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Analysis of Three Outcome Measures in Moderate to Severe Psoriasis –A Registry Based Study of 2.450 Patients

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Conflict of Interest
PsoReg has received financial support from Swedish Board of Health and Welfare, Swedish Association of Local Authorities and Regions, Västerbotten County Council, Pfizer, Abbott, Jansen-Cilag Leo Pharma and MSD. This research has, in addition, received financial support from Pfizer, Abbott, Jansen-Cilag and Leo Pharma. Sponsors had no access to data. Data collection, study design, interpretation, and analysis have been carried out with authors' independence.

Bulleted Statements
What's already known about this topic? Psoriasis has a large impact on health related quality of life (HRQOL). Previous small sample studies have mainly assessed the relationship between clinical outcome and dermatology-specific HRQOL.
What does this study add?
This large sample study analysed the relationship between EQ-5D, DLQI and PASI, which were shown to be complementary as they capture different aspects of the systemic disease moderate to severe psoriasis. The generic preference-based measure EQ-5D was significantly lower among psoriasis patients than the general population.

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ABSTRACT

Background: As psoriasis is a systemic disease with large effects on health related quality of life (HRQOL) generic measures that include overall health, not only skin involvement, are necessary when assessing psoriasis. Furthermore, whereas disease-specific outcome measures are essential in studies assessing efficacy of treatments, generic preference-based measures are needed for resource allocation decisions. The knowledge about the relationship between the generic preference-based EQ-5D and dermatology-specific measures in psoriasis is limited. *Objective:* The objective was to compare the EQ-5D among patients with moderate to severe psoriasis in Swedish clinical practice to population values, and to analyse how EQ-5D related to Dermatology Life Quality Index (DLQI) and Psoriasis Area and Severity Index (PASI). *Methods:* This observational cohort study included 2450 patients registered in PsoReg, the Swedish National Registry for Systemic Treatment of Psoriasis. EQ-5D of psoriasis patients was compared to a defined general population in Sweden, retrieved from a previous study. Relationships between measures were examined with correlation tests and regression analysis. *Results:* Psoriasis patients had a significantly lower EQ-5D compared to the defined general population. EQ-5D correlated strongly with DLQI (-0.55) and weakly with PASI (-0.25) ($p<0.001$). *Conclusions:* When assessing psoriasis treatments and making decisions about treatment guidelines and resource allocation, EQ-5D, DLQI and PASI provide a useful set of complementary tools, answering to different needs. The relationship between DLQI and EQ-5D estimated in this study may be useful for mapping in cost-effectiveness studies that do not include EQ-5D.

INTRODUCTION

Psoriasis has earlier been perceived as a skin disease, but the burden of the disease goes beyond skin involvement. Moderate to severe psoriasis is not only associated with psoriasis arthropathy (PsA) but also cardiovascular disease[1,2] and depression[3,4]. Psoriasis has a major impact on health related quality of life (HRQOL), which is not necessarily in proportion to clinical severity[5-9]. Furthermore, moderate to severe psoriasis is associated with high health care costs and societal costs[10-12].

There are a number of outcome measures available when assessing clinical severity and HRQOL of psoriasis. Patient reported outcome measures of HRQOL have gained acceptance in the management of psoriasis as a complement to clinical assessment. Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI) are the most widely used clinical and HRQOL measures, respectively[13-15]. The dermatology-specific measure DLQI has shown to be a valid measure to assess the HRQOL in psoriasis patients[16-19]. However, the DLQI is insufficient to capture the overall HRQOL in patients with moderate to severe psoriasis.

Disease-specific measures are essential in efficacy studies, demanded by regulatory agencies, in order to ensure efficacy of medical interventions. Generic preference-based measures, such as the EQ-5D, are essential in cost-effectiveness analyses estimating cost per quality-adjusted life year (QALY)[20] demanded by various price and reimbursement agencies. As EQ-5D is the suggested measure by the reimbursement agencies in e.g. Sweden (TLV) and the UK (NICE), it is essential to investigate that the measure captures HRQOL in patients with moderate to severe psoriasis.

In this paper we argue that the generic EQ-5D, the dermatology-specific DLQI and the clinical outcome measure PASI, are complementary as they have different scopes of use. EQ-5D is important in moderate to severe psoriasis since it is a systemic disease which affects overall health and which is not only limited to skin. The relationship between measures is clinically important to investigate, as it may have implications for resource allocation.

