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## Lymphedema and Health-Related Quality of Life

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# Lymphedema and Health-Related Quality of Life



# Lymphedema and Health-Related Quality of Life

Pia Klernäs



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DOCTORAL DISSERTATION

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<p>Abstract: The overall aim of this thesis was to develop a lymphedema-specific instrument for measuring health-related quality of life (HRQoL) and to evaluate how persons with lymphedema experience HRQoL. Lymphedema is defined as swelling in one or more parts of the body that is due to impaired lymph drainage and transport. The impairments in the lymph system can be congenital or secondary to, e.g., cancer treatment. The fact that lymphedema is often chronic emphasizes the importance to measure HRQoL. To this purpose the Lymphedema Quality of Life Inventory (LyQLI) was developed and psychometrically tested in two studies [Papers I and II presented here]. Further, the LyQLI was used to evaluate HRQoL in a cross-sectional study [Paper III] and a longitudinal study of two different interventions [Paper IV]. Methods: In Study I, 126 patients with lymphedema in the limbs and/or genital, breast, or head and neck regions participated by twice completing the LyQLI, to assess the validity and reliability of the instrument. In Study II, 68 patients with upper (ULL) or lower limb lymphedema (LLL) participated in a trial to examine the responsiveness and sensitivity of the LyQLI. The standardized response means (SRM) was used to evaluate responsiveness, and box plots were applied for sensitivity. In Study III, Spearman's correlation coefficient, Kruskal-Wallis test, and Mann-Whitney U-test were performed to compare different lymphedema subgroups. The Wilcoxon signed-rank tests was applied to compare the lymphedema population to the general Swedish population using the 35-item Short-Form Health Survey (SF-36). In Study IV, changes in HRQoL after two different interventions, conservative treatment with a rehabilitation program (RP) and surgical treatment with liposuction (LS), were evaluated. The RP was conducted in one site in Sweden, and LS was performed in three different countries, Australia, Scotland, and Sweden. In total, 75 persons with lymphedema completed the LyQLI before the interventions and after 1, 3, 6, and 12 months. Results: In Paper I, the results of the reliability tests show that the intraclass correlation coefficient (ICC) was moderate, and Cronbach's alpha was moderate to high. The concurrent validity was considered moderate. Also the results of the SRM and box plot calculations [Paper II] were considered moderate. Paper III, shows that the majority of the participants experienced low impact of the lymphedema on HRQoL, although 20% reported high impact. The study's results also show that some subgroups, e.g., younger persons, persons with LLL, and persons working part-time experienced high impact on HRQoL. Further, the results show that the lymphedema population rated lower HRQoL than the general Swedish population. In Paper IV, results show that 45% of participants in the LS sample experienced high impact on HRQoL at baseline. Both interventions improved the participants' HRQoL. In the LS sample, the improvement continued to increase until the end of the study, 12 months after surgery.</p> <p>Conclusions: The LyQLI is a reliable and valid HRQoL instrument suitable for use in the clinic or in cross-sectional studies including patients with lymphedema, irrespective of which part of the body is affected. Responsiveness and sensitivity were tested in patients with LLL or ULL consequently, the LyQLI can be used in longitudinal studies in patients with lymphedema in the limbs. Altogether 20% of the persons with lymphedema had high impact of the disease on HRQoL, but in some subgroups the impact was even higher and it is important that these individuals be identified. For this purpose, the LyQLI may be an important instrument, which can also be used to identify patients' lymphedema-related problems and concerns, and determine the kind of support they need.</p>		
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# Lymphedema and Health-Related Quality of Life

Pia Klernäs



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*Till Magnus, utan dig hade det bara blivit en tumme.*

*"Det är skönare lyss till en sträng, som brast, än att aldrig  
spänna en båge" - Verner von Heidenstam*



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# List of publications

- I. Klernäs P, Johnsson A, Horstmann V, Kristjanson L. J, Johansson K. Lymphedema Quality of Life Inventory (LyQLI) – development and investigation of validity and reliability. *Quality of Life Research* 2015. 24(2), 427-439. doi:10.1007/s11136-014-0783-8  
  
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- II. Klernäs P, Johnsson A, Boyages J, Brorson H, Munnoch A, Johansson K. Test of responsiveness and sensitivity of the questionnaire “Lymphedema Quality of Life Inventory (LyQLI)”. *Lymphedema Research and Biology*. Accepted in Oct. 8th 2017
  
- III. Klernäs P, Johnsson A, Horstmann V, Johansson K. Health-related quality of life in patients with lymphoedema - a cross-sectional study. *Scandinavian Journal of Caring Science* 2017. doi:10.1111/scs.12488.
  
- IV. Klernäs P, Johnsson A, Boyages J, Brorson H, Munnoch A, Johansson K. Experiences of HRQoL in Patients with Lymphedema Using Two Different Interventions with 1–Year Follow-Up. In manuscript.



# Abstract

The overall aim of this thesis was to develop a lymphedema-specific instrument for measuring health-related quality of life (HRQoL) and to evaluate how persons with lymphedema experience HRQoL. Lymphedema is defined as swelling in one or more parts of the body that is due to impaired lymph drainage and transport. The impairments in the lymph system can be congenital or secondary to, e.g., cancer treatment. The fact that lymphedema is often chronic emphasizes the importance to measure HRQoL. To this purpose the Lymphedema Quality of Life Inventory (LyQLI) was developed and psychometrically tested in two studies [Papers I and II presented here]. Further, the LyQLI was used to evaluate HRQoL in a cross-sectional study [Paper III] and a longitudinal study of two different interventions [Paper IV].

**Methods:** In Study I, 126 patients with lymphedema in the limbs and/or genital, breast, or head and neck regions participated by twice completing the LyQLI, to assess the validity and reliability of the instrument. In Study II, 68 patients with upper (ULL) or lower limb lymphedema (LLL) participated in a trial to examine the responsiveness and sensitivity of the LyQLI. The standardized response means (SRM) was used to evaluate responsiveness, and box plots were applied for sensitivity. In Study III, Spearman's correlation coefficient, Kruskal-Wallis test, and Mann-Whitney U-test were performed to compare different lymphedema subgroups. The Wilcoxon signed-rank tests was applied to compare the lymphedema population to the general Swedish population using the 36-item Short-Form Health Survey (SF-36). In Study IV, changes in HRQoL after two different interventions, conservative treatment with a rehabilitation program (RP) and surgical treatment with liposuction (LS), were evaluated. The RP was conducted in one site in Sweden, and LS was performed in three different countries, Australia, Scotland, and Sweden. In total, 75 persons with lymphedema completed the LyQLI before the interventions and after 1, 3, 6, and 12 months.

**Results:** In Paper I, the results of the reliability tests show that the intraclass correlation coefficient (ICC) was moderate, and Cronbach's alpha was moderate to high. The concurrent validity was considered moderate. Also the results of the SRM and box plot calculations [Paper II] were considered moderate. Paper III, shows that the majority of the participants experienced low impact of the lymphedema on HRQoL, although 20% reported high impact. The study's results also show that

some subgroups, e.g., younger persons, persons with LLL, and persons working part-time experienced high impact on HRQoL. Further, the results show that the lymphedema population rated lower HRQoL than the general Swedish population. In Paper IV, results show that 45% of participants in the LS sample experienced high impact on HRQoL at baseline. Both interventions improved the participants' HRQoL. In the LS sample, the improvement continued to increase until the end of the study, 12 months after surgery.

Conclusions: The LyQLI is a reliable and valid HRQoL instrument suitable for use in the clinic or in cross-sectional studies including patients with lymphedema, irrespective of which part of the body is affected. Responsiveness and sensitivity were tested in patients with LLL or ULL; consequently, the LyQLI can be used in longitudinal studies in patients with lymphedema in the limbs. Altogether 20% of the persons with lymphedema had high impact of the disease on HRQoL, but in some subgroups the impact was even higher and it is important that these individuals be identified. For this purpose, the LyQLI may be an important instrument, which can also be used to identify patients' lymphedema-related problems and concerns, and determine the kind of support they need.

