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Original Article

Title: Impact of atopic dermatitis on quality of life in adults: A systematic review and meta-analysis

G Birdi, MSc

R Cooke, PhD

R C Knibb, PhD

Psychology, School of Life and Health Sciences, Aston University, Birmingham, U.K.

Running Head: **Atopic dermatitis and quality of life in adults**

Corresponding Author

Gurkiran Birdi

Psychology, School of Life and Health Sciences, Aston University, Aston Triangle, Birmingham, B4 7ET.

Tel:0121 204 3402. Email: birdigk@aston.ac.uk

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- What is already known about this topic?

Atopic dermatitis (AD) has been found to affect quality of life (QoL) in adults with, studies reporting a greater impact on QoL with increased severity of AD. Adults with AD also report poorer QoL compared to a healthy population and those with other medical skin conditions such as urticaria and psoriasis.

- What does this study add?

This paper provides the first systematic literature review and meta-analysis of the impact of AD on QoL in adults. Across studies, increased disease severity significantly related to poorer QoL. Compared to healthy controls, adults with AD demonstrated significantly lower QoL but findings were mixed in studies that compared QoL in AD to other chronic conditions. Research exploring gender differences in QoL and the use of longitudinal study designs is lacking.

SUMMARY (ABSTRACT)

Background: Atopic dermatitis (AD) can affect quality of life (QoL) of adult patients, in whom the condition can be severe and persistent. There are currently no systematic reviews of the impact of AD on adults.

Objective: This paper provides the first systematic literature review and meta-analysis of the impact of AD on QoL in adults.

Methods: A systematic search was conducted using MEDLINE, Scopus, and Web of Science for articles published until October 2018. Inclusion criteria were a clinical diagnosis of AD, adult patients and QoL as an outcome measure. Interventions were excluded.

Results: A total of 32 studies were included. While QoL was assessed using Dermatology Life Quality Index (DLQI) in 25 studies, there was heterogeneity in the tools used to measure disease severity across studies. Meta-analysis of the seven studies that used the SCORAD to measure disease severity showed severity to be significantly related to poorer QoL. The remaining 18 studies also found increased disease severity significantly related to poorer QoL. When compared to healthy controls, AD patients demonstrated significantly lower QoL but findings were mixed in studies that compared QoL in AD to other skin conditions.

Conclusions: The findings highlight the significant impact that AD has on QoL in adults and the need for validated and relevant QoL measures to be implemented in clinical assessments for AD. Areas that require further research include an exploration of gender differences in QoL and the use of longitudinal study designs to explore factors that may cause differences in QoL ratings.

INTRODUCTION

Atopic dermatitis (AD) is a chronic debilitating inflammatory skin condition which mainly affects children but can also be present in adulthood¹. AD is a significant health issue globally, with prevalence in children of 15-30% and 2-10% in adults². The prevalence of AD in developed countries has increased two-to threefold over the past thirty years³. AD is characterised by symptoms such as itchy, red, dry and inflamed skin. It is a chronic condition in most people, and despite there being no cure for the condition, it can be managed well using emollients, topical corticosteroids and oral treatments such as antihistamines and immunosuppressant tablets. In the UK, 10-20% of all referrals to dermatologists and 30% of dermatology consultations are for AD⁴. A community study conducted in Scotland estimated that 38% of AD cases comprised adults over 16 years old⁵. Thus, although a relatively small percentage patients with AD are adults, studies also indicate a large percentage of adults seek treatment when compared to other age groups with AD.^{5,6}

AD has been shown to have an impact on quality of life in children and adults⁷⁻⁹. Quality of Life (QoL) is defined by the World Health Organization Quality of Life (WHOQoL) Group¹⁰ as an “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” (p. 5). Health related QoL (HRQoL) is considered a valid indicator when monitoring health and service needs of patients¹¹. Measuring HRQoL can help inform interventions to alleviate health conditions and is of potential value in performing risk-benefit analyses of clinical decisions for treatment, especially where systemic therapy with possible side effects is prescribed. A review of the literature by Lifshitz⁷, which focused on the impact of AD on QoL primarily of infants, children, adolescents, and their families, reported that AD had a significant and lasting effect on HRQoL, in particular on psychological wellbeing and social functioning. A review by Lewis-Jones⁸ on QoL and childhood AD confirmed that QoL in children and adolescents was severely impaired with issues such as embarrassment and bullying affecting children psycho-socially and physically.

Relatively little research has been conducted with adults who have AD, but the research that has been conducted suggests that all aspects of HRQoL are affected in adults with AD, and that HRQoL is more compromised in adults with AD when compared to adults with chronic urticaria and psoriasis⁹.

In addition, little is known about how HRQoL of AD patients varies with disease severity; the literature that has investigated this issue has found that greater disease severity is related to poorer HRQoL^{12,13}. To draw together what is currently known in this area and identify gaps in knowledge, the present study reports the results of a systematic review and meta-analysis of the impact of Atopic Dermatitis on QoL in adult patients.

METHODS

Study searches were conducted using three electronic databases: MEDLINE, Scopus and Web of Science Core Collection. Databases were searched up to 24th October 2018 with no limit to the start date. Search terms can be found in the supplementary information. The initial search was conducted by the lead author; all members of the study team reviewed all full papers retrieved for evaluation.

Inclusion/exclusion strategy and data extraction

To be included in this review studies had to report data from adults. The legal age of adulthood differs according to country. This review included participants aged 18 and above or 16 and above if defined as an adult in a study, adolescents were excluded. Studies that combined adult and children data into one analysis were excluded. Studies that collected data from both adults and children, but reported data separately for these sub-groups, were retained in the review. Studies that measured QoL as a result of medical or psychological interventions were excluded. Study search was limited to English-language articles on human populations. Case-reports and conference abstracts were excluded. All study types were included if they reported on a QoL measure.

Outcomes

The primary outcome in this review was QoL in adult patients with AD. QoL was measured either on its own, in relation to disease severity, compared to healthy controls or compared to patients with other conditions, such as psoriasis.

Quality Appraisal

The quality of the included studies was assessed using the Mixed Methods Assessment Tool (MMAT)¹⁴. All members of the study team reviewed and agreed on the quality ratings for each paper.