The objective of this observational cohort study was twofold: Firstly, the objective was to analyse EQ-5D, DLQI and PASI in patients with moderate to severe psoriasis in Swedish clinical practice by demographic characteristics, and to compare EQ-5D scores to the Swedish general population. Secondly, the objective was to analyse how the EQ-5D related to DLQI and PASI.

MATERIALS AND METHODS

Study Patients

This observational study was based on PsoReg, the National Registry for Systemic Treatment of Psoriasis in Sweden[21,22]. 2450 patients at local, regional and university hospitals as well as private praxis and treatment centres driven by the patient organisation PSO were registered when data were retrieved in June 2010. Observations at the time of enrolment for each patient, which occurred between April 2006 and June 2010, were used. The inclusion criteria to PsoReg were that the patient was diagnosed with psoriasis and using systemic treatment, or about to start systemic treatment, at time of registration.

Outcome Measures and Variables

The EQ-5D is a generic preference-based HRQOL measure, based on five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression[23]. Respondents

report (1) no problems (2) some or moderate problems (3) extreme problems, which results in 243 possible health profiles. The measure is preference-based as health profiles are associated with utility weights. Utility, derived from patients in a particular health condition or general population sample, is estimated by asking people to theoretically give up or risk something of value (e.g. money, time, lifetime) in order to avoid a particular health state. The weights range from zero to one, where one equals perfect health and zero equals death. Generic preference-based measures are appropriate when comparing costs and benefits across medical conditions to make resource allocation decisions as they reflect the social preferences of a population.

DLQI is a non-preference-based, dermatology-specific, HRQOL measure that relates to how the skin disease has affected patients' lives over the previous week[24]. The DLQI questionnaire includes 10 questions. Each question is scored on a 4-point scale: Not at all/Not relevant (0), A little (1), A lot (2) and Very much (3), which results in a score ranging from 0 (best health state) to 30 (worst health state).

The clinical outcome measure PASI includes the severity of the three main signs of psoriasis (redness, scaliness and thickness) weighted by the coverage of the affected body part (legs, body, arms and head). PASI results in a score ranging from 0-72, where a higher score is more severe disease[25].

The demographic variables gender and age were included.

Analysis and Statistical Methods

The first objective was to analyse EQ-5D, PASI and DLQI by gender and age, and by comparing the EQ-5D to a defined general population, matched on gender and age. The non-

parametric Mann-Whitney U test was used to test for differences in the distribution of EQ-5D, DLQI and PASI by gender and age in the PsoReg data.

Estimates of EQ-5D in the defined general population were retrieved from a study conducted in Stockholm county, Sweden in 2001[26]. The study included 3069 respondents (Men N=1389; Women N=1680). In accordance with this study, the UK population-based utility weights[27] were used and negative values were truncated to zero[26]. The same age categories were used. The most appropriate method to examine the mean difference between the sample and of the defined general population was the one sample t-test, as mean values were reported in the study. A two-sided significance level of $p<0.05$ was applied.

The second objective, to analyse how the EQ-5D related to DLQI and PASI, was carried out by 1) analysing the relationship between the total EQ-5D and DLQI and PASI scores by the means of correlation tests and simple regression analyses 2) analysing how EQ-5D related to the DLQI questions, controlling for gender and age using multiple regression analysis, and 3) analysing how the single EQ-5D dimensions correlate with the single DLQI questions.

Data was non-normally distributed and Spearman's correlation test for the analysis of measures, EQ-5D dimensions and DLQI questions was used. Correlations were categorized in accordance with Cohen: strong correlation was absolute value of Spearman's rho >0.5, moderate correlation ranged between 0.30–0.49, and weak correlation ranged between 0.10–0.29[28]. This categorization has previously been used when assessing measures of disease severity in PsA[29]. The scatterplot was weighted by frequency where EQ-5D was rounded down to one decimal. Non-linear relationships were also estimated by including the coefficients $DLQI^2$ and $PASI^2$ in Equations 1 and 2, respectively.

$$EQ\text{-}5D = f(DLQI) \quad \text{(Equation 1)}$$

$$EQ\text{-}5D = f(PASI) \quad \text{(Equation 2)}$$

The multiple linear regression method [30] allowed analysing the impact of certain DLQI questions controlling demographic factors and remaining questions. Responses to DLQI questions are ordered categorical and were included in the regression as dummy variables. "Man" and no impact on health, "Not at all"/ "Not relevant", was used as reference categories. Stepwise regression and backward elimination was used and insignificant variables were treated as reference categories. The primary estimated model was reduced to include only variables significant at the 10 percent level. The final model was compared to the primary model using an F-test.

$$EQ\text{-}5D = f(age, gender, DLQI\ (Q1), DLQI\ (Q2), \ldots, DLQI\ (Q10)) \quad \text{(Equation 3)}$$

Statistical analysis was performed using Stata Statistical Software: Release 11.1. College Station, Texas, USA.

