choose one that meets all requirements.[5,7,8,59,67,68,74,75,76,77] Preferably, a multi-dimensional questionnaire with a limited number of scales should be used, because the repeated measurement of scales enlarges the volume of statistical tests needed, which enlarges the number of measurement errors. For that matter, finally, the choice of longitudinal statistics could direct possibilities in studying the changeability of QoL. For instance, correlations test the strength of a relation between time points, but not differences in height. This will imply that changes in QoL cannot be studied using correlations.

In conclusion, since many publications from the selection used large age ranges, various disorder groups, different QoL assessments and assessment periods, results of these studies can not be generalised. Five publications defined and measured QoL according to the current consensus (multi-factorial, self- or parent-administered, subjective). Only two of these papers met the longitudinal requirements as well (clear assessment period, recall period, sample size at end of study, longitudinal statistics). Thus, more studies are needed that meet QoL as well as longitudinal requirements. Despite the growing consensus that QoL is variable over time, information about the underlying approach to change is scarce: Can QoL be stable over time (predictability), or if it changes, by what did it change (plasticity)? In our selection a mixed model of predictability and plasticity is used but seldom explicitly tested: stable physical health gives stable QoL and changes in physical health change QoL. As described in the

discussion this mixed model can not be supported by current scientific knowledge. It is rarely acknowledged that psychological, social and situational variables can change QoL as well. In future, more discussion is needed about how variable with time QoL really is, as this influences the planning of the assessments and guides the interpretation of changes in children as well as in adults.

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Table 1. General characteristics of the reviewed studies

Refr. nr.	First author	Publ. Year	Country	Years of birth	N	Age at first assessment(1)	Description of subjects characteristics: children with ...(2)	Study aim	QOL main or side objective? (3)	Other variables measured next to QOL?(4)
22	Juniper	1998	Canada	±1987	75	M=9.8 y, SD=1.9 y.	rhinoconjunctivitis (In retrospect: I1=stable, I2=changed)@2	G	main	Ph (#3)
23	Barr	1997	Canada	±1983-1996	18	Med=3y11m, range=11m. to 14y.	standard (I1t) and high risk (I2t) cancer @2	F	main	Ph (-)
24	Cantani	1997	Italy	±1983-1989	300	range=3.5-7.5, Med=4.4	asthma(It=treatment, Ic=control) @2	F	side	Ph (-)
25	Bartholomew	1997	USA	±1979-1996	199	M=8.6, range= 0-18y	cystic fibrosis (It=treatment group,Ic=control group)@2	F	side	Psy (-)
26	Guyatt	1997	Canada	±1979-1989	52	M=12, SD=3.1, range=7-17 (age groups: 7-10 y., 11-17 y. results separately reported)	asthma	G	main	Ph (-) or (#3)
27	Gill	1997	Great Britain	±1979-1989	50	range= 6-16	sickle cell disease(I1=sickle cell anaemia, I2=sickle cell disease) and R=healthy children @2	G	main	Ph (#3)
28	Juniper	1997	Canada	±1979-1989	52	range=7-17y	asthma (In retrospect: I1=stable, I2=changed)@2	E+G	main	Ph(#3), Psy (#3), S (#3)
29	Meltzer	1997	USA	±1978-1990	204	range=6-18y	It=perennial rhinitis treatment group, Ip=perennial rhinitis placebo group @1	F	side	Ph (-)
30	Parkin	1997	Canada	±1976-1991	35	range=5-20, separate results on 5-12y and 13-20y	spina bifida	E	main	Psy (#1)
31	Iorio	1997	Italy	±1976-1987	94	Med=8 y., range: 3-14 y.	chronic viral hepatitis	F	main	Ph (-)
32	Rosenfeld	1997	USA	±1975-1996	186	Med=3.4 y., range 6m-12y.	otitis media (In retrospect: I1=stable, I2=changed)@2	E+G	main	Ph (#1)
33	Donadieu	1997	France	±1966-1991	19	range= 0.4-23.7, Med=5,25	severe chronic neutropenia	F	side	Ph (-)
34	Kazak	1996	USA	±1989	162	M=5.69, SD=4.39	leukemia (It1=medical intervention, It2=medical and psychological intervention, Ic=control) @2	F	side	Psy (-)
35	Dossetor	1996	Australia	±1982-1995	28	M=5y5m; range=7m-13y6m	inpatients of children's hospital	G	main	Ph (-)
36	Berth-Jones	1996	England	±1979-1993	27	M=9y, range 2-16y	eczema	F	side	Ph (-)
37	Carpay	1996	The Netherlands	±1979-1991	80	range=4-16	epilepsy	E	main	Ph (#1)
38	Juniper	1996	Canada	±1979-1989	52	M=12, SD=3.1, range: 7-17 (age groups: 7-10 y., 11-14 y., 15-17 y.)	asthma (In retrospect: I1=stable, I2=changed)@2	G	main	Ph (#3)
39	Spencer	1996	England	could not be deduced	168	"infants and pre-schoolers"	'normal' children, developmental problems, acute illnesses, and chronic illnesses (-)	E	side	Ph (-)