Data synthesis

Where studies reported QoL scores using the same instruments, results were pooled using meta-analysis. In cases where pooling was not considered appropriate, detailed descriptions of study characteristics and results were reported alongside study quality.

RESULTS

Figure 1 outlines the search strategy following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards¹⁵. A total of 32 papers met inclusion criteria and were included in this systematic review. No mixed methods or qualitative papers included a measure of QoL, therefore all included papers in this review are quantitative and reviewed using narrative synthesis. Seven papers reported a correlation between the Dermatology Life Quality Index (DLQI) and a validated measure of AD severity (SCORAD). Correlations from these papers were pooled using random-effects meta-analysis in Comprehensive Meta-Analysis Version 3 (2005, Biostat Inc.). Table 1 reports study characteristics. Using the MMAT, 24 studies were of higher quality, scoring 75-100% and eight studies were of lower quality, scoring 25-50% (see supplementary Table 1).

Quality of Life

The DLQI was used to measure QoL in 25 out of 32 studies included in this review. Mean overall DLQI scores ranged across studies from 4.9 (small effect on patient's QoL) to 20.5 (very large effect on patient's QoL). In studies which looked at differences across the dimensions of QoL, the areas that were most affected as measured using the DLQI were symptoms and feelings surrounding AD; patients felt embarrassed or self-conscious due to their AD and symptoms such as itchy, sore, painful and stinging skin had a detrimental impact on their QoL¹⁶⁻²¹. Personal relationships were the least affected dimension of QoL^{16,17,19,20}. Mozaffari et al²² found that patients perceived dressing, undressing and bath-time as being most problematic while the dimension 'family activities' was least affected. Holm et al²¹ also found that dressing was particularly problematic. Using the EQ-5D as a measure of QoL, daily activity and pain/discomfort parameters were reported to be most affected in patients²³. Other less frequently used measures included the EQ-VAS, VQ-dermato and Skindex.

Quality of Life and Disease Severity

Twenty studies explored the relationship between disease severity and QoL. Nineteen studies looked at this using DLQI in AD patients (see Table 2). Eighteen of these reported significant correlations between disease severity and DLQI; the more severe the disease, the lower the QoL. In seven of these studies, QoL using the DLQI was compared with disease severity measured using the SCORAD^{12,16,26,27,28,29,30}. These studies were pooled together using random effects meta-analysis (See Figure 2). The sample-weighted average correlation between HRQoL and disease severity was $r_+ = .44$ (CI 0.27; 0.59), indicating a medium-sized relationship³¹, with greater disease severity relating to poorer QoL. There was significant heterogeneity in the results ($\chi^2 = 13.78$, $p < .05$). This could partly be explained by the small correlation reported by Haeck et al¹².

Two studies^{25,32} used the EASI to measure AD severity in relation to QoL. Both studies found statistically significant relationships between QoL and disease severity ($p_s < .05$); QoL was perceived as being poorer with increasing disease severity, with personal relationships being related to a lesser extent to disease severity than other domains. .

Nine studies^{13,17,18,19,22,23,24,34,35} explored relationships between patient-assessed disease severity and DLQI scores and reported statistically significant medium to large sized correlations whereby an increase in disease severity was associated with a decrease in QoL.. Two studies^{37,38} explored gender differences and found a significant positive correlation between patient-assessed disease severity and DLQI score ($p < .001$) and between visible regions and DLQI score ($p = .001$) for women, however neither of these correlations were observed in men.

Two studies^{33,39} assessed severity using the Rajka & Langeland scoring system which measures clinical course, severity, and extent of AD. Both studies found statistically significant correlations between disease severity and QoL. Highest correlations found were between disease severity and symptoms and feelings; higher disease severity was related to worsening symptoms and feelings as a result of AD.

Ten studies used the SF-36 to measure QoL; six of these looked at the relationship between SF-36 scores and disease severity^{17,19,24,25,32,33,40,41}. Five studies found significant correlations between disease severity and the SF-36, with increased severity associated with poorer QoL. However one study²⁵ found no significant correlations between any SF-36 subscales and clinically measured disease severity (EASI). The correlations between the SF-36 and disease severity across the six studies were small to large-sized. The mean physical dimension scores appeared to be less impaired in AD patients compared to the mean mental component scores of the scale^{17,24,32,33,42,43}.

Quality of life in patients with AD compared to healthy controls or other patient groups

A total of 15 studies compared adults with AD QoL to that of healthy controls. Ten studies used generic QoL scales such as the SF-36 to enable comparison across groups^{19,23,24,25,33,35,40,41,43,44}, three studies used dermatology specific QoL scales to make comparisons^{22,26,45} and three studies^{35,37,46} used both generic and dermatology specific scales. Overall QoL was significantly poorer in those with AD compared to healthy controls and, domains such as mental health and social functioning were affected to a greater extent in AD patients^{17,22,29,35}. In a recent study by Misery et al⁴⁶ scores on the mental dimension of the SF-12 were lower in AD patients with visible area involvement compared to those without ($p < 0.001$).

Two studies compared QoL between vitiligo and AD patients^{34,45} and found significantly lower QoL in the AD groups compared to the vitiligo groups ($ps < 0.001$). Four studies compared QoL between psoriasis and AD patients^{9,19,34,41}. Two of these studies found that AD patients had significantly lower QoL than patients with psoriasis^{9,34} whereas Lunderberg et al.¹⁹ found significant differences in the physical and mental functioning domains; with AD patients scored better than patients with psoriasis. Eckert et al⁴¹ found no significant differences in QoL ratings in patients with psoriasis or AD. Grob et al⁹ also compared AD with chronic urticaria and found that AD patients were more affected by skin discomfort than chronic urticaria patients. They also had lower scores in relation to 'treatment induced restrictions' compared to those with chronic urticaria.

DISCUSSION

This systematic review examined the impact of AD on QoL in adults. The DLQI and the SF36 were the most frequently used scales to measure QoL in patients with AD, and studies in this review looked at QoL in relation to disease severity, other chronic skin conditions, or healthy controls. The qualitative synthesis of results and meta-analysis show that there is a consistent relationship between increasing AD severity and poorer QoL in adults, and adult patients with AD have poorer QoL than healthy groups. Findings are more equivocal for comparisons with other chronic skin conditions.