Ethical Concerns

This research was done in adherence to the Declaration of Helsinki guidelines and has been approved by the Umeå Ethical Review Board, Sweden. The project was conducted with informed consent from patients.

RESULTS

PsoReg patients had significantly lower EQ-5D scores then the defined general population for both men and women and for all age groups, but 80-88 year olds (n=32). PsoReg patients had an EQ-5D mean of 0.76 and the defined general population had an EQ-5D mean of 0.84. The greatest difference was found in the youngest age category, where the defined general population and the PsoReg population had average EQ-5D scores of 0.89 and 0.75, respectively. In the defined general population the EQ-5D decreased with age (Fig. 1). There were no evident age group difference in EQ-5D within the psoriasis population (p=0.136). Older age groups had significantly higher HRQOL in DLQI and less severe psoriasis in PASI, than younger age groups. The youngest age group, 20-29 years old, had a DLQI median of 6 and PASI median of 5.75, while the oldest age group, 80-89 year olds, had a DLQI median of 2 and PASI median of 3 ($p<0.001$).

In accordance with the defined general population, women in PsoReg reported significantly lower EQ-5D averages than men, median value 0.67 and 0.80, respectively ($p<0.001$). Women also reported significantly lower HRQOL in DLQI; median value 4 compared to 5 for men (p=0.003). However, men had significantly more severe psoriasis in PASI. Median PASI was 5.4 for men and 3.7 for women ($p<0.001$).

In PsoReg 27.4 percent of respondents reported full health by the EQ-5D (no reported problem in any dimension), compared to 45.6 percent in the defined general population.

Most problems, for the defined general population and PsoReg patients alike, were reported in the dimension pain/discomfort (44 percent compared to 63 percent reported any problem, respectively). The second most reported dimension with problems was anxiety/ depression, in

both populations (29 percent and 43 percent respectively). Least problems were reported in the self-care dimension (2 percent and 7 percent respectively).

EQ-5D and DLQI were strongly correlated by Spearman according to Cohen's categorization of correlations (Fig. 2). The correlation was negative as a high score on EQ-5D indicates high HRQOL, whereas a high score of DLQI indicates a low HRQOL. The correlation between EQ-5D and DLQI was stronger with higher levels of clinical severity of skin in PASI.

The simple linear regression with EQ-5D as a function of the total DLQI score was estimated (Equation 1, Fig. 3). Hence, an one point increase in DLQI is expected to result in 0.02 fall of EQ-5D. The adjusted R-squared suggested that DLQI alone explained approximately 28 percent of the variation in EQ-5D. The model was applied on different levels of severity (PASI<10 and PASI ≥10), but the relationship only changed slightly (EQ-5D=0.8780-0.0196 DLQI and EQ-5D =0.8746-0.0194 DLQI, respectively). The non-linear relationship including the coefficient $DLQI^2$ ($p=0.019$) was significant, but it only improved the model marginally (Adjusted R-squared 0.2795).

EQ-5D and PASI showed a weak correlation whereas DLQI and PASI showed a strong correlation (Fig. 2). All correlations were significant ($p<0.001$). The linear relationship between EQ-5D and PASI is EQ-5D=0.8170-0.0089PASI (Equation 2) ($p<0.001$). The adjusted R-squared of 0.06 suggests that PASI explained the variation in EQ-5D to a small extent. A non-linear relationship including $PASI^2$ was not significant ($p=0.388$).

The multiple linear regression (Equation 3) showed how the total EQ-5D score related to different DLQI questions, controlling for gender and age. The third response level "very

much" was the most frequently significant response level in all questions. The questions about how itchy, sore, painful or stinging skin had been (Q1) and whether skin interfered with going shopping or looking after home or garden (Q3) had the highest impact on EQ-5D. These responses had a predicted fall in EQ-5D of approximately 0.2 compared to a patient that reported full health in DLQI, all else equal. Questions relating to embarrassment (Q2), social activities (Q5), problems at work or studying (Q7), sexual difficulties (Q9) and treatment (Q10) also had significant relationships with EQ-5D. Gender and age were significant ($p=0.033$ and $p<0.001$). The adjusted R-square suggested that DLQI questions, gender and age explained about 32 percent of the EQ-5D variation. The primary model, including all DLQI questions and levels, did not significantly improve the model ($p=0.394$).