Refr. nr.	First author	Publ. Year	Country	Years of birth	N	Age at first assessment(1)	Description of subjects characteristics: children with ...(2)	Study aim	QOL main or side objective? (3)	Other variables measured next to QOL?(4)
40	Konishi	1995	Japan	±1983-1991	5	range=2y5m-10y11m	epilepsy	F	side	Ph (-)
41	Marrero	1995	USA	±1981	106	M=13.3y, SD=4.5y	diabetes (It=treatment group, Ic=control group)@2	F	side	Ph (-), Psy (-) and S (-)
42	Buchanan	1995	Australia	±1980-1991	15	range=3-26y. Separate results of children 3-14 y and adolescents/young adults 15-26y	epilepsy	F	side	Ph (-)
43	Gemke	1995	The Netherlands	±1976-1991	468	M=55mnd=4,58y, range=1m-16y	children from a tertiary paediatric ICU (trauma patients excluded)	A	main	Ph (#2)
44	Eiser	1995	England?	±1975-1987	35	M=14,4, range=8-20	cancer or a medical history of cancer	E	main	Ph (#1) Psy (#1)
45	French	1994	England	±1981-1989	535	range=4-16y. Separate results for 4-7y.(M=5.5), 8-11y(M=9.7), 12-16y (M=13.8).	I=asthma , R=healthy children @2	E	main	Ph (-)
46	Aldenkamp	1994	The Netherlands	±1981	200	I: M=12,8 ; R: M=12.6	I=outgrown epilepsy, R=healthy children @2	C	main	Ph (-)
47	Cleary	1994	England, France, Germany and Poland	±1976-1993	130	range=4,5m(0,375y)-18y	congenital agranulocytosis	F	main	not reported
48	Van-Damme-Lombaerts	1994	Switzerland	±1968-1988	107	Med=11,6, range 6m - 20 y	chronic renal failure	F	side	Ph (-)
49	Morris	1993	England	±1980-1990	11	Med=6.7y, range=2.3-12.3	end stage renal failure (It1=treatment arm one, It2=treatment arm two) @2	F	side	Ph (-)
50	Wray	1992	UK	±1972-1990	28 + ?R	I: M=8.63, range=0.1-16.0y, R: M=8.59, range=0.3-15.8y	I=heart or heart-lung transplantation, R= healthy children @2	F	main	Ph (-)
51	Hoppe-Hirsch	1990	France	±1957-1986	120	range=1-15, peak at 5-6 years	operated for medulloblastoma	A	side	Ph (-)
52	Becker	1988	USA	±1987	51	range=2w-12w	healthy infants with infant colic	F	side	Ph (-)
53	Kekomäki	1981	Finland	±1963-1975	7	range=5-17y	incontinence due to congenital abnormalities (It1=treatment arm one, It2=treatment arm two) (-)	F	side (in introduction), main (in discussion)	Ph (-)

(1) M=average,Med=median, m=months, y=years, I=indexed group, R=healthy reference group

(2) @1: between group comparison, not tested; @2 : between group statistics; (-): no test or comparison

(3) A=describing a group, B=describing QOL development, C=identifying determinants, D=predict morbidity/mortality from baseline QOL, E=testing instruments reproducability, F=treatment evaluation, G=testing instruments responsiveness to change

(4) Ph=physical, Psy=psycological,S=sociological (#1)= comparison between QOL and other parameter,not tested ; (#2) = statistics between QOL and other parameter; (#3) = statistics between change in QOL and other parameter; (-): no test or comparison