QoL and disease severity

Nineteen of the 20 studies that measured QoL in relation to disease severity found increased disease severity was significantly related to poorer QoL. This finding is consistent with reviews looking at QoL in children with AD^{8,47}. Almost all adult patients had mild to moderate AD in the studies included in this review. Interestingly, in paediatric studies where more patients had moderate to severe AD, QoL correlated less well with disease severity than the adult patients with mild to moderate AD in this review^{48,49}. The consistent finding that disease severity was related to QoL underscores not only the importance of offering both dermatological and psychological treatment to patients, but also the need to incorporate QoL screening tools in dermatology. Nonetheless, AD is a complex condition and QoL cannot solely be explained by severity of the disease as most studies reported low to medium correlations between the two variables. One factor that may influence QoL and may explain differences between studies is time of recruitment whereby patients could be experiencing a flare-up during recruitment, thus affecting QoL scores; this is especially the case if participants were recruited during dermatology visits.

QoL and patients with AD compared to other healthy controls

All studies that compared QoL in AD patients to healthy controls found significantly lower QoL in AD patients. However, four studies used the DLQI measure to explore this difference; the DLQI is a dermatology specific questionnaire with questions that are not suitable for use in a sample of the general population. In such cases, generic QoL measures such as the SF-36 should be employed. When using the SF-36, better physical QoL was reported by studies in this review compared to mental QoL. This is in line with a systematic review carried out looking at QoL in psoriasis patients⁵⁰.

The SF-36 is probably not sensitive enough to measure the physical limitations of AD due to its generic nature; questions relating to walking abilities for example are unlikely to be relevant to this group.

QoL and patients with AD compared to other chronic skin conditions

Studies comparing QoL to other chronic skin conditions had mixed results, but for those comparing vitiligo and AD patients, significantly lower QoL was seen for AD. This may be because vitiligo is not accompanied by symptoms such as itching, inflammation, and sleeplessness. Symptoms such as pruritus have more of an impact on QoL than visual aspects; indeed, this review found that the area of QoL most affected was symptoms surrounding AD. Studies reporting better physical and mental functioning scores in patients with AD compared to those with psoriasis and poorer scores in patients with AD regarding skin discomfort compared to urticaria suggests that pruritus is the dominant factor that interferes with everyday life. Further, the contrast between lower scores related to 'treatment induced restrictions' in patients with AD and better scores in patients with chronic urticaria suggest that topical treatments can be highly restrictive to patients. Indeed, alternative/complementary therapies for AD, such as Chinese herbal therapy have become increasingly popular^{51,52,53}

Demographic characteristics of patients

Many of the participants in the included studies were female. Partly this reflects health care utilization, whereby women use more health services and an estimated 67% of women worldwide make all medical choices in society⁵⁴; in this case, most of the participants were out-patients in dermatology clinics. Only one study looking primarily at gender differences in QoL and AD and found no significant correlation between disease severity and QoL in males but a significant positive correlation was present in females. Thus, the extent to which the AD severity is correlated with QoL in relation to females rather than males deserves further research attention. Lesions located in visible areas have been found to affect women more than men³⁷ possibly because women may have a higher ideal of culturally determined physical appearance than men so more attention is given to the skin. Gender differences have been found in other allergic conditions with females presenting more complex allergy-related conditions compared to males^{55,56} and so further research in relation to AD is needed.

Limitations of the studies in this review

The heterogeneity in tools used to measure disease severity made it impossible to pool results across all included studies. The SCORAD and EASI are generally preferred by researchers over patient-assessed severity or visual analogue scales as they are validated measures of disease severity. However, they do not cover all issues affected in AD patients, for example, SCORAD only measures disease severity over the preceding three days, therefore long-term severity effects on QoL cannot be inferred. Nevertheless, studies that included both patient-assessed severity and objective measures found relatively strong correlations between the two, indicating that patients can self-assess their disease severity accurately.

All studies included in this review used cross-sectional methods to assess QoL in relation to disease severity. Results using this methodology should be interpreted with caution as it's impossible to determine cause and effect. Future studies should utilise prospective designs and collect more longitudinal data to strengthen predictive power of psychological and clinical variables of QoL. AD is generally better during the summer and worse in winter⁵⁸. Only one study specified the season.

Although the quality appraisal for the studies showed that the majority had good to excellent ratings, many suffered from methodological weaknesses, such as the use of small sample sizes, or the use of non-validated measures. Other issues included absence of statistical testing and incomplete presentation of QoL data such as descriptive statistics. In addition, some studies used dermatology specific questionnaires to determine QoL in healthy controls.

Conclusions and directions for future research

This study is the first systematic review and meta-analysis conducted on adults and demonstrates that AD influences all aspects of the lives of adult sufferers. Results support findings from previous research on similar skin conditions^{50,60} and in children^{7,8,47}. The present review points to several areas for future research. In the present review, overall scores were difficult to interpret because of the variability of scores and the absence of formal reference values or norm scores, or the absence of

formal comparisons with population norms. More research with validated psychometric scales is needed to generate a consistent body of knowledge of overall QoL of patients with AD. Furthermore, application of both generic and disease- or dermatology-specific quality-of-life questionnaire which cover the full range of quality-of-life issues are needed.

Second, data on the relationship between specific AD characteristics and QoL suggest that itch, sleep disturbances, and exacerbations in facial and genital body areas³⁴ could be relevant predictors of quality of life, as reported by a few studies in this review,^{13,34,45} A deeper insight into these relationships is important because of consequences for disease-severity measurement in quality-of-life research; indeed, a more qualitative approach would help uncover some of these issues.

Researchers in dermatology are encouraged to utilise validated and clinically relevant QoL measures for patients that provide accurate measurement of quality of life and allow for subsequent comparison of results across studies. Factors such as sleep disturbances and pruritus should be included when determining QoL and future studies should also further explore gender differences in QoL in adults with AD; only a few studies in this review considered these factors. Longitudinal study designs are also needed to explore what factors related to AD cause differences in QoL ratings.