On average, over all DLQI questions, 60 percent of respondents reported "Not at all", 22 percent "A little", 10 percent "A lot" and 7 percent "Very much". However, in how itchy, sore, painful or stinging the skin has been (Q1), only 24 percent reported "Not at all", while 79 percent reported that the disease did not interfere at all with going shopping or looking after home or garden (Q3).

Although total EQ-5D score correlated strongly with total DLQI, the different questions correlated only moderately as questions captures detailed aspects rather than over-all health. Moderate correlations were found in the three dimensions "Usual activities", "Pain/Discomfort" and "Anxiety depression" in EQ-5D. "Usual activities" correlated strongest with whether the skin interfered with going shopping or looking after home or garden (Q3). "Pain/Discomfort" correlated strongest with how itchy, sore, painful or stinging the skin had been (Q1). "Anxiety depression" correlated strongest with embarrassment and self-consciousness (Q2). Correlations in EQ-5D dimensions "Mobility" and "Self-care" were

weak. As most patients (74 percent and 94 percent, respectively) did not report any problems at all in these dimensions, there was a lack of variance.

DISCUSSION

This study shows that patients with moderate to severe psoriasis had significantly lower HRQOL, measured by EQ-5D, compared to the defined general population. EQ-5D by psoriasis patients and the general population tend to converge with age. The result was consistent with the findings that elderly in the general population tend to have lower HRQOL and that patients in our study population have less severe psoriasis in DLQI and PASI with increasing age. In accordance with the general population, women reported lower HRQOL, whereas men had higher PASI scores.

As expected, EQ-5D had a weak relationship to PASI, which assess the clinical impact of skin involvement. In accordance with our results, previous findings show weak or moderate correlations between PASI and DLQI[8,31].

The strength of this study, based on the Swedish national registry, is the large sample of unselected patients with moderate to severe psoriasis in everyday clinical practice[21,22]. To our knowledge, only one other study based on a limited sample (n=35) has compared EQ-5D among psoriasis patients to the general population[32]. The EQ-5D is still uncommon in psoriasis studies[14]. Previous studies including generic measures of psoriasis have used Short Form 36[14,33,34] which is not a preference-based measure, and hence not as useful in cost-effectiveness analysis of alternative treatment options.

The result showed a strong correlation between EQ-5D and DLQI, which indicate that both measures assessed HRQOL, nevertheless, capturing different perspectives. These measures are not unnecessary duplications. The dermatology-specific DLQI includes important clinical aspects of HRQOL centred on the skin, and may therefore be more sensitive to differences. EQ-5D captures the over-all HRQOL including the impact of psoriasis which is not limited to the skin, such as co-morbidities and depression. We found two small sample studies by Shikiar[18] (n=147) and Hjortsberg[35] (n=273) that assessed the correlation between EQ-5D and DLQI. They found correlations of a similar magnitude.

The relationship between EQ-5D and DLQI is clinically important to scrutinize, as it may be used for "mapping" in order to estimate utility in cost-effectiveness analysis when no preference-based generic measure has been included in a study. This method is, despite its limitations, increasingly used. Mapping is dependent on the degree of overlap between measures. Our large sample allowed for a detailed analysis of the EQ-5D dimensions and DLQI questions. The result showed that EQ-5D and DLQI overlap in the total measures as well as in the detailed questions reflecting e.g. pain and daily activities.

For obvious reasons, mapping is not applicable in conditions where generic measures are not sensitive. In mild forms of skin disease there may be a ceiling effect in EQ-5D. Our results have shown that EQ-5D is significantly lower in our patient group of patients with moderate to severe disease, than in the general population.

The simplest model for mapping is to regress the generic preference-based measure onto the total score of the disease-specific measure in a simple regression model. Woolacott and colleagues used mapping between DLQI and EQ-5D, based on a limited sample of 86

psoriasis patients at a single acute hospital, as EQ-5D were missing[36]. That result differed slightly from our estimates; the intercept was higher and each DLQI score was associated with a slightly larger change in EQ-5D. Patient characteristics were not reported in detail in Woolacott's study and the difference may be related to population differences. In this study, we also estimated the EQ-5D relationship to DLQI depending on PASI severity; the result was similar for PASI<10 and PASI ≥10.