Table 2. QOL assessment in the reviewed studies

Refr. nr.	Name QOL instrument (1)	Generic or specific instrument	Type of instrument	Informant (2)	Objective or subjective evaluations	QoL domains (3)	QoL definition
22	Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) (!)	specific	multi-dimensional	children, clinicians, parents ($2)	subjective	O, Ph.	HRQoL not only measure how much patients are bothered by their symptoms, they also measure the impact that the symptoms have on the day-to-day functioning (physical, social, occupational and emotional).
23	A. Overall assessment of Health status (?); B.classification into 4 temporary health states (?); C.Health utilities index mark 2 (HUI2) (!); D.Health utilities index mark 3 (HUI3) (!)	A, C and D are generic; B. is specific	A. global, B. multi-dimensional, C&D. Utility	nurse, physicians, parent ($2)	A,B,C,D :subjective	A: O B: Ph, Psy C&D: Ph,Psy	HRQoL: A: global rating of the subject's health status, B: classification into temporary health states C+D: health state.
24	diary card (?)	specific	multi-dimensional	parent	subjective	Ph	QOL: not reported (limitations of the quality of life per year).
25	"measures of health and quality of life variables" (11 different instruments) (! + ?)	generic	battery	child-or-parent (-)	subjective	Ph,Psy,S	HRQoL: not reported
26	Paediatric Asthma Quality of Life Questionnaire (PAQOL) (!)	specific	multi-dimensional	child, parent ($1)	subjective	Ph, Psy	HRQoL: not reported
27	Central Middlesex Hospital Children's Health Diary (CMHCHD) (!)	generic	multi-dimensional	child (11-16) child-or-parent (6-10) (-)	subjective	Ph,Psy,S	QOL: not reported (health status)
28	A:Paediatric Asthma QOL questionnaire (PAQLQ) (!), B: Health Utilities Index (HUI) 2 and 3 (!), C: the Feeling Thermometer (!), D: Standard Gamble (!)	A: specific, B: generic, C:specific, D:specific	A: multi-dimensional, B: utility, C:global, D: utility	child	A to D: subjective	A&B: Ph, Psy C&D: O	HRQoL: A. impact of asthma condition on children's day-to-day life, B:health status, C. health state and the value children place upon it D: value that patients place on their own health state.
29	Assessment of quality of life in adolescents and children with allergic rhinoconjunctivitis (!)	specific	multi-dimensional	child	subjective	Ph,Psy,S	QOL: relevance of rhinitis to activities and moods.
30	A: spina bifida HRQOL instrument (!), B:global question of well-being (?)	A: specific, B: generic	A: multi-dimensional, B: global	parent (5-12y) and child (13-20y) (-)	A&B: objective	A: Ph, Psy, S, B: O	HRQoL: construct encompasses physical and occupational function, psychological state, social interaction and somatic sensation.
31	Sickness Impact Profile (SIP)(!)	generic	multi-dimensional	child-or-parent (-)	subjective	Ph,Psy,S	HRQoL: evaluates the impact of a disorder on the patient's HRQoL as perceived through its effect on patient daily activities, feelings and attitudes.
32	A. The 6-item health-related QOL survey (OM-6) for chronic and recurrent otitis media (!), B. Global measure of ear-related QOL (!)	A. specific, B. specific	A. multi-dimensional, B.global	caregiver	A. subjective, B. subjective	A: Ph,Psy, B: O	HRQoL is a subjective outcome that reflects the patient's perception of his or her health status.
33	self-made questionnaire (?)	specific	multi-dimensional	parents	subjective	Ph	QOL: not reported
34	Pediatric Oncology Quality of Life Scale (POQOLS) (!)	specific	multi-dimensional	mother, father ($1)	subjective	Ph,Psy,S	QOL: frequency of paediatric oncology patients' daily activity.
35	The RAHC Measure of Functioning (MOF) (!)	generic	global, utility?	clinicians and parents ($2)	subjective	O	HRQoL: a broad concept of child health covering 'physical, mental and social well-being, not merely the absence of disease and infirmity.
36	self-made questionnaire (?)	specific	multi-dimensional	child, parent ($1)	subjective	Ph,Psy,S	QOL: impact of the disease on child an family.
37	The Hague seizure severity (SS) and The Hague side-effects(SE) scales (!)	specific	multi-dimensional	parent	subjective	Ph	QOL is a multidimensional concept with physical and psychosocial issues.