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Table 1. Study characteristics

Authors	Country	N	Participants	Measures used		Outcomes measured	Outcomes measured
				Disease severity	Quality of life		
Arima et al (2018)	Japan	638	Mean age- 38.67 years, 52.37% female. 45.45% rated severity as moderate/severe, 54.54% rated severity as mild. Comparisons with 1268 non-AD controls	Self-rated severity	SF-36	QoL comparisons between patient groups and healthy controls	AD patients reported significantly reduced HRQoL relative to matched non-AD controls ($p < 0.001$) for mental and physical domains of the SF-36.
Baron et al (2006)	UK	63	Mean age – 34 years, Mean duration of AD- 15.2 years, 26 men and 37 women	SCORAD	DLQI	Relationship between disease severity and QoL	The mean DLQI reduced over all three visits from 9.5 to 8.8 at T2 to 7 at T3. The DLQI was significantly correlated with SCORAD at T1 ($r = 0.389$, $p < 0.01$) and at T2 ($r = 0.321$, $p < 0.01$) but not at T3. Mean SCORAD reduced by 52% from T1 to T2 ($F_{2,62} = 37.9$, < 0.001) but there was no significant change in SCORAD from T2 to T3.
Beikert et al (2014)	Germany	384	384 AD patients (mean age 42, range- 18-92, 69.8% female). Patients with AD aged > 18	Patient-assessed severity	DLQI	Relationship between disease severity and QoL; Comparisons between AD patients and patients with other conditions.	The mean DLQI total score in AD was 8.5, compared to 7.0 in Vitiligo and 6.7 in psoriasis and 4.3 in rosacea. Impairment of QoL measured by DLQI correlated positively with the affected body surface area ($r = 0.46$, $p < 0.001$). Characteristic AD symptoms such as skin dryness, pruritus, and sleep disturbances also correlated significantly with the DLQI total score ($r_s = 0.34$ to 0.53 , $p < 0.001$).

Chen et al (2012)	Taiwan	1132	The participants were categorized in to 3 groups: 1) AD (n=90), 2) non-atopic hand eczema (n=205), 3) control group with no aforementioned skin conditions (n=837), average age- 30.5 years, 100% female.	-	SF-36	QoL comparisons between patient groups and healthy controls; Comparisons between AD patients and patients with other conditions.	QoL was significantly lower for patients with AD compared to controls in 5 out of 8 domains including social functioning, bodily pain, vitality, mental health and general health (<i>ps</i> <0.05). No significant difference was found between the AD group and the non-atopic eczema group in all domains of QoL investigated.
Chrostowska-Plak et al (2013)	Poland	89	59 females and 30 males. Mean age- 31.6 years. Mean disease duration- 22.8 years.	SCORAD	DLQI	Relationship between disease severity and QoL.	There was a significant correlation between pruritus and HRQoL ($r = 0.5, p < 0.001$) DLQI also correlated with periods without itching indicating that patients with longer itching-free periods had better HRQoL ($r = 0.23, p < 0.05$) There was a significant correlation between the severity of the disease (using SCORAD) and HRQOL ($r = 0.65, p < 0.001$)
Coghi et al (2007)	Brazil	75	Patients were diagnosed and treated as isolated AD by the attending clinician; 65.33% were females, mean age -26.28 years, average years of duration of AD- 16.74 years.	EASI	DLQI, SF-36	Relationship between disease severity and QoL	QoL and disease control were found to be related but with low scores both in DLQI ($r = 0.26$) and in SF-36 ($r = 0.2$) but with greater correlation for SF-36 mental components. Both correlations were significant ($p < 0.001$).
Eckert et al (2017)	USA	349	Mean age- 46.1 years; 68.3% women; 66.8% White. Matched with 698 non-AD controls.	Self-rated severity	SF-36	QoL comparisons between patient groups and healthy controls; Comparisons between AD patients and patients with other conditions.	AD patients reported significantly reduced HRQoL relative to matched non-AD controls for both mental and physical domains of the SF-36 ($P < 0.001$ & $p = 0.004$ respectively). Compared with psoriasis, AD had a similar impact on HRQoL.

Finlay (1996)	UK	92	43 males and 49 females; average age 33.2 years (range 16-67).	Physician assessed severity	DLQI	Comparisons between AD patients and patients with other conditions.	The mean DLQI index was 18 with subsections relating to 'symptoms and feelings' and 'treatment effects' scoring highest. Disease comparison utility questions demonstrated that patients consider diabetes and hypertension would be better than having eczema whereas bronchitis would be worse than having eczema.
Fivenson et al (2002)	USA	107	Cohort- 298; 107 adults; mean age of whole group- 17.22 years; 62% female.	Rajka & Langeland scoring system, patient-assessed severity	DLQI, SF-36	Relationship between disease severity and QoL, QoL comparisons between patient groups and healthy controls.	46% of adults had mild disease, 11% adults had severe disease. In terms of provider assessed severity, 51% adults had mild disease. The mean DLQI score was 6.6 for adults with a range of 0 to 27. The mean score for DLQI increased with increasing disease severity for all but two questions. For the SF-36, statistically significant differences were detected between the study group and the US population norms for vitality, social functioning, and mental health. Patient-assessed severity had a stronger association with DLQI ($r = 0.57$, $p = 0.0001$) than provider-assessed severity ($r = 0.27$, $p = 0.0036$).
Grob et al (2005)	France	1356	An investigator had to recruit clusters of three patients, one with chronic urticarial (CU), one with psoriasis (PSO) and one with AD, matched by sex and age. Subjective impression of severity was rated by the physicians as minimal/moderate/severe/very severe	Physician assessed severity	VQ-Dermato	Comparisons between AD patients and patients with other conditions.	After adjustment for confounders, HRQoL dimensions were differently affected in the three diseases. The 'physical discomfort' dimension was more degraded in AD and CU than in PSO ($p < 0.001$) and 'leisure activities more in PSO than in CU ($p < 0.001$). No aspect of HRQoL was spared in AD. The mean overall VQ-Dermato index