# Populärvetenskaplig sammanfattning

## *Lymfödem och Hälsorelaterad livskvalitet*

Lymfödem är en svullnad som kan uppkomma i olika delar av kroppen. Svullnaden uppstår på grund av att lymfvätska inte hinner dräneras bort i tillräcklig takt, utan blir kvar i vävnaden. Orsaken kan vara en medfödd genetisk svaghet i lymfsystemet alternativt en skada på lymfsystemet orsakat av operation, infektion, inflammation eller annan kroppsskada. Vanligast i Sverige är lymfödem i arm eller ben, som uppstått efter cancerbehandling. När man behandlar cancer opererar man ofta bort inte bara tumören, utan också närliggande lymfkörtlar. Lymfkörtlarna fyller en viktig funktion i lymfsystemet, både för att lymfvätska tas upp via dem, men också för att de innehåller vita blodkroppar och de är en viktig del i kroppens immunförsvar.

Lymfödemet kan medföra fysiska, psykiska, sociala och/eller praktiska problem. Många upplever tyngd och spänningskänsla, minskad rörlighet eller styrka i den svullna kroppsdel. Risken för att få infektioner i kroppsdel ökar också, som exempelvis rosfeber (erysipelas) vilket behöver behandlas med antibiotika för att inte utvecklas till blodförgiftning (sepsis). Många personer upplever att livskvaliteten har försämrats sedan de fått lymfödem. Det huvudsakliga syftet med denna avhandling är att utveckla ett instrument för att mäta hälsorelaterad livskvalitet hos personer med lymfödem.

I de första två studierna i avhandlingen vidareutvecklas och testas en enkät: ”Frågeformulär om hur lymfödemet påverkar din livskvalitet, Lymphedema Quality of Life Inventory (LyQLI)”. Enkäten innehåller 45 frågor, varav 41 är indelade i tre domäner: fysisk, psykosocial och praktisk. Den sista delen av enkäten innehåller fyra frågor som handlar om hur de senaste fyra veckorna har varit i förhållande till lymfödemet, samt om hur personen upplevt sin generella livskvalitet under samma period.

För att man ska kunna använda resultaten från en enkätundersökning är det viktigt att enkäten är testad och uppfyller kraven på god validitet, reliabilitet, responsivitet och sensitivitet. I studie I ingår 126 patienter och där undersöks om enkäten mäter det som den är tänkt att mäta (validitet) och om den gör detta på ett säkert sätt (reliabilitet). I studie II ingår 68 patienter och där undersöks enkätens förmåga att



mäta en förändring av livskvalitet över tid (responsivitet) samt enkätens känslighet för att kunna skilja olika patientgrupper från varandra (sensitivitet).

Resultaten från studie I visar att enkäten är tillräckligt valid och reliabel för att kunna användas i studier på personer med lymfödem oavsett i vilken kroppsdel ödemet sitter. Resultaten från studie II visar att den är tillräckligt responsiv och sensitiv för att användas i behandlingsstudier med uppföljning (longitudinella studier) på personer med lymfödem i armar eller ben.

Studie III är en tvärsnittsstudie där de personer som deltog i studien skattade sin hälsorelaterade livskvalitet i förhållande till lymfödemet. Resultaten av den analysen visar att majoriteten av deltagarna inte upplevde så stor påverkan på sin livskvalitet, men att 20 % av dem gjorde det. I en annan analys jämförs sedan de olika subgrupperna med varandra och då framkommer det att yngre personer, personer med lymfödem i benen och/eller i underlivet, samt personer med lymfödem som arbetade deltid, var de som hade störst negativ påverkan på sin livskvalitet.

I studie IV ingick patienter med lymfödem i arm eller ben och i denna studie jämfördes livskvalitet före och efter två olika behandlingsinsatser. Den ena patientgruppen hade stora fettomvandlade lymfödem (57 personer) vilka behandlades med kirurgi (fettsugning). I denna grupp hade 45 % stor negativ påverkan på sin livskvalitet före behandlingen. Den andra gruppen (18 personer) hade något mindre och inte så fettomvandlade lymfödem och deltagarna i denna grupp fick konservativ behandling i 2-3 veckor. I denna grupp hade 21 % stor negativ påverkan på sin livskvalitet före behandlingen. Den konservativa behandlingen bestod av manuellt lymfdränage (massage) och bandagering av den svullna kroppsdel, samt träning och information om lymfsystemet och om egenvård. Resultaten från denna studie visar att båda grupperna förbättrade sin livskvalitet efter respektive behandling. Förbättringen fanns inom såväl fysisk, psykosocial som praktisk domän. Förbättringen höll i sig upp till ett år i den fysiska domänen för de som fick konservativ behandling och i alla tre domäner för de som blev behandlade med fettugning. I den sistnämnda gruppen fortsatte dessutom personernas hälsorelaterade livskvalitet att förbättras, i alla domäner, i upp till ett år.

Sammanfattningsvis visar resultaten av studie III och IV att de flesta deltagarna hade relativt liten påverkan av lymfödemet på livskvaliteten. Men resultaten visar också att i vissa subgrupper var den negativa påverkan på livskvaliteten stor och därför är det viktigt att hälso- och sjukvården uppmärksammar detta. LyQLI har visat sig vara ett användbart instrument för att hitta dessa personer och hjälpa dem att förbättra sin hälsorelaterade livskvalitet.

# Thesis at a glance

Paper	Aims	Methods	Results
I	To develop a shortened HRQoL PROM for patients with lymphedema. To test the new PROM for validity and reliability.	Multicenter study. The PROM was shortened by lymphedema experts using factor analysis. Test-retest reliability was evaluated using the intraclass correlation coefficient (ICC). Cronbach's alpha was used to estimate internal consistency in each of the three domains. Spearman's rank correlation coefficient was used to assess the correlation between the LyQLI and the SF-36.	The 45-item LyQLI was shortened to three domains, the physical, psychosocial, and practical. 126 patients completed the LyQLI twice and the SF-36 once. In the physical and psychosocial domains, the ICC was 0.88 and in the practical 0.87. Cronbach's alpha was 0.88, 0.92, and 0.88 for the three domains, respectively. The correlations between the LyQLI and the SF-36 was low to moderate. The LyQLI was found to be reliable and valid.
II	To test the LyQLI for responsiveness and sensitivity in two different interventions the rehabilitation program (RP) and liposuction (LS).	Multicenter study. The standardized response means (SRM) and Pearson's correlation coefficient were used to test for responsiveness. Box plots were applied for sensitivity including the RP-, LS- and reference lymphedema population (Paper III).	18 patients in RP and 50 patients in LS completed the LyQLI before and 1 month after intervention. The SRM in the RP was >0.80, in psychosocial domain, <0.80 in physical, and <0.5 in the practical. In the LS sample the SRM was >0.80 in psychosocial and practical domains and <0.80 in physical. Box plots showed differences between the three samples. The LyQLI was found to be responsive and sensitive.
III	To evaluate how lymphedema impacts patients' HRQoL and to compare the impact of HRQoL in patient groups with different kinds of lymphedema. The second aim was to compare HRQoL in the whole sample to the general Swedish population, using the SF-36. The third aim was to evaluate the influence of the cancer disease, using FACT-G.	Cross-sectional, multicenter study. For analysis Spearman's correlation coefficient, Kruskal-Wallis test, Mann-Whitney U-test, and Wilcoxon signed-rank test were performed. All patients had to complete the LyQLI and SF-36 once and those with a cancer diagnosis also completed the FACT-G.	129 patients completed the LyQLI and SF-36, and 79 completed the FACT-G. The majority reported low impact of lymphedema on HRQoL, but 20% reported their HRQoL to be strongly impacted by the disease. Patients with LLL, younger patients and patients who worked part-time were most affected. Compared to the general Swedish population lymphedema patients estimated lower HRQoL. The FACT-G scores were equal to other studies.
IV	To evaluate HRQoL in lymphedema patients after two different interventions, RP and LS, at the 1, 3, 6 and 12-month follow-up.	Longitudinal, multicenter study. The last and next imputation and last-observation-carried-forward (LOCF) imputations were used. To detect and analyze differences in LyQLI responses in the three domains, from baseline to the 12-month follow-up, the Wilcoxon signed-rank test was used.	18 patients in the RP and 57 in the LS sample answered the LyQLI before and 1, 3, 6, and 12 months after the intervention. The patients in both samples experienced higher HRQoL after the intervention and the results persisted up to 1 year for the RP sample in the physical domain, and for the LS sample in all three domains.