A limitation of this study was that only patients with moderate to severe psoriasis who received systemic treatments were included. The definition of "moderate to severe" psoriasis is thus based on physicians' over all judgments about whether patients were to receive systemic treatments. Patients not currently on systemic treatment were consequently not included in this analysis. In clinical trials severity is often defined by PASI and/or DLQI above certain values measured before systemic treatment is initiated. Patients in our study population were often using systemic treatment when measures were assessed, which may result in higher HRQOL values and lower clinical skin severity than in comparable studies.

There is no perfect measure when assessing the burden of disease in patients with moderate to severe psoriasis. We argue that the solution is not to search for new measures that can capture all aspects of disease, but rather to use existing measures, which are widely used across countries and over time. The measures EQ-5D, DLQI and PASI are good complements, used for different purposes. PASI and DLQI are useful for regulatory agencies when evaluating efficacy as well as for clinicians individualizing treatments and providing optimal care for patients. Complementary, the EQ-5D is useful for policy makers in order to ensure that patient utility corresponds to expenses of treatments. The best option is always to include EQ-5D in the study population of interest. Mapping is an option when patient characteristics are

similar in the population under investigation as the populations from which the mapping was derived. Furthermore, we argue that EQ-5D, which has shown to be significantly lower in our study population compared to the general population, is useful in the systemic disease moderate to severe psoriasis as it captures more than the skin's influence on HRQOL.

The introduction of biologic agents to patients with severe psoriasis is a challenge for the dermatologic community, and new tools are needed to face this situation. The EQ-5D is applicable in two central questions when evaluating biologics: the overall improvement of the patients' health and the allocation of resources by policy makers.

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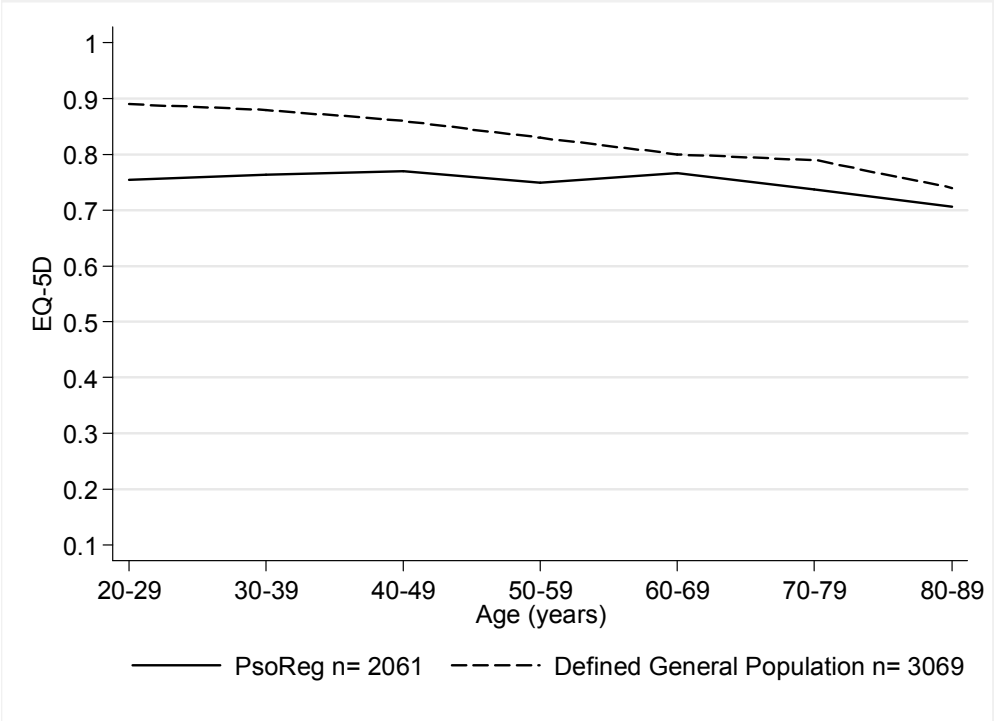
Table 1. Patient Characteristics

		n
Men, %	60.4	
Women, %	39.6	
Age, median (IQR)	54 (42-64)	
Plaque Psoriasis %	84.8	
Psoriasis Arthropathy %	28.6	
PASI, median (IQR)	4.7 (2.2-9.4)	2213
DLQI, median (IQR)	4 (1-9)	2190
EQ-5D, median (IQR)	0.80 (0.691-1)	2104
		N= 2450

Fig. 1 EQ-5D mean in PsoReg Population and Defined General Population by age groups



Differences between the PsoReg population and the defined general population was significant for all age groups (p< 0.001) but the 80-88 age group (p =0.4955).