							was significantly lower in CU (M= 36.93) and in PSO (M= 38.88) than in AD (M= 44.62, p < 0.001).
Haeck et al (2012)	Netherlands	54	Average age of the patients was 37.3. At inclusion, the average objective SCORAD was 43 indicating severe AD, average DLQI was 14.6 indicating a large effect on QoL.	SCORAD,	DLQI	Relationship between disease severity and QoL	At t=0, there was a small non-significant correlation between the DLQI and objective SCORAD, 'rule of nine' or serum TARC level. At t=6 the objective SCORAD, serum TARC and the 'rule of nines' scores showed moderate and significant correlations with the DLQI (r = 0.34, p = 0.02; r = 0.31, p = 0.03; r = 0.49, p < 0.001). An individual's improvement in disease activity (SCORAD, SASSAD and 'rule of nines') with 10 points was associated with an improvement in DLQI.
Higaki et al (2004)	Japan	162	162 patients with AD ranged in age from 17-77 years: the mean age was 29 years; 55% were female. 17 had mild, 107 had moderate and 36 had severe AD.	Rajka & Langeland scoring system (mild, moderate and severe)	Skindex-16	Relationship between disease severity and QoL	Each of the three scale scores (symptoms, emotions and functioning) of the patients with AD were significantly higher than those of patients with isolated lesions. Patients with severe AD showed significantly higher scores in the three scales, as well as the Global Scale than those with moderate dermatitis. There was a significant positive correlation between the severity and each of the three scale scores (r's= 0.32 to 0.45, p < 0.001).
Holm et al (2004)	Denmark	112	Mean duration of AD of 28.6 years. Females (n=88) and males (n=24); mean age of females- 34.2, males- 39.2.	Patient assessed severity.	DLQI	Relationship between disease severity and QoL, Differences in QoL	For women, there was a significant positive correlation between disease severity ad DLQI score (KW test, 15.9; p < 0.001) and also between DLQI score and visible regions affected by disease (KW test, 14.2; p = 0.001);

						between men and women with AD	these correlations were not observed in men. No significant differences between men and women were noted for age, disease duration, overall disease severity or QoL as assessed using the DLQI.
Holm et al (2006)	Denmark	101	101 atopic eczema patients, 66 adults with AD, and 23 adults without AD (control group).	SCORAD, patient-assessed severity	DLQI, SF-36	Relationship between disease severity and QoL, QoL comparisons between patient groups and healthy controls.	Patients with AE had significantly lower QoL ($p < 0.05$) than healthy controls (median DLQI score 5 in AD patients vs. 0 in controls) and the general population. DLQI, pruritus and patient and investigator overall assessment of eczema severity were significantly ($p < 0.0001$) and positively correlated with SCORAD, while the generic questionnaire showed only poor correlation.
Holm et al (2016)	Denmark	191	Mean age- 31.32 years, 59.2% females	SCORAD	DLQI	Relationship between disease severity and QoL	Significant relationship between disease severity and HRQoL ($r = 0.42$, $P < 0.001$), with increase disease severity significantly associated with worsening HRQoL. There was also a significant relationship between DLQI and self-rated health ($r = -0.37$, $p < 0.001$).
Kiebert et al (2002)	USA	239	Mean age- 36 years, 79% female; 18.2 years mean duration of disease, 46% mild severity, 41% moderate severity, 11% severe severity.	Patient assessed severity	DLQI, SF-36	Relationship between disease severity and QoL; QoL comparisons between patient groups and healthy controls.	SF-36 scores showed a significant decrease with increasing disease severity. DLQI scores correlated well with patients ratings of disease severity. The SF-36 scores correlated significantly with DLQI scores. The SF-36 scores of patients with AD were significantly lower (indicative of more impairment) than those of the general population. The mental component score of the SF-36 was significantly correlated with patient severity

							rating ($r=-0.41$, $p<0.001$), the physical component was not.
Kim et al (2012)	Korea	415	Subjects were divided in to three groups; infants, children and adults ((75 males and 72 females). Mean age of adults= 25.8 years.	SCORAD	DLQI	Relationship between disease severity and QoL.	The total mean DLQI score was 10.7. No significant differences in gender and age were observed. Adults with atopic disease including AD with concomitant asthma, allergic rhinitis or allergic conjunctivitis had higher total scores than those with AD alone. Both the Rajka & Langeland eczema severity score ($r=0.261$, $p<0.05$) and SCORAD index correlated significantly with all the total QoL scores ($r=0.432$, $p < 0.001$).
Kong et al (2016)	Korea	50	22 men and 28 women, mean age 26.4 years.	SCORAD	DLQI	Relationship between disease severity and QoL	Significant relationship between disease severity and HRQoL ($r=0.237$, $P<0.001$), with increase disease severity significantly associated with worsening HRQoL. There was also a significant association between sleep disturbance and QoL ($r=0.388$, $p=0.04$), with increase sleep disruption associated with worsening QoL.
Kwak et al (2017)	Korea	157	Mean age- 35.2 years; 51.8% Males; 11,756 non-AD controls (mean age- 45.3 years; 49.3% male)	-	EQVAS	QoL comparisons between patient groups and healthy controls	Adults with AD had lower HRQoL ($p=0.013$) and more stress ($p=0.002$) than those with AD. Even when controlling for demographic characteristics, HRQoL of adults with AD was lower than adults without AD.
Lee et al (2018)	Korea	677	Mean age 36.1 years; 47.8% females; 36,901 controls- mean age 45.4 years, 50.8% females	-	EQ-5D and EQ-VAS	QoL comparisons between patient groups and healthy controls	EQ-VAS scores were significantly higher in patients with AD than in those without AD ($p=0.004$). A higher rate of pain/discomfort, and anxiety/depression was found on