Refr. nr.	Name QOL instrument (1)	Generic or specific instrument	Type of instrument	Informant (2)	Objective or subjective evaluations	QoL domains (3)	QoL definition
38	A. Paediatric Asthma Quality of Life Questionnaire (PAQOL) (!); B: The Feeling Thermometer (!), C: Global rating of change questionnaire (!)	A. specific, B. generic, C:specific	A. multi-dimensional, B: global, C: multi-dimensional	child	subjective	A: Ph,Psy, B: O, C: Ph,Psy	QOL: A: the impact of asthma on their lives. B: how the patient feels about his or her own health state, C: not reported.
39	one domain of The Warwick Child Health and Morbidity Profile (WCHMP) (interview or postal questionnaire) (!)	generic	global	parent	subjective	O	HRQoL: overall picture of perception of the child's health and illness experience.
40	not reported (?)	not reported	not reported	not reported	not reported	Ph, Psy	QOL: demonstrated by (increases in) activity, appetite, conversation and good humour.
41	Diabetes QOL for youth (DQOLY) measure	specific	multi-dimensional	not reported	subjective	O, Ph, Psy, S	QOL: not reported
42	"observations" "could not be assessed in a quantitative fashion" (?)	not reported	not reported	parents, carers, physicians (-)	subjective	Ph, Psy	QOL manifest by improved alertness, cognition and general functioning.
43	multiattribute health status classification (MAHSC) (!)	generic	utility	parent	subjective	Ph, Psy	HRQoL: functional abilities from a patient's perspective, health status.
44	Perception of illness experience (PIE) (!)	specific	multi-dimensional	child, parent ($2)	subjective	Ph,Psy,S	QOL: child's perception of the illness experience; multi-dimensional; subjective.
45	Childhood Asthma Questionnaires: CAQA (4-7y), CAQB (8-11y.), CAQC (12-16y.) (!)	specific and generic part	multi-dimensional	child	subjective	Ph,Psy,S	QOL = HS related to how a person feels, and how he/she functions in daily activity". QOL=multidimensional.
46	Holmfrid Quality of Life Inventory (?!)	generic	multi-dimensional	parents and children (#1)	subjective	Ph, Psy	QOL: defined as a multidimensional construct that covers physical, emotional, mental, social and behavioural components of well-being and function as perceived by patients and observers.
47	HRQOL instrument self-made based on a synthesis of existing measures (?!)	generic and specific	multi-dimensional	parent	subjective	Ph	HRQoL: not reported
48	self-made questionnaire (?)	generic	multi-dimensional	parent (<8y) and child (>7y) (-)	subjective	Ph,Psy	QOL: not reported
49	self-made instrument (?)	generic	multi-dimensional	parent	subjective	Ph,Psy,S	QOL: various aspects of the child's well being and behaviour.
50	various instruments (!) and self-made instrument (?)	generic	battery	parents, children, teachers, test-results (psychologist) (-)	objective and subjective	Psy, O	QOL is being used as an indicator of the success of a particular intervention with increasing frequency, although as a concept it is subjective and therefore unscientific.
51	various instruments (?)	generic	battery	not reported	objective	Ph, Psy	QOL: not reported
52	self-made questionnaire (?)	not reported	global	parent	subjective	not reported	QOL: not reported
53	self-made questionnaire (?)	specific	not reported	parent	subjective	not reported	QOL: not reported (leading a normal life).

(1) (!)=good measurement properties, (?)=no measurement properties provided, (?!)=suggested good properties
(2) ($1)=cross-informant comparison, not tested; $2=cross-informant statistics; (-)=no test or comparison
(3) Ph=physical, Psy=psychological, S=social, O=overall or global