Fig.2 Correlations (Spearman's rho) between EQ-5D, DLQI and PASI

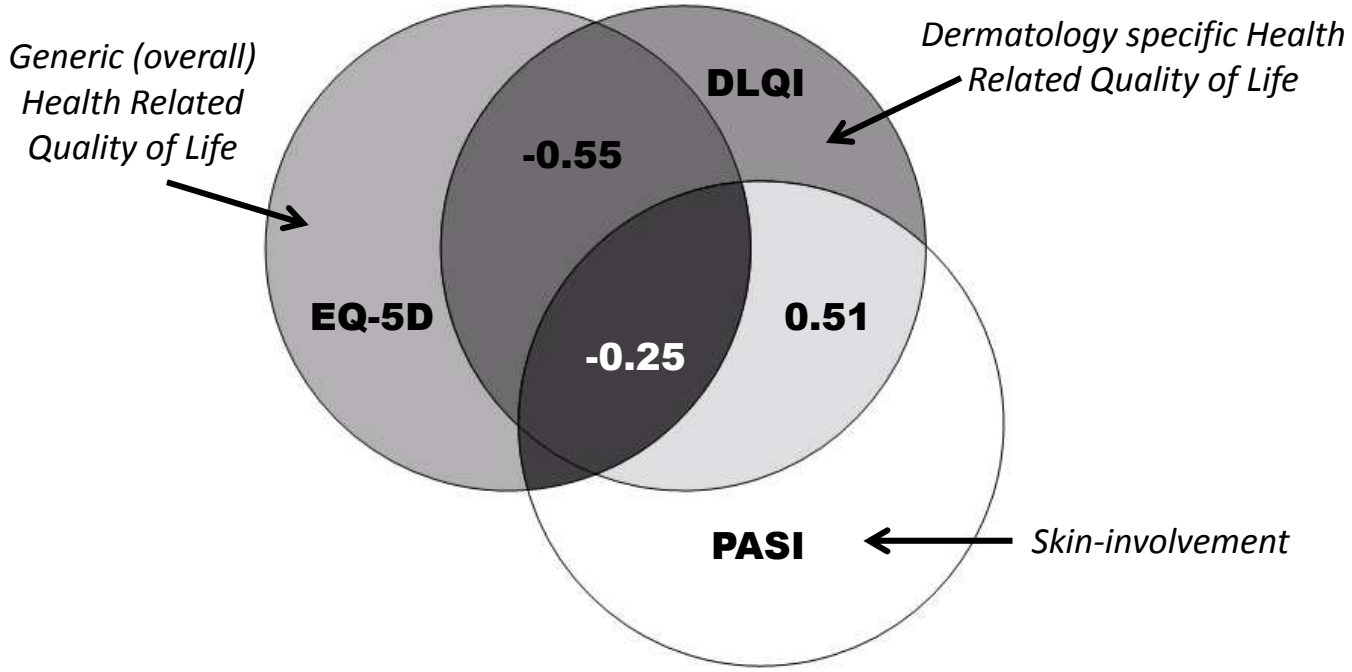
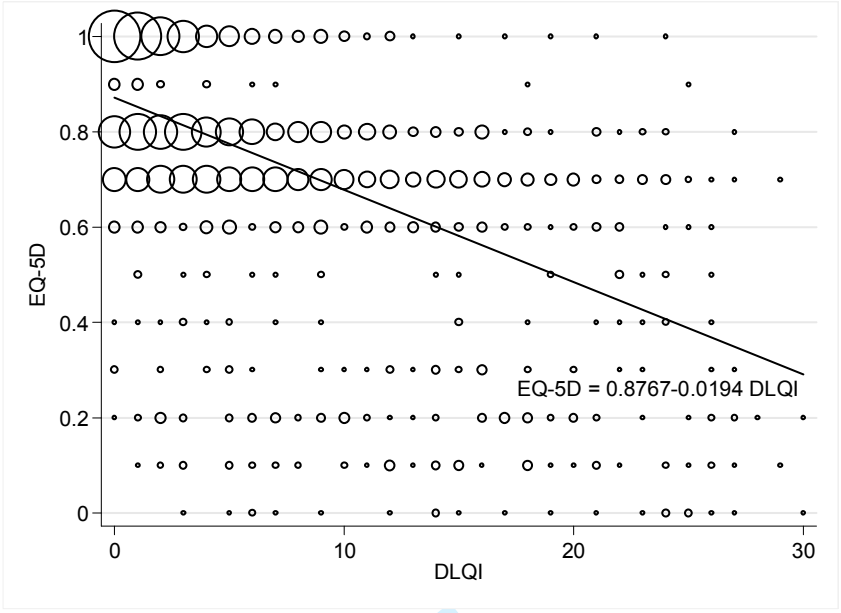