# Abbreviations

CCT	controlled compression therapy
CDT	complex (or complete) decongestive therapy
CL sample	common lymphedema sample
COSMIN	COnsensus-based Standards for the selection of health status Measurement INstruments
EORTC	European Organization for Research and Treatment of Cancer
EORTC QoQ-C30	EORTC quality of life core questionnaire
FACT-G	Functional Assessment of Cancer Therapy Scale-General
HADS	Hospital Anxiety Depression Scale
HREC	Human Research Ethics Committee
HRQoL	health-related quality of life
ICC	intraclass correlation coefficient
ICF	International Classification of Functioning, Disability and Health
LLL	lower limb lymphedema
LOCF	last observation carried forward
LQOLI	Lymphoedema Quality of Life Inventory (the Australian questionnaire)
LS	liposuction
LSIDS-H&NI	Lymphedema Symptom Intensity and Distress Survey-Head and Neck
Lymph-ICF	Lymphedema functioning, disability and health questionnaire focusing on ULL

Lymph-ICF-LL	Lymphedema functioning, disability and health questionnaire focusing on LLL
LYMQOL	Lymphedema quality of life
LyQLI	Lymphedema Quality of Life Inventory
MCS	mental health, component summery
NHP	Nottingham Health Profile Part 1 and 2
NHP-1	Nottingham Health Profile Part 1
PCS	physical health, component summery
PRO	patient-reported outcome
PROM	patient-reported outcome measure
RL population	reference lymphedema population
ROC curve	receiver operating characteristic curve
RP	rehabilitation program
SD	standard deviation
SF-36	36-item Short-Form Health Survey
SLQOLI	Swedish Lymphedema Quality of Life Inventory
SRM	standardized response means
ULL	upper limb lymphedema
ULL-27	Upper Limb Lymphedema 27 questionnaire
US	ultra sound
VAS	visual analog scale
WHO	World Health Organization

# Definitions

Concurrent validity	is the agreement with a previous value. Since no previous established value is available for the HRQoL questionnaire, other well-established questionnaires are often used (1).
Content validity	refers to whether the items in an instrument are sensible and comprehensive enough to reflect the domains of interest (1).
Criterion validity	measures whether a scale has empirical association with external criteria, such as other established instruments. Criterion validity can be divided into concurrent and predictive validity (1).
Cross-cultural validity	involves the process of translation into another language and adaption to another culture (2).
External responsiveness	refers to the extent to which changes in a measure agree with changes in a reference measure of clinical or health status (3).
Face validity	addresses whether an instrument does what it is intended to in a clear way, when looking at it “on the face of it” (1).
Internal reliability	or “internal consistency,” is based on item to item correlations in multi-item scales, and is often measured with Cronbach’s alpha (1).
Internal responsiveness	is the ability of a questionnaire to measure changes over a pre-specified time frame (3).
Reliability	has to do with determining whether a questionnaire generates replicable and consistent results (1).
Responsiveness	is the ability of a scale to detect changes (1).
Sensitivity	is the ability to detect differences between groups (1).

Test–retest reliability

or “repeatability,” refers to the agreement between results obtained at two repeated measurements taken over a certain time frame. With a stable condition, the respondent is supposed to deliver the same answer at both times (1).

Validity

is the capacity of an instrument to measure what it is intended to measure (1).

# Introduction

## The lymphatic system

The lymphatic system consists of the tonsils, adenoids, spleen, thymus, lymph vessels and lymph-nods and has three major functions (4). One is to maintain the fluid balance in the body, by transporting filtrated lymph fluid containing plasma proteins collected through the lymph capillaries, from the tissues back to the blood circulation. Another is related to nutritional function and fat absorption from the digestive system. A third important function is immune surveillance (4). The lymphatic vessels are generally parallel to the veins and arteries in the circulation system, and the lymph collectors have a contracting function which helps collect the fluid and move it along. The vessels are connected to lymph nodes, where about 50% of lymph is filtered. Lymph fluid consists primarily of protein, water, fatty acids, salts, inorganic material, microorganisms, and immune cells and is transported from the interstitial space to lymph collectors, through larger collecting lymph vessels, to the lymph nodes, and eventually into the venous circulation (4, 5). Together with the cardiovascular system the lymphatic system is responsible for maintaining tissue (and plasma) volume homeostasis (4, 6-8).





Primary lymphedema with skin problems such as papillomas, cysts and hyperkeratosis. © Imke Wallenius

## Lymphedema

The lymphatic system may fail if the microvascular filtration rate is high, the lymph flow is low, or if there is a combination of the two over a sufficient period (4). The impaired lymph drainage and/or lymph fluid transport capacity results in swelling, defined as lymphedema, of one or more parts of the body (6, 8). The accumulation of lymph fluid in the interstitial space may not be clinically evident in the early stages of the disease, but the patients may experience a tension, tightness, or heaviness in the swollen part (6). As the impaired drainage continues, a soft edema, called “pitting edema” occurs (6). If the edema is not treated adequately the edema increases and intradermal fibrosis develops, which reduces elasticity in the tissue. Skin infections such as erysipelas and cellulitis become more common while the volume of the edema increases, and the impaired lymphatic function predisposes to infections due to the reduced ability of the immune system to respond to bacteria (4). If the disease increases further, the severity of the fibrotic reaction, tissue volume, and other skin problems such as papilloma, cysts, fistulas, and hyperkeratosis may occur. This last stage of lymphedema is known as “lymphostatic elephantiasis” (5, 6, 8).



**Primary lymphedema in a teenaged girl. © Imke Wallenius**

### *Primary lymphedema*

Lymphedema can be classified as *primary* or *secondary*. Primary lymphedema is caused by genetic mutations that damage lymphatic vascular development. This may in turn lead to structural and/or functional abnormality, which impairs lymph drainage (4). The etiology of primary lymphedema has until recently been relatively

unknown. Previously patients were classified according to e.g., age of onset, and the condition was categorized as congenital lymphedema (occurring before 2 years of age), lymphedema praecox (occurring during the adolescence or early adulthood), and lymphedema tarda (over 35 years old) (9). Now that research has identified causal mutations and the role of these genes in lymphedema, these categories are rarely used. To classify the disease according to age of onset may be misleading. Still, much more research is needed to diagnose, and also to find ways to cure, lymphedema (4, 10). One problem for persons with primary lymphedema is that the time from symptom onset to diagnosis is often long, 14 years on average, compared to 2 years for persons with secondary lymphedema (see below) (11).

The prevalence of primary lymphedema, including all forms of genetically determined lymphedema, has been estimated to range from 1/6,000 to 1/10,000 live births (12). Lymphedema in children is rare and almost all are classified as primary, with an estimated prevalence of 1.15/100,000 persons up to 20 years old (6). Usually one or two limbs are affected. Many other parts of the body can also be affected, for instance the trunk or visceral organs, such as the heart, lungs, or intestines. About 14% of individuals with primary lymphedema have a family history of lymphedema (6).