Table 3. Longitudinal QOL research design in the reviewed studies

Refr. nr.	Research type (1)	Assessment diagram (2)	Total period (in months)	Instrument(s) recall period	Sample size at start (3)	Sample size at end (3)	Longitudinal statistics
22	obs.	I: O1 - 1w-> O2 -2w-> O3	0.75	previous 7 days	75	74 (Istable=13, Ichange=61)	paired t-test, intraclass correlation coefficient
23	quasi.	It1: StartMI -1w-> O1 - 1w-> O2 -1w-> O3 It2: StartMI -1w-> O1 - 1w-> O2 -1w-> O3	0.75	A+B not reported, C+D: at that point of time	18 (It1=9, It2=9)	18 (I1=9, I2=9)	ANOVA, paired t-test, intra-class correlations
24	quasi.	It: start MI -1year(daily dairy)->O1 -1year(daily dairy)-> O2-1year(daily dairy)->O3 Ic: start -1year(daily dairy)->O1 -1year(daily dairy)-> O2-1year(daily dairy)->O3	36	1 day	300 (It=151, Ic=149)	not reported	not reported
25	quasi.	It: O1 ->PI -18/32mm-> O2 Ic: O1 -18/32m->O2	24	not reported	199 (It=104, Ic=95)	184 (It=95, Ic=89)	ANCOVA between groups with the pretest as covariates
26	obs.	I: O1 -1w-> O2 -4w-> O3 -4w-> O4	2.25	not reported	52	52	not reported
27	obs.	I1: O1-every day->O28 I2: O1-every day->O28 R: O1-every day->O28	1	1 day (missing data retrospectively completed within 1 week)	50 (I1=14, I2=11, R=25)	50 (I1=14, I2=11, R=25)	Mann-Whitney U test
28	obs.	enrolment -1w-> O1 -4w-> O2 -4w ->O3	2.25	A: previous week, B:"time frame is not specified", C:previous week, D:previous week.	52	52 (Istable=37, Ichange=15)	Intra-class correlation coefficient (ICC) and paired t-test
29	exp.	It: O1 -1w-> start Pla -1w >-start MI -4->end MI-1->O2 Ic: O1 -1w-> start Pla -1w >-start Pla -4->end Pla-1->O2	1.75	not reported	204 (It=102, Ip=102)	not reported	percentage
30	obs.	O1 -2w-> O2	0.5	A: not reported, B: at present	35	28	intra-class correlation coefficient
31	quasi.	O1,startMI - 1m-> O2 -3/12 m-> O3,endMI -1m-> O4 -2m-> O5	7 to 16	not reported	94	not reported	Student t-test
32	quasi.	phase I responsiveness: O1 -±2w-> MI -±2w-> O2 phase II test-retest: O1 -1w-> O2	1 (phase I); 0.25 (phaseII)	A+B: during the past 4 weeks	186	110 (phase I=50 phase II=60)	A: standardised response mean SRM (mean change score divided by its SD and 95% confidence interval. B: correlations
33	quasi.	O1 -15d-> O2 start MI -1m->O3-1m->O4-1m->O5-1m-> O6-1m->O7-1m->O8	6.5	not reported	19	17	analysis-of-variance model

Refr. nr.	Research type (1)	Assessment diagram (2)	Total period (in months)	Instrument(s) recall period	Sample size at start (3)	Sample size at end (3)	Longitudinal statistics
34	quasi.	It1: DstartMI -1m-> O1 -1m-> O2 -4m-> O3 It2: DstartMI&PI -1m-> O1 -1m-> O2 -4m-> O3 Ic: D -6m-> O3	6	previous 2 weeks	162 (It1=45, It2=47, Ic=70)	not reported	repeated measure analyses of covariance (ANCOVA)
35	obs.	O1A -?->O2Di	not reported	current level of functioning	28	not reported	Wilcoxon's signed rank test
36	quasi.	O1startMI-6w->O2endMI -2w->O3	2	not reported	27	20	Wilcoxon matched-pairs, signed ranks test (two-tailed)
37	obs.	O1 -14d-> O2	0.5	not reported	22	18	test-retest reliability: Pearson's R
38	obs.	I: O1 -1w-> O2 -4w-> O3 -4w-> O4	2.25	A: previous week, B: not reported, C: since previous visit(1 to 4 weeks)	52	100 observations of 4 weeks (Istable = 46 obs., Ichanged =54 obs.)	paired t-test, Pearson correlations, within-subject standard deviation of change
39	obs.	phase 1: O1 -2w to 3 m-> O2 phase 2: not longitudinal phase 3: VO1 -?w->VO2	phase 1: 0.5 to 3. phase 3: not reported	not reported	phase 1: 128, phase 3: 40	phase 1: 88, phase 3: not reported	weighted kappas
40	quasi.	MI -1to3m->O1 -3mto11m->O2	6 to 12	not reported	5	5	not reported
41	exp.	It: O1 start SI -12?m->O2 Ic O1 -12?m-> O2	12	not reported	106 (It=52, Ic=54)	not reported	repeated measurement statistic
42	quasi.	startMI -1 to 2 m.-> O1 -1 to 2 m.->O2 -1 to 2 m.-> O3 -1 to 2 m.-> O4)	6	not reported	15	not reported	percentage of children with improvement
43	obs.	O1 -±3m-> A -4.4d-> Di -1y-> O2	18	previous 3 months	468	254	described (in %) by comparing the number of affected domains before admission with that one year after discharge
44	obs.	VO1 -(≤2m)->VO2	2 or less	as they felt 'now'	35	28	test-retest reliability