							the EQ-5D in AD patients compared to controls ($p=0.003$ and $p<0.001$, respectively).
Linnet & Jemec (1999)	Denmark	54	23 women (mean age=27.5), 9 men (mean age=30.3); average duration of condition=26.1 years. Aged 18-60 years.	SCORAD	DLQI	Relationship between disease severity and QoL; QoL comparisons between patients groups and healthy controls.	AD patients- significantly lower dermatological life quality ($Z= 5.1$, $p<0.001$) and higher state ($Z= 2.14$, $p<0.032$) and trait ($Z= 3.49$, $p<0.001$) anxiety compared to the control group. Significant positive correlation between SCORAD and DLQI ($r= 0.54$, $p<0.002$).
Lundberg et al (2000)	Sweden	366	The average duration of AD was 25.83 years and the mean age of AD patients was 34.79 years old; 92% were male. The average duration of psoriasis was 18.39 years and the mean age of psoriasis patients was 49.87 years old; 51% were male.	Patient assessed severity	DLQI, SF-36	Relationship between disease severity and QoL; QoL comparisons between patients groups and healthy controls; Comparisons between AD patients and patients with other conditions.	DLQI scores showed poorer HRQoL for patients with AD compared to psoriatic patients but this was not significant when controlling for confounding factors. No significant difference on the SF-36 between patients with AD and patients with psoriasis. There was a decreasing DLQI score for patients of higher ages; improved HRQoL. Spearman's correlation coefficients showed that all SF-36 dimensions were significantly correlated with all measures of disease activity ($r= 0.182$ to 0.526), the DLQI correlations with VAS were also significant ($r=0.005$ to 0.595).
Maksimovic et al (2012)	Serbia	130	Adults- 56.1% female, mean age 34.18 years, mean age of onset of disease - 13.95 years, mean duration of disease- 20.23 years..	EASI	DLQI, SF-36	Relationship between disease severity and QoL, QoL comparisons between patient groups and healthy controls.	The DLQI scores corresponded well with disease severity; increased disease severity was associated with greater impairment in HRQoL ($r=0.14$ to 0.47 for all domains of the DLQI). In adults, significant differences were only found between DLQI scores for mild and severe AD. The highest correlations were seen between

							symptoms and feelings and daily activities ($r = 0.75$, $p < 0.01$), symptoms and feelings and work/school ($r = 0.53$, $p < 0.01$) and leisure and work/school ($r = 0.59$, $p < 0.01$). Patients with AD had inferior social functioning and mental health scores compared with the general population.
Mikolajczyk et al (2017)	Poland	59	36 women and 23 men with AD; aged 18 to 46 years; mean age- 26.9 years; mean disease duration- 15.1 years	-	DLQI	Gender differences in QoL; impact of illness duration on QoL	No significant differences between women and men for DLQI scores ($p > 0.05$); significant correlations between QoL and health evaluation and body areas satisfaction ($r = -0.48$), appearance orientation ($r = 0.31$).
Misery et al (2007)	France	266	34.2% patients were males and 65.8% were females. The mean age was 32.7 years and mean duration was 19.3 years. 1,6% had mild AD, 42.9% had moderate AD, and 55.6% had severe AD.	SCORAD, patient-assessed severity	DLQI, SF-36	QoL comparisons between patient groups and healthy controls.	The mean DLQI score was 8.8 and the physical and mental composite 12 scores were 50.7 and 39.5 respectively. Analyses according to SCORAD showed DLQI scores 6.8 (SD=4.4) and 10.2 (SD=5.6) for moderate and severe AD groups ($p < 0.0001$).
Misery et al (2018)	France	1024	58.3% female; 27.6% mild AD, 40.4% moderate AD, 31.9% severe AD	PO-SCORAD	DLQI; SF-12; EQ-5D	Differences in QoL by visible area involvement	Patients with visible area involvement were found to have lower QoL than those without ($p < 0.0001$), EQ-5D ($p < 0.05$), and the mental score of the SF-12 ($p < 0.0001$). No differences in physical score of SF-12.
Mozaffari et al (2007)	Iran	184	75% AD adults were female, 57.2% control group adults were female. Mean age of AD adults was 38.25 and mean duration of disease was 20.6 years, 9.5%	Patient assessed severity	DLQI	Relationship between disease severity and QoL, QoL comparisons between patient groups and healthy controls.	Significant differences between DLQI mean scores in AD group ($M = 20.5$ SD=4.7) and control group ($M = 1.15$, SD=0.85) mean score ($p < 0.001$). Scores of each question were significantly higher in the AD group than in the control group ($p < 0.001$). Correlation between

			had mild AD, 12% had moderate AD, and 18% had severe AD.				DLQI and AD severity was significantly positive ($r=0.88$, $p < 0.001$).
Noh et al (2013)	Korea	180	27 males (45%), 33 females (55%) with AD, mean age 32.4 years. Mean age of Vitiligo patients was 35.1 (31 males and 29 females), mean age of normal controls was 31.9 (25 males and 35 females).	EASI	DLQI	QoL comparisons between patient groups and healthy controls; Comparisons between AD patients and patients with other conditions.	AD patients- significantly higher scores for all 5 questionnaire items compared with normal controls ($p<0.001$). In the comparison between the AD and Vitiligo groups, AD patients reported lower QoL ($\beta=0.752$, $t=11.522$, $p < 0.001$)
Sanchez-Perez et al (2012)	Spain	323	Adults mean age was 32.3 years and 58.7% were women; over half of adults (55.8%) were aged between 18 and 30 years. Concomitant disease was observed in 40% of adults.	EASI, patient assessed severity	DLQI	Relationship between disease severity and QoL	Significant differences in QoL observed according to investigator assessed severity (mild disease – $M=5.5$, $SD=5.3$; Moderate disease- $M=7.5$, $SD=4.8$; severe disease- $M=12$, $SD=5$; $p < 0.05$). Pruritus caused everyday problems related to sleep and sexual function. The presence and intensity of pruritus was very closely related to HRQoL, with a high correlation coefficient between overall itch severity scale (ISS) score and overall DLQI score (0.72).
Silverberg et al (2018)	USA	602	53.6% female and 71.9% White, with mean age of 52 years. AD severity was measured using self-reported global severity- 53.1% mild, 38.8% moderate, 8.1% severe AD.	POEM, PO-SCORAD	DLQI;SF-12	Relationship between disease severity and QoL; Comparisons between AD patients and patients with other conditions.	SF-12 mental health sub-scores for moderate AD were lower than all other disorders (e.g. diabetes, asthma, anxiety/depression, heart disease) and for severe AD, dramatically lower than all other disorders. Little difference between physical health scores across disorders. Moderate and severe AD (using PO-SCORAD,