**Secondary lymphedema after breast cancer treatment. Scrotum edema with the patient wearing a compression garment. © Imke Wallenius**

### *Secondary lymphedema*

Secondary lymphedema is much more frequent than primary lymphedema. It is the result of an obstruction or disturbance of the lymphatic system, with a resulting mechanical insufficiency, which can lead to accumulation of fluid in the interstitial tissues (4, 13). Not infrequently the underlying cause for secondary lymphedema can be a congenital susceptibility (11). The obstruction or disturbance can occur as a consequence of inflammations or infections such as filariasis or erysipelas, surgery, radiation therapy, trauma, malignancy, or burns (4, 13).

The most common cause of secondary lymphedema worldwide is an obstruction of the lymphatic drainage due to filarial infection. Endemic lymphatic filariasis is a major mosquito-borne tropical disease with enormous health implications (6, 14). In 2000, over 120 million people were affected, with about 40 million suffering from disfiguring and disabling lymphedema (15). The incidence of other non-cancer-related lymphedema is hard to estimate. In the United Kingdom the incidence has been estimated at 80,000, but with more knowledge about the disease this number will probably increase (16, 17).

In the Western society, the most common cause for lymphedema is cancer treatment (9). The exact incidence rate of cancer treatment-related lymphedema is difficult to accurately assess due to a lack of standardized definitions and measuring techniques for the disorder (5, 18). The reported incidence of upper limb lymphedema (ULL) after breast cancer treatment varies widely, ranging from 0% to 63% depending on the therapy and whether a combination of surgery and radiation therapy is performed and, further, whether, axillary lymph node dissection is performed. The reported incidence also varies depending on the population studied, measurement criteria used, and the reported length of follow-up (5, 13). However, in Sweden, the increased risk of developing ULL is estimated to be 40% when the treatment includes axillary dissection and post-surgery radiation therapy to the breast and axilla. It has been estimated that 4,000–6,000 women have ULL after breast cancer treatment, with 800 new cases a year (19).

Secondary lymphedema can also be a consequence of treatment for other cancer diseases, e.g., melanoma, cancer in the head and neck region, and gynecological and genitourinary malignancies (13). Lower limb lymphedema (LLL) can occur with or without genital lymphedema with varying incidence. The reported incidence of LLL after gynecological cancer varies between 7% and 78% depending on whether lymph node dissection and/or radiation therapy is performed. The highest incidence of genital lymphedema has been reported to occur with radiation therapy alone (18). After treatment of prostate cancer, the reported incidence differs from 25% to 66%. The lower incidence occurs in patients undergoing a limited, or diagnostic dissection, followed by pelvic irradiation. However, if the patient has a complete dissection followed by irradiation, the risk for developing lymphedema increases to 66% (5). After melanoma, the reported incidence of lymphedema ranges from 1.7% to 53%, depending on the type and degree of lymph node dissection performed. With sentinel lymph node biopsy the incidence has been reported to 1.7%, rising to 53% after axillary lymph node dissection with additional axillary radiation therapy (5). The incidence of lymphedema after treatment for cancer in the head and neck region is hard to estimate. In a study examining prevalence of late-effect lymphedema in 81 patients with head and neck cancer, 75.3% (61/81) had lymphedema. Of those, 9.8% had external lymphedema, 39.4% had internal lymphedema, and 50.8% had both types (20).

Among patients who develop lymphedema after cancer treatment, it is estimated that 80% will develop lymphedema in the first 2 years after surgery. Main risk factors are, as mentioned above, extensive node surgery combined with radiation therapy. Other factors that can increase the risk of developing lymphedema are infections, post-operative wounds, and obesity (5, 21).



Secondary lymphedema. © Imke Wallenius

## **Impairments from lymphedema**

Lymphedema can result in several complications, such as poor skin condition which can lead to lymphangitis, erysipelas, and cellulitis, and massive edema which can impair limb function and create limb heaviness and tension, pain, disfiguring, and psychosocial disability (5, 6, 9, 16, 22). If the lymphedema is internal in the head/neck region, problems with swallowing and speaking can occur. If it is external in the head/neck region, the face can be disfigured, with a swelling of the eyelids or lips, etc. (23). Several qualitative studies have been performed to examine the impairments lymphedema may cause (22, 24, 25). Bogan et al. (22) performed a qualitative interview study in seven patients with non-cancer-related LLL and found that the lymphedema had led to psychosocial problems, e.g., depression and poor self-image, which could end in social isolation. They also reported practical problems in performing activities of daily living, such as bathing, dressing, self-care, and walking. More than half of the patients in their study had difficulties in

continuing to work (22). In a qualitative study using creative writing performed by Ridner et al. (24), 39 women with ULL expressed that they felt marginalized and diminished and they also reported great loss. The physical body change made them feel ugly and fat, thus impacting their body image. They also felt a loss in body function which resulted in difficulties exercising and doing practical things at home and at work (24). In their qualitative study of breast cancer survivors with ULL, Johansson et al. (25) noted, that the women had difficulties to relate to attitudes in their surroundings and to the fact that the disease is chronic. The authors concluded the importance of examining practical, emotional, and psychosocial problems experienced in daily life, which could be related to the lymphedema (25).

## **Lymphedema treatments**

Lymphedema is a chronic condition which requires lifelong treatment. The overall purpose of lymphedema treatment is to decrease the excess volume of the lymphedema (12). Excess volume is defined as the volume in the affected limb minus the volume in the unaffected limb, measured in ml (8). In a 10-year follow-up in women with ULL after breast cancer treatment, it was concluded that the best way to keep the excess volume low was early diagnosis and treatment (19).

When the excess volume had increased, the action to reduce it and once it is reduced to keep it down, often requires a great amount of self-care (12, 26). Self-care usually includes daily use of compression garments, self-massage, skin care, lymph transport-promoting exercises and activities, and sometimes home treatment with intermittent pneumatic compression (12, 26). In the 20th century, exercise was thought to increase lymphedema, but several studies including women with ULL secondary to cancer treatment have confirmed that exercise can increase strength without increasing the excess volume (27-30). On the other hand, these studies did not notice any decrease in lymphedema volume. Exercise as a method to actually reduce excess volume has been discussed. In a study of patients with LLL who performed water exercise for 5 days, Gianesini et al. found a significant reduction in volume in both legs (31). Similar results have been reported by Fukushima et al. (32). Lindquist et al. (33) found that women with ULL can significantly reduce the lymphedema in the affected arm through a water exercise program. Still more research is needed to find effective exercise methods to reduce excess volume (31, 33).

When doing self-care is not enough, further therapy, such as the complex (or complete) decongestive therapy (CDT), can be performed over the short term at an indoor clinic to enhance the reduction (5, 22, 34-36). Usually this comprises manual lymphatic drainage, fitting with non-elastic bandages and/or compression garments, skin care and exercises to enhance lymphatic pumping, but may also include other

components to enhance lymphatic flow (5, 22, 34-36). Since peripheral tissue lipid transport and homeostasis may be disturbed by decreased lymphatic drainage, increased fat deposition may occur in lymphedema due to chronic inflammation (37, 38). The deposition of fat starts already when lymphedema develops (38). As a consequence conservative treatments may fail to reduce the excess volume and surgical treatments like liposuction (LS) can be performed (39, 40).



**Liposuction of arm lymphedema. The procedure takes about 2 hours. From preoperative to postoperative state (left to right). © Håkan Brorson**

This surgical method was introduced by Professor Håkan Brorson, a Swedish plastic surgeon, in 1987. The LS should be followed by controlled compression therapy (CCT) and thereafter lifelong use of compression garments is required (41). Liposuction of lymphedema is a surgical method that works in all stages of lymphedema (40).