Fig. 3 Scatterplot and linear relationship between EQ-5D and DLQI



Number of observations: 2091 Adjusted R-squared: 0.2779 Root Mean Square Error: 0.1971
Prob > F= 0.0000

Supplementary file: Summary Statistics of EQ-5D, DLQI, PASI over Gender and Age

	EQ-5D			**DLQI**			**PASI**		
	Median	**IQR**	**n**	**Median**	**IQR**	**n**	Median	IQR	n
Gender									
Men	0.796	0.725-1	1275	4	1-8	1317	5.4	2.6-10.5	1343
Women	0.76	0.656-0.848	829	5	1-11	873	3.7	1.8-8	870
P-value	*<0.0001*			*<0.0033*			*<0.0001*		
Age									
20-29	0.804	0.725-1	120	6	2-14	126	5.75	2.85-12.1	128
30-39	0.796	0.725-1	275	5	2-14	285	6	2.8-10.5	287
40-49	0.796	0.725-1	416	4	1-9	428	5.7	2.6-10.2	447
50-59	0.796	0.691-1	482	4	1-10	500	4.8	2.2-9.85	508
60-69	0.796	0.691-1	526	3	1-7	553	3.75	1.8-8	552
70-79	0.727	0.656-0.848	210	3	1-7	220	3.6	1.8-8.1	211
80-88	0.726	0.62-1	32	2	1-7	35	3	1.2-11.1	35
P-value	*0.1361*			*0.0001*			*0.0001*		
Total									
	0.796	**0.691-1**	**2104**	**4**	**1-9**	**2190**	**4.7**	**2.2-9.4**	**2213**

IQR= Inter Quartile Range

Supplementary file: Linear Regression of EQ-5D and DLQI questions, Gender and Age

Number of obs	= 2063	F (16, 2046)	= 62.16	Adjusted R-squared	= 0.3218
		Prob > F	= 0.0000	Root Mean Square Error	= 0.1909

EQ-5D	Coefficient	P >t
Gender		
Man (reference)		
Woman	-0.019	0.033
Age[1)]	-0.001	0.000
Over the last week, how itchy, sore, painful or stinging has your skin been? (Q1)		
Not at all (reference)		
A little	-0.066	0.000
A lot	-0.112	0.000
Very much	-0.167	0.000
Over the last week, how embarrassed or self-conscious have you been because of your skin? (Q2)		
Not at all or a little (reference)		
A lot	-0.054	0.000
Very much	-0.078	0.000
Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden? (Q3)		
Not at all (reference)		
A little	-0.090	0.000
A lot	-0.122	0.000
Very much	-0.172	0.000
Over the last week, how much has your skin affected any social or leisure activities? (Q5)		
Not at all, A lot or Very much (reference)		
A little	-0.027	0.013
Over the last week, has your skin prevented you from working or studying? (Q7)		
No (reference)		
Yes	-0.091	0.000
Over the last week, how much has your skin caused any sexual difficulties? (Q9)		
Not at all, A little or A lot (reference)		
Very much	-0.109	0.000
Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time? (Q10)		
Not at all (reference)		
A little	-0.033	0.001
A lot	-0.037	0.012
Very much	-0.085	0.000
Constant	0.971	0.000

[1)] The coefficient of age (continuous variable) measures the marginal effect on the EQ-5D of being one year older. A 60-years old person would then have 0.01 lower EQ-5D compared to a 50 years old person, all else equal.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	18
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	18
		(b) Indicate number of participants with missing data for each variable of interest	18
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5 Supp. File. Table of Sum. Stat.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.