							PEOM and global severity) were significantly associated with DLQI (ps<0.0001).
Torrelo et al (2013)	Spain	282	48.2% were male and mean age of the adults was 33.06 years. 79.4% had moderate AD and 19.9% had severe AD. Mean duration of AD for adults was 19 years.	Patient assessed severity	DLQI	Differences between groups for disease severity.	Statistically significant impact on the daily lives of patients receiving maintenance therapy. However patients with moderate AD had higher levels of emotional, physical and social well-being compared to those with severe AD (p < 0.05).
Wittkowski et al (2004)	England	125	23 males, 102 females; aged 18 to 66 (mean age of 37.2 years). The mean duration of AD was 30.7 years.	Patient assessed severity	DLQI	Relationship between disease severity and QoL	Disease severity was significantly correlated with QoL (r = 0.49, p < 0.01), perceptions of stigma (r = -0.28, p < 0.01) and depression (r = 0.18, p < 0.05). 46.7% of the variance in DLQI scores (p<0.001) was explained by depression and disease severity. Disease severity accounted for 23% of the variance in DLQI scores (p < 0.001)

Table 2 Questionnaires used by studies reporting correlations or mean differences across groups for quality of life.

Study	Correlations between AD and disease severity	Differences between groups		
		AD and control group	AD and other skin conditions	Differences in severity within AD groups
Arima, Gupta, Gadkari, Hiragun, Kono, Katayama, & Eckert(2018)		****		
Baron, Morris, Dye, Fielding, & Goulden (2006)	**			**
Beikert, Langenbruch, Radtke, Kornek, Purwins, & Augustin (2014)	***		***	
Chen, Wu, Li, Ko, Yu, & Chen et al, (2012)		***	***	
Chrostowska-Plak, Reich, & Szepietowski (2012)	**			
Coghi, Bortoletto, Sampaio, Junior, & Aoki (2007)	*			*
Eckert, Gupta, Amand, Gadkari., & Mahajan (2016)		****	****	
Finlay (1996)			***	
Fivenson, Arnold, Kaniecki, Cohen, Frech, & Finlay (2002)	***	***		
Grob, Revuz, Ortonne, Auqueir, & Lorette (2005)			****	
Haeck, Berge, Velsen, Bruin-Weller, Bruijnzeel-Koomen, & Knol (2011)	**			
Higaki, Kawamoto, Kamo, Ueda, Arikawa, & Kawashima (2004)	****			****
Holm, Agner, Clausen, & Thomsen, (2016)	**			
Holm, Esmann, & Jemec (2004)	***			***
Holm, Wulf, Stegmann, & Jemec (2006)	***	**		••
Kiebert, Sorensen, Revicki, Fagan, Doyle, Cohen & Fivenson (2002)	***	***		
Kim, Li, Seo, Jo, Yim, Kim, et al (2012)	**			
Kong, Han, Lee, & Son (2016)	**			
Kwak & Kim (2017)		****		
Lee, Lee, Lee, Lee, Lee, & Park. (2018)		****		
Linnet & Jemec (1999)	**	**		
Lundberg, Johannesson, Silverdahl, Hermansson & Lindberg (2000)	***	***	***	
Maksimovic, Jankovic, Marinkovic, Sekulovic, Zivkivic, & Spiric (2012)	*			*
Mikołajczyk, Rzepa, Król, & Żaba, (2017).				***
Misery, Finlay, Martin, Bousetta, Nguyen, Myon, et al (2007)				**
Misery, Seneschal, Ezzedine, Heas, Merhand, Reguai, & Taieb, (2017)				**
Mozaffari, Pourpak, Pourseyed, Farhoodi, Aghasmohammadi, & Movahadi et al (2007)	***	***		
Noh, Kim, Park, Hann, & Oh (2013)		*	*	
Sanchez-Perez, Dauden-Tello, Mora, & Surinyac (2012)	***			***
Silverberg, Gelfand, Margolis, Boguniewicz, Fonacier, Grayson, & Fuxench. (2018)	**		**	
Torrelo, Ortiz, Alomar,Ros, Pedrosa, & Cuervo (2013)				***
Wittkowski, Richards, Griffiths, & Main (2003)	***			***

*NOTE: *- studies measuring DLQI in relation to EASI, **studies measuring DLQI in relation to SCORAD, ***Studies measuring DLQI using another measure of severity or no severity measure, ****studies using other QoL measures.*

CPD questions

1. How prevalent is atopic dermatitis in adults?
 - a) 0.1-1%
 - b) 1-5%
 - c) 5-10%
 - d) 10-20%
 - e) 20-25%

2. How does disease severity relate to quality of life in patients with atopic dermatitis?
 - a) There is no relationship between disease severity and quality of life in patients with atopic dermatitis
 - b) There is a significant positive relationship between disease severity and quality of life such that quality of life gets worse as severity increases in patients with atopic dermatitis
 - c) There is a significant negative relationship between disease severity and quality of life such that quality of life improves as severity increases in patients with atopic dermatitis
 - d) It is unclear from the literature if there is a relationship between disease severity and quality of life in patients with atopic dermatitis
 - e) There is a positive relationship between disease severity and quality of life, but it is not significant

3. What does the DLQI stand for in Dermatology?
 - a) Dermatological Life Quality Index
 - b) Dermatology Life Quality Index
 - c) Dermatology Life Quality Indicator
 - d) Dermatological Life Quality Indicator
 - e) Dermatology Life Quality Indices

4. Why might the Short-form Survey (SF-36) not be useful to use with patients with atopic dermatitis?
 - a) It contains questions that may be too sensitive for patients with atopic dermatitis
 - b) It contains questions that may not be relevant to patients with atopic dermatitis
 - c) It is not a good measure of quality of life
 - d) It is not a validated psychometric scale

e) It takes too long to complete

5. What aspect of quality of life has been found to be most affected in atopic dermatitis patients?

- a) Personal relationships
- b) Symptoms and feelings surrounding atopic dermatitis
- c) Social relationships
- d) Daily activity
- e) Leisure activities