To be continued at the next page.

(1) obs=observational, quasi= quasi-experimental, exp: experimental; [Decision rule: I: are the subjects randomly assigned to conditions? II: has the experimenter functional control over independent variable(s): I yes+ II yes = exp.; I no+II yes = quasi.; I no+ II no = obs.]

(2) O=observation, D= newly diagnosed, MI=medical intervention, PI=psychological intervention, SI=sociological intervention, V=clinical visit, A=admission to clinic, Di=discharge from clinic, Pla=placebo

(3) I=indexed group, It=indexed treatment, Ic=indexed control, Ip= indexed placebo, R=healthy reference group

Continuation of Table 3

Refr. nr.	Research type (1)	Assessment diagram (2)	Total period (in months)	Instrument(s) recall period	Sample size at start (3)	Sample size at end (3)	Longitudinal statistics
45	obs.	I4-7y: O1 -1w-> O2 R4-7y: O1 -1w-> O2 I8-16y: O1 --3w-> O2 R8-16y: O1 --3w-> O2	4-7y: 0.25 ; 8-16y 0.75	not reported	535 (I4-7y=80 ; R4-7y=103; I8-11y=103; R8-11y=153; I12-16y=98)	not reported	test-retest: Pearson corr., median scores, intraclass correlations
46	quasi.	I: O1 -3m withdrawal of medication-> end medication -4m -> O2 R: O1 -7m -> O2	7	not reported	200 (I=100, R=100)	166 (I=83, R=83)	difference scores
47	quasi.	O1 -2w-> O2 ->startMI -1m->O3 -1m-> O4 -1m-> O5 -1m-> O6 -1m->O7 -1m->O8	6.5	"previous two weeks" or not reported	19	14	repeated measures analysis of variance
48	quasi.	O1 start MI-6m-> O2 -6m-> O3	12	not reported	107	44	Friedman's test
49	exp.	It1: O1 -2w->start MI -12w-> O2 -12w->O3 start Placebo-12w-> O4 -12w->O5 endMI It2: O1 -2w->start Placebo -12w-> O2 -12w->O3 start MI -12w-> O4 -12w->O5endMI	12	not reported	11 (It1=6, It2=5)	not reported	paired t-test
50	obs.	I: O1 -(M=8m,range 1-18m)->MI -3m->O2 R: O1	4 to 21	not reported	28+? (I=28, R=not reported)	28 + ? (I=28, R=not reported)	t-tests and Mann-Whitney U-test
51	obs.	MI -5y-> O1 -5y->O2	120	not reported	120	64	percentages (not tested)
52	quasi.	V-1d-> O1-1w->O2	0.25	not reported	51	51	not reported
53	exp.	It1: O1 MI-3->O2 Pla -3w->O3 MI -3w->O4 Pla-3w-> O5MI -3w->O6 Pla-3w->O7 It2: O1 Pla-3->O2 MI -3w->O3 Pla -3w->O4 MI-3w-> O5 Pla -3w->O6 MI-3w->O7	4.5	not reported	7 (3 versus 4 since randomization table is used)	not reported	binomial test for paired observations

(1) obs=observational, quasi= quasi-experimental, exp: experimental; [Decision rule: I: are the subjects randomly assigned to conditions? II: has the experimenter functional control over independent variable(s): I yes+ II yes = exp.; I no+II yes = quasi.; I no+ II no = obs.]

(2) O=observation, D= newly diagnosed, MI=medical intervention, PI=psychological intervention, SI=sociological intervention, V=clinical visit, A=admission to clinic, Di=discharge from clinic, Pla=placebo

(3) I=indexed group, It=indexed treatment, Ic=indexed control, Ip= indexed placebo, R=healthy reference group