Other surgical methods have been performed to increase lymphatic drainage in lymphedema patients, but the effectiveness of these need to be improved (42). However, in early edemas reconstructive surgery with lymphatic microsurgery can be sufficient (12). In China, Yang et al. (43) performed a study in which ten women with ULL underwent surgery with lymphatic transverse rectus abdominis

myocutaneous/deep inferior epigastric perforator (TRAM/DIEP) flaps. After surgery, all participants reported a significant improvement in the affected limb. However, only one had an objectively significant reduction in excess volume (43). Pharmacological treatments to reduce excess volume have also been evaluated in different studies though with conflicting results, and no recommendations can be given so far (12).

The fact that lymphedema is mostly chronic highlights that lymphedema treatment should aim to more than reduce excess volume. Treatments for lymphedema should include treatments to optimize well-being and health-related quality of life (HRQoL) as well as volume reduction (44, 45).

## Health, quality of life and health-related quality of life

The concepts of health, quality of life and HRQoL can be used to explore the problems that patients with lymphedema face. The World Health Organization (WHO) in 1948 defined “health” as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity“(46).

Lindstrom (47) said in 1992 that the health concept was too closely connected with disease, and argued the need to develop a new concept that would contain positive values. He suggested that quality of life should serve as a possible framework for this approach, and formed a new definition which he thought should emphasize quality of life as a global concept, a concept that embraces the whole existence: ”Quality of life is the total existence of an individual, a group or a society.“(47). In 1993, the WHO (48) based on Lindstrom’s definition recommend a definition of quality of life linked to health: “the perception by individuals 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” (48).

In a report from WHO in 2003 (46), “quality of life” should highlight the role of perception, i.e., how a person evaluates cognitive and emotional health-related information, which is not the same as only self-reported symptoms, problems, behaviors, or functions. In this thesis, I embrace the concept of HRQoL as a concept in which it is possible to distinguish between a person’s “quality of life” in its more general meaning compared to the person’s “quality of life” related to health and sickness (1).



Other researchers who have studied HRQoL are Fayers and Machin (1) and their definition of HRQoL is not specific or concrete; rather, it is more inclusive:

It is generally agreed that the relevant aspects may vary from study to study, but can include general health, physical functioning, physical symptoms and toxicity, emotional functioning, cognitive functioning, role functioning, social well-being and functioning, sexual functioning, and existential issues (page 5). (1)

The ability to measure HRQoL is an important issue particularly in chronic disease, since the goals of medical care are not only for the patient to be cured, but also him or her to have an active life and to maintain good functioning and well-being (45).

### **International Classification of Functioning, Disability and Health**

To develop a worldwide health dictionary to be used in clinical research and health projects, the WHO in 2001 published a document titled, “International Classification of Functioning, Disability and Health (ICF)” (49). The ICF is a classification of health and health-related domains intended to be a framework for measuring health and disability at both the individual and the population levels (49).

Since the ICF is implemented in at least 190 countries and is used worldwide, it would be of interest to use the patient-reported outcome measures (PROMs) in addition to the ICF to compare results between different countries and cultures (50). The ICF includes more than 1,400 categories which makes it problematic to use in the clinic and in clinical trials consequently, ICF core sets for different kinds of diseases and chronic conditions have been developed (51). Recently two core sets to be used in lymphedema patients had been developed in the Netherlands by Viehoff et al. (51). They developed one comprehensive and one brief core set, both including categories for persons with LLL and ULL and for persons with lymphedema in other parts of the body, such as breast, head, neck, genitals, and trunk (midline) (51).

### **Patient-reported outcomes measures**

Measuring generic health and HRQoL and being able to compare different populations with different diseases has during the last 50 years become more and more important, both nationally and internationally (45). As mentioned above the most significant aspect of measuring HRQoL is the person’s individual experience of a symptom or concern. This kind of outcomes, where the person’s own opinion is required, is called “patient-reported outcome (PRO),” (1, 52) defined as “any

report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" (1).

To be able to collect the person's own opinion, some kind of tool is needed. A tool for reporting a person's PRO is called a "patient-reported outcome measure (PROM)." In other words, the way to measure HRQoL would be by using a PROM (52). A PROM needs to be multi-item and multi-dimensional and it can be either generic, domain-specific or disease-specific. To evaluate how symptoms of a specific disease impact a person's HRQoL, it needs to be disease-specific (1).

### **Psychometric testing of patient-reported outcome measures**

When using a PROM to evaluate HRQoL in, e.g., a clinical trial or when performing a cross-sectional study to describe a population, the PROM must have the necessary psychometric properties. The PROM needs to be valid and reliable, responsive and sensitive, so it can measure what it intends to (1). In 2011, an international study from Delphi developed a standard called the "CONsensus-based Standards for the selection of health status Measurement INSTRUMENTS (COSMIN)"-checklist to be used when developing PROMs or selecting PROMs for use in research or in the clinic (2, 53). The checklist contains twelve boxes. Ten boxes can be used to assess whether a study meets the standard for good methodological quality. Nine of these boxes contain standards for the included measurement properties and it is proposed that these properties should be tested on a new PROM (2).

When developing a disease-specific PROM, content validity is often the first property to address, i.e., ensuring that the instrument's items relate to the specific problem that the patient group with this disease may have. A widespread coverage, meaning that all possible symptoms for a specific disease are included, are an important characteristic (1). For this reason, the patients have to be involved in the item selection. It is also important to involve health professionals with expertise in the specific disease (1, 54). A related property is criterion validity, usually divided into concurrent and predictive validity, where concurrent validity involves assessing an instrument against the true value or, if no true value is available against a gold standard (1). The examination of the instrument's validity is an ongoing process and the more the PROM is used and tested the more sensible and valid it will become. However, according to Fayer and Machin (1), it is not possible ever to say that a PROM is absolutely valid, especially not an HRQoL PROM.

Reliability is the second important issue and includes both repeatability and internal reliability. Repeatability (test-retest reliability) means that if the patient's condition is stable, the answer in a test taken twice in succession should be the same. The time period between the repeated measurements should be long enough to prevent recall,

but short enough to ensure that the condition has not changed. Internal reliability (internal consistency) is based on item to item correlations, in multi-item PROMs, to evaluate whether the scales and domains measure the same concept (1, 54).

Responsiveness and sensitivity are usually understood to be a part of the reliability assessment, and both are basic for a PROM used in interventions and clinical trials. High responsiveness means that the PROM can detect differences over time, e.g., investigating HRQoL in longitudinal studies. Sensitivity is the ability to distinguish between patient groups with different illness severity. Both properties are important for a PROM to be reliable and valid (1, 54).

## Impact of lymphedema on health-related quality of life

As mentioned above, it is obvious that, without adequate treatment, lymphedema can result in several complications (5, 6, 9, 22, 23). Even when the lymphedema is adequately treated many problems and concerns may remain, such as pain, discomfort, dysfunction, disfiguring, changes in appearance, social and practical problems, and emotional effects. These complex problems can strongly influence HRQoL (55, 56). Persons with non-cancer-related lymphedema may also have associated problems, such as difficulties to be diagnosed and to be offered the right treatments, which can further affect their HRQoL (22, 57). The lifelong self-care they must do to maintain a reduced excess volume and the worries about the lymphedema getting worse will lower HRQoL further in these persons (24).

Several researchers have investigated the influence on HRQoL in women with ULL after breast cancer treatment, using generic PROMs (58, 59) or cancer-specific PROMs (60, 61) or both (62, 63). Bogan et al. (22) examined persons with non-cancer-related lymphedema in the lower limb in a study with a qualitative approach and found that the lymphedema had high impact on their HRQoL. In a literature review of both qualitative and quantitative studies, Morgan et al. (56) showed similar results.