6) Approximately 20% of adults with AD were first diagnosed with the condition after the age of 18:

- a) True
- b) False

7) Atopic dermatitis patients report significantly poorer quality of life compared to those with Vitiligo:

- a) True
- b) False

8) The SF-36 questionnaire is a measure used only for patients with atopic dermatitis:

- a) True
- b) False

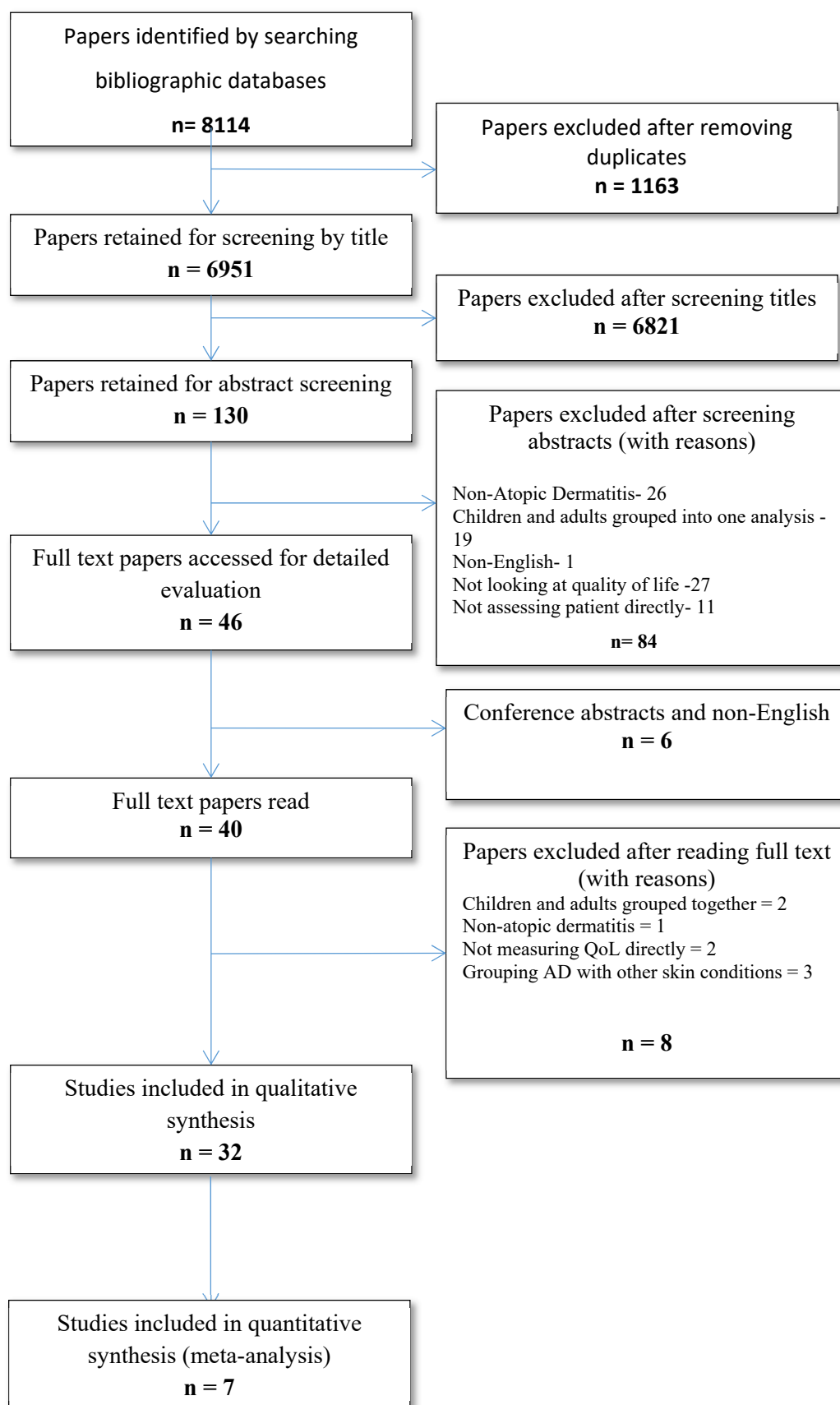
9) when using the SF-36, better physical quality of life was reported in patients compared to mental quality of life:

- a) True
- b) False
- c)

10) Most patients with atopic dermatitis who take part in studies assessing their quality of life are female:

- a) True
- b) False

Fig 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.



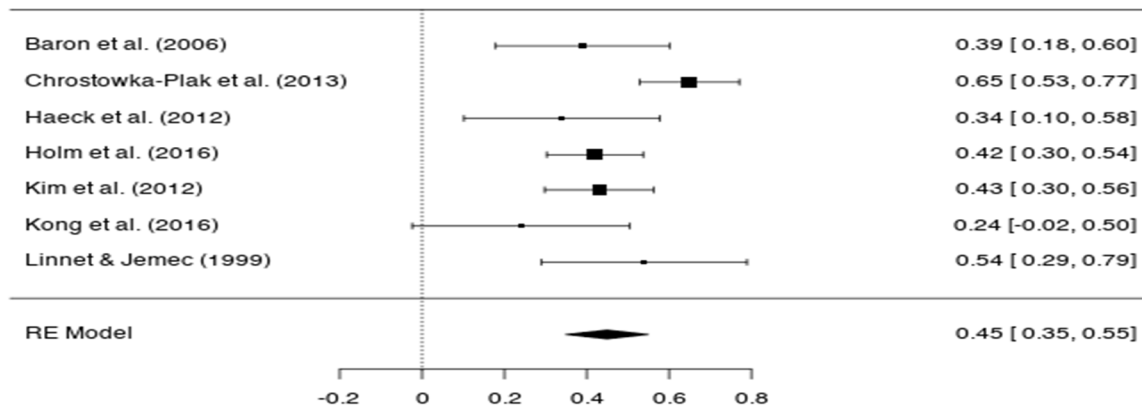


Fig 2: Meta-analysis of studies measuring QoL using DLQI in relation to SCORAD.