Franks et al. (64) used a number of generic HRQoL PROMs to examine HRQoL and pain in patients with LLL. They found the 36-item Short-Form Health Survey (SF-36) to be the most appropriate generic HRQoL PROM for use in this patient group, even though a lymphedema-specific PROM may be more accurate (64). In a study using the Nottingham Health Profile Part 1 (NHP-1) (65), Sitzia and Sobrido (66) showed that changes in limb volume in the patients were not associated with a change in any dimension of the NHP-1. They concluded that the PROM was not sensitive enough (66). In a review, Pusic et al. found that only two out of 17 PROMs were lymphedema-specific (67). Ferrandina et al., using one cancer-specific and

one domain-specific PROM, discovered that patients with LLL after treatment for endometrial cancer experienced reduced HRQoL (68). In a review, Morgan et al. (56) found that the most used PROMs were either generic or specific to certain cancer diagnoses. Due to the special symptoms and problems related to lymphedema they concluded the importance of using HRQoL PROMs developed for patients with all kinds of lymphedema (56). Cemal et al. (69) concluded that there is a need for lymphedema-specific PROMs to better examine lymphedema symptoms and their impact on HRQoL and so did Hoffner et al. (58) when investigating HRQoL in ULL patients after LS.

Recently there has been more interest in developing lymphedema-specific HRQoL PROMs. The Upper Limb Lymphedema 27 (ULL-27) questionnaire is a 27-items tool specially designed and validated for assessing HRQoL in patients with ULL (70). In Belgium, two lymphedema-specific PROMs have been developed and tested for reliability and validity, the Lymphoedema Functioning, Disability and Health (Lymph-ICF) questionnaire focusing on ULL (71) and the Lymph-ICF-LL questionnaire focusing on LLL (72). In the United Kingdom, Keeley et al. (73) have designed a PROM, the Lymphoedema Quality of Life (LYMQOL) PROM, which consists of two questionnaires, one for patients with ULL and one for patients with chronic lower limb edema. In the United States, the Lymphedema Symptom Intensity and Distress Survey–Head and Neck (LSIDS–H&NI) questionnaire was developed for patients with lymphedema in the head/neck region (23).

Disease-specific PROMs can be expected to show intervention-related changes in HRQoL more precisely compared to generic ones (74). The lymphedema-specific HRQoL PROMs that have recently been developed (23, 70-73) all target one specific part of the body and therefore make it difficult to include and compare different patient groups within the same study. Accordingly, an HRQoL PROM that is lymphedema-specific, rather than body part-specific, is needed. The Swedish Lymphoedema Quality of Life Inventory (SLQOLI) is available in English and Swedish and is a lymphedema-specific PROM that measures HRQoL in patients regardless of the body part affected by the lymphedema. It has been developed and tested for reliability and validity (75).

## **Development of the Swedish Lymphedema Quality of Life Inventory**

The Lymphoedema Quality of Life Inventory (LQOLI) was originally developed and tested in Australia, and presented by Professor Linda Kristjanson at the 5th biennial conference of the Australian Lymphology Association in Brisbane, Australia, in 2004 (not published). A three-stage project was carried out to develop and test its reliability and validity. Stage I used qualitative interviews with women who had experienced lymphedema, to elicit their perceptions of the impact on their

quality of life and activities of daily living. The interviews were transcribed and content analyzed. This resulted in development of the LQOLI. Stage II involved a pilot test of the tool for clarity, face validity, content validity, and internal consistency using a panel of women and health professionals with expertise in the treatment of lymphedema. Stage III involved 196 individuals who completed the LQOLI to assess the instrument's internal consistency, internal dimensions, and concurrent validity. Men and women with LLL or ULL were included in this third stage. Findings from this study resulted in the PROM LQOLI (not published).

The Australian LQOLI was brought to Sweden and a study was conducted to translate the PROM into Swedish and adapt it to Swedish conditions (76) and to test it for face, content, criterion, and cross-cultural validity and reliability (1, 54). The study was performed in four stages (75).

Stages I–III involved face, content, and cross-cultural validity. At Stage I, the instrument was translated into Swedish during a four-step process. In Step 1, three independent translators, who had Swedish as their native language and who also had a lot of experience in the lymphedema area, independently translated the LQOLI. In Step 2, the three versions were linked together and only a few changes were made for consensus. In Step 3, a fourth person, a native English speaker with excellent knowledge of Swedish and with personal experience of lymphedema, translated the LQOLI back into English. In Step 4, the two documents were compared. The agreement was perfect (75).

In Stage II, a list of all items (n=58) in the Australian LQOLI together with some added questions, concerning which words patients normally use to describe their lymphedema problems, were sent to lymphedema health professionals (n=11) distributed across Sweden. In this process, three items concerning infection (erysipelas, cellulitis), compression garments, and diet were added none were pulled out.

In Stage III, 19 patients were strategically selected with regard to sex, age, time since lymphedema diagnosis, primary or secondary lymphedema, and affected part of the body, to comprise a sample representative of lymphedema patients in Sweden. Patients were chosen from three Swedish hospitals to guarantee geographic inclusion of both sparsely and densely populated areas. The patients received information on the study and were instructed to fill out the translated form of the Australian LQOLI, clock the time it took and answer some added questions, concerning whether the instrument was easily understood, and the design was relevant, e.g., if the last two questions options were needed considering that they probably increased the time to complete the PROM.

Sixteen patients completed the PROM and after analyzing the responses, some small changes were made to the instrument. The most important change was increasing the time period from “the last week” to “the past 4 weeks”. One reason

for making this change was that we consider HRQoL to be an issue that does not change so rapidly and therefore 4 weeks would be suitable. At least three of the patients had the same opinion. Another reason was that the SF-36 uses the past 4 weeks. The two last question options were kept, even though some patients with primary lymphedema found them difficult to answer; however, most patients found them relevant.

The three stages above resulted in the SLQOLI, consisting of 61 items structured in four domains: physical, emotional, social, and practical. The respondent had to consider these items over the past 4 weeks and respond to three question options, where question option 1 = “How much do these concerns affect your quality of life?,” question option 2 = “How many changes have you had to make in your everyday life because of these concerns?,” and question option 3 = “How difficult have these changes been for you?” A 4-point Likert scale was applied for each question option. The second part of the PROM contains five items, the first concerning general quality of life during the past 4 weeks and the second concerning quality of life specific to the lymphedema experience during the past 4 weeks. A 10-point Likert scale was applied for these two items. The third and fourth items considered whether the past 4 weeks had been a typical period, or, if not, whether it had been “worse” or “better” on a 10-point Likert scale. The fifth question was open-ended (75).

In Stage IV, test–retest reliability and concurrent validity were tested and analyzed. Altogether 100 patients with different kinds of lymphedema, from two different sites in Sweden, were included and the SLQOLI was sent to them by mail twice and the SF-36 once. Test–retest reliability of the questionnaire was assessed using the responses from 58 patients who completed the PROM twice. The kappa coefficients in test-retest varied (range 0.25–0.83). According to Altman (77), the lowest kappa values are considered “fair” and the highest “very good” (75). Sixty-three patients completed the SLQOLI and SF-36 and concurrent validity was analyzed using Spearman’s correlation coefficient. The correlation between the SF-36 and SLQOLI was moderate. The time needed to complete the SLQOLI varied from 15 minutes to 2 hours and 40 minutes (median = 30 minutes). Test–retest reliability demonstrated moderate reliability and the SLQOLI was considered to be valid. However the authors suggest that before the PROM can be used in intervention studies, the items that were considered “fair” should be removed (75).

## Rationale for the thesis

During my first years as a physiotherapist, I worked with elderly patients and after approximately 6 years I began to work in palliative care with cancer patients at the

end of life. One of the problems the patients had was massive edemas of different origins. One of my assignments at work was to treat the patients' lymphedema. However, my education physiotherapy did not include the treatment of lymphedema. Fortunately, in 2002, I had the opportunity to attend a course to become a lymph therapist and after that my career path was straightforward. I started to work at a lymphedema clinic, to which patients with all kinds of lymphedema were admitted. In 200, I became involved in an exercise study including women with ULL after breast cancer treatment, conducted by Associate Professor at Lund University, Karin Johansson. Working as a physiotherapist, I know the importance of exercise, not only to increase strength and functioning but also in terms of quality of life. The issue of HRQoL and especially how lymphedema affected my patients' HRQoL became more and more important. Many patients told me that they felt that the lymphedema itself affected their HRQoL more than the cancer disease had done. So I was motivated to examine and treat and, where possible, through my interventions increase HRQoL of the lymphedema patients I meet in the clinic.

Lymphedema is a chronic disease which doubtless has a great impact on a person, both functionally and physically, psychosocially, and practically. In light of this, it is extremely important to measure not only the magnitude of the impairments, but also the impact these impairments may have on the person's HRQoL. Health-related quality of life includes a person's perceptions and attitudes towards dimensions of their life that are influenced by the disease. Generic PROMs have been unsuccessful in investigating the impact of all possible problems and impairments that lymphedema can generate. In recent years, the possibility to cure patients with cancer diagnosis has highlighted the importance of investigating how chronic impairments from cancer treatment may impact HRQoL. Several cancer-specific PROMs have been used to investigate HRQoL after cancer treatment. However, since lymphedema can be both primary and secondary to diseases other than cancer, cancer-specific PROMs will not be appropriate for all lymphedema patients.

To be able to follow improvements both during and after an intervention, a lymphedema-specific PROM that is both reliable and valid, as well as responsive, and sensitive is needed. When I started the research for this thesis a few PROMs had already been developed abroad. However, they did not measure HRQoL in lymphedema patients regardless of which body part was affected or of the causes of the lymphedema. On the other hand, the SLQOLI, recently adapted to Swedish conditions, has these properties. In this PROM the patients are asked to relate their concerns to their quality of life. However, the instrument is lengthy (188 items), creating a burden for patients to complete. Therefore, it seemed appropriate to develop and test a shortened PROM, based on the SLQOLI, to be used in both clinical and research settings.

# Aims

## Overall aim

The overall aim of this thesis was to develop a lymphedema-specific instrument and use it to determine how persons with lymphedema experience HRQoL.

## Specific aims

- To reduce the SLQOLI to an abbreviated, clinically useful version while at the same time keeping the structure of the original instrument.
- To test the new Lymphedema Quality of Life Inventory (LyQLI) for reliability, validity, responsiveness, and sensitivity.
- To evaluate, in two lymphedema clinics in Sweden, how lymphedema impact the patients' HRQoL and to compare different patient groups.
- To investigate HRQoL in patients with lymphedema before conservative treatment or LS, and after 1, 3, 6, and 12 months.
- To evaluate the effect of conservative treatment and LS interventions on lymphedema and lymphedema-related concerns.





# Methods

## Participants and procedures

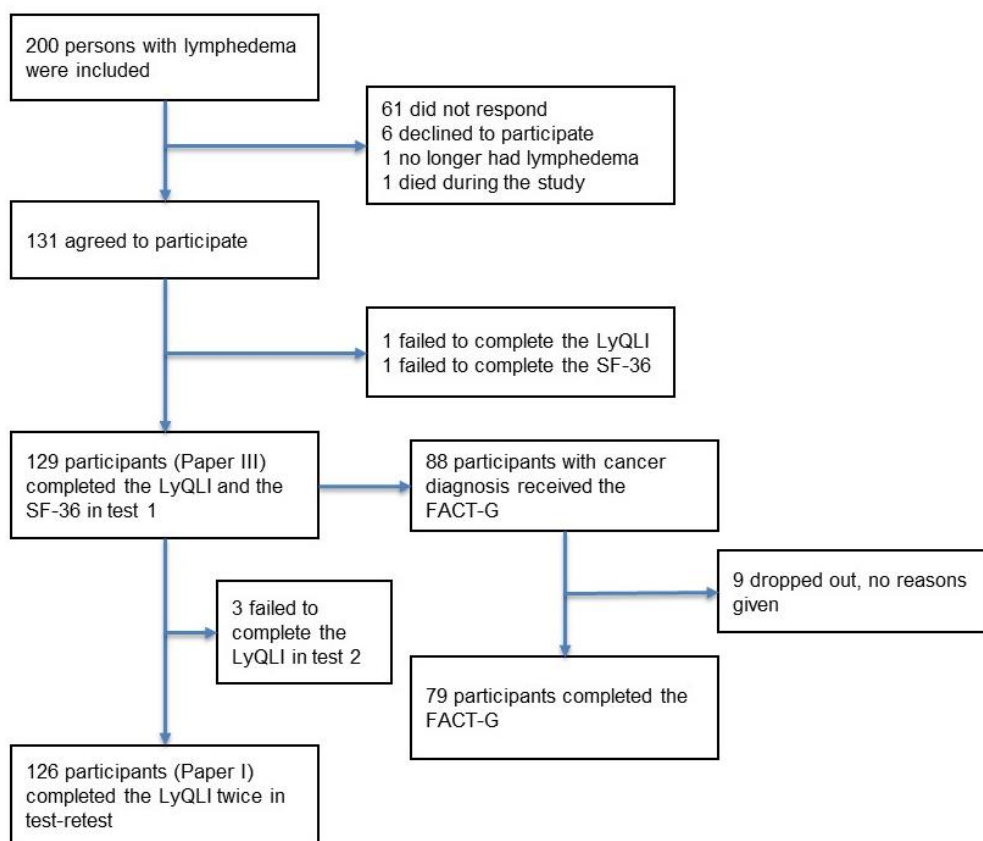
### **Common lymphedema sample/cross-sectional sample**

To test the LyQLI for validity and reliability, a consecutive sample of 200 outpatients, selected from the registers of two lymphedema units in Sweden, the Skåne University Hospital, Lund (n=100), and Bräcke diakoni, Rehabcenter Sfären, Solna (n=100), were used. Inclusion criteria were adults, 18 years and older, diagnosed with lymphedema for at least 6 month, who further were of sufficient mental health and knowledge of Swedish to read and complete forms in Swedish.

Three sub-groups were recruited by strategic selection: secondary lymphedema in the upper limbs/head and neck (n=80), secondary lymphedema in the lower limbs/genitalia (n=60), and primary lymphedema (n=60). The selection was consistent with the incidence of lymphedema patients at both clinics. Characteristics of the common lymphedema (CL) sample and the cross-sectional sample/reference lymphedema (RL) sample are presented in Table 1.

### *Procedure*

The procedure is described in detail in Paper I and III. During the period April to June 2012, the LyQLI was mailed twice to the study participants in a test–retest procedure. In the first test, the LyQLI was sent along with a consent form, a clinical–sociodemographic questionnaire, and the SF-36. Directly after the first response was received, the questionnaire was sent again to achieve a no more than 2-week gap between the two tests. In the second test, those participants who had lymphedema secondary to cancer treatment received the Functional Assessment of Cancer Therapy scale–General (FACT-G) together with the LyQLI. A flow chart of the inclusion process is given in Figure 1.



**Figure 1**  
Flow chart of inclusion in Papers I and III. Lymphedema Quality of Life Inventory (LyQLI); Functional Assessment of Cancer Therapy scale–General (FACT-G); 36-item Short-Form Health Survey (SF-36)

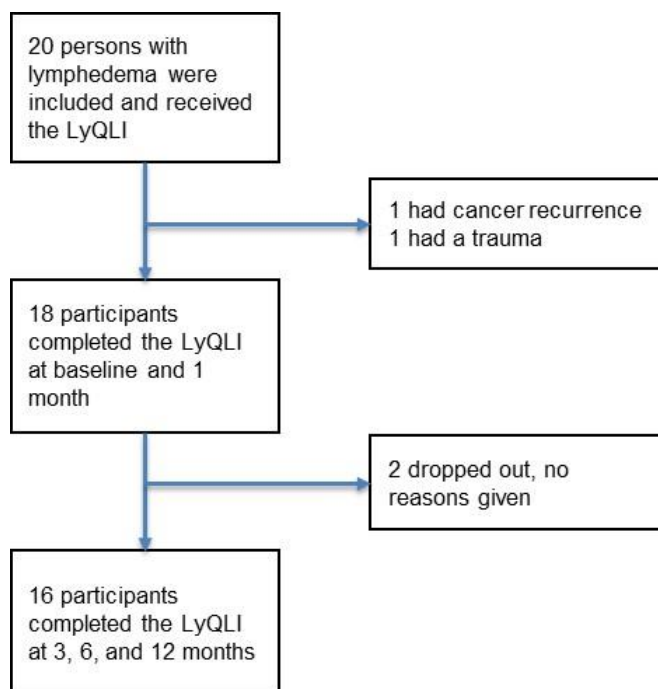
## Rehabilitation program sample

Patients diagnosed with ULL or LLL were consecutively invited to the study when they were registered for a 2 (ULL) or 3-week (LLL) rehabilitation program (RP), at Brücke diakoni Rehabcenter Sfären, Solna, Sweden. The program included the most common components of CDT (34), complemented with relaxation, weight-lifting, water-based exercise, and education about the lymphatic system, ergonomic matters, and self-care. Inclusion criteria were adults, 18 years or older, diagnosed with lymphedema for at least 6 months and with no previous participation in an RP. Patients with concurrent cancer disease or cognitive or communication difficulties were excluded. Characteristics of the RP sample are shown in Table 1.

### Procedure

The procedure is described in detail in Papers II and IV. The patients were invited to the study before the RP and if they agreed to participate they had to complete the LyQLI, a consent form and a clinical–sociodemographic questionnaire before the start of the program. On the first and the last day of the RP, the author (P.K.) measured the limb volume and asked the participants to rate experience of heaviness and tension of the affected limb using a visual analog scale (VAS). The treatments during the RP were performed by experienced lymph therapists other than the author.

Follow-up measurement using the LyQLI were made 1, 3, 6, and 12 months after the RP. The participants received and answered the LyQLI by mail. At 6 months the participants were summoned for a visit to the clinic, and limb volumes and the participants' experiences of heaviness and tension were measured. A flow chart of the inclusion process is given in Figure 2.



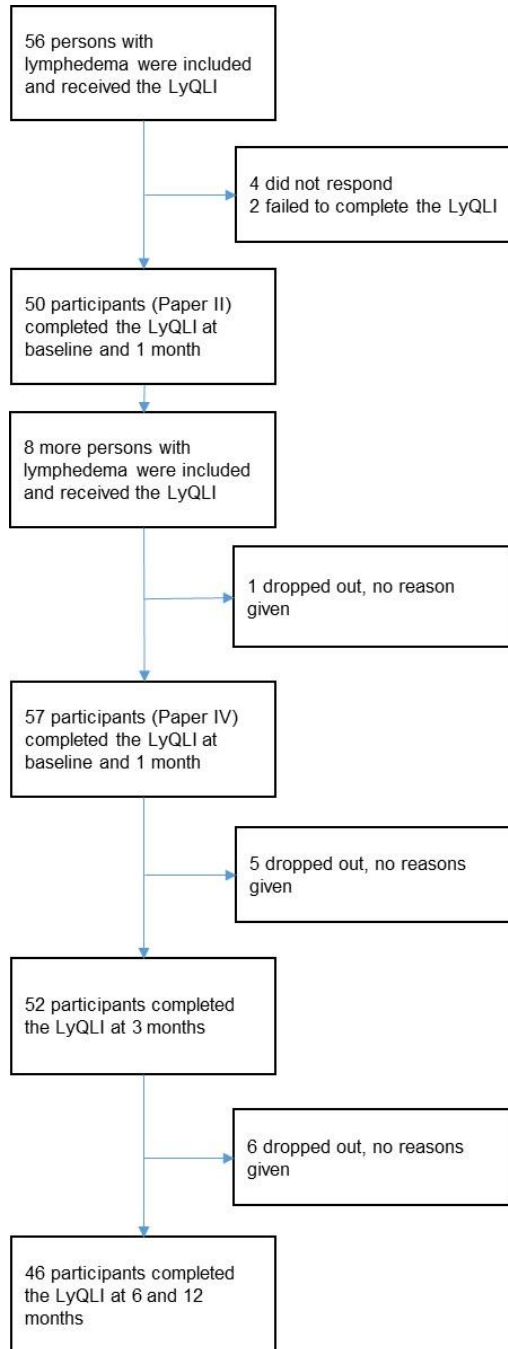
**Figure 2**  
Flow chart of inclusion in the rehabilitation program (RP), Papers II and IV. Lymphedema Quality of Life Inventory (LyQLI)

## **Liposuction samples**

The LS samples included patients with ULL or LLL undergoing surgery (41) for management of lymphedema at the Advanced Lymphedema Assessment Clinic at Macquarie University in Sydney, Australia, the Plastic Surgery Clinic at Ninewells Hospital in Dundee, Scotland, and the Department of Plastic and Reconstructive Surgery, Skåne University Hospital, Malmö, Sweden. Characteristics of the LS samples are shown in Table 1.

### *Procedure*

The procedure is described in detail in Papers II and IV. The patients were invited to the study before LS and those who agreed to participate were asked to complete the LyQLI, a consent form, and a clinical–sociodemographic questionnaire before the surgery. Limb volumes were collected as a regular part of care within the clinics, pre-surgery, and at 1, 3, 6, and 12 months post-surgery. One, 3, 6, and 12 months after LS, the participants received and answered the LyQLI by mail or via a website link. The surgeons were not involved in data collection. A flow chart of the inclusion process is given in Figure 3.



**Figure 3**  
Flow chart of inclusion in the liposuction samples (LS), Papers II and IV. Lymphedema Quality of Life Inventory (LyQLI)

**Table 1**

Characteristics of the participants in Papers I–IV

Characteristics	Paper I	Paper II			Paper III	Paper IV	
Sample	CL sample	RL population	RP sample	LS sample	Cross-sectional sample	RP sample	LS sample
Number	126	129	18	50	129	18	57
Age, yrs, median (range)	62 (19–92)	62 (19–92)	61 (46–76)	55 (23–75)	62 (19–92)	61 (46–76)	53 (23–75)
Female/male %	87/13	86/14	83/17	90/10	86/14	83/17	91/9
Country of residence							
Australia %	–	–	–	18	–	–	16
Scotland %	–	–	–	44	–	–	51
Sweden %	100	100	100	38	100	100	33
Time with lymphedema, yrs, median (range)	7 (0.5–70)	7 (0.5–70)	2.5 (0.5–57)	12 (2–66)	7 (0.5–70)	2.5 (0.5–57)	13 (2–66)
Type of lymphedema							
Primary %	26	26	22	30	26	22	33
Secondary %	74	74	78	70	74	78	67
Body part affected							
Lower limb %	55	56	39	68	56	39	72
Upper limb %	40	38	61	32	38	61	28
Other body parts %	5	6	–	–	6	–	–

CL= common lymphedema sample, LS = liposuction sample RL = reference lymphedema population, RP = rehabilitation program sample

## Ethical approvals

All studies in this thesis involved human participants and were performed in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards (78). All patients provided written informed consent before participation in the studies.

The Swedish studies were approved by the Regional Ethical Review Board at Lund University, Sweden (Dnr 2012/146, Dnr 2013/628 and 2014/208). The Australian part was approved by the Macquarie University Human Research Ethics Committee

(HREC (Medical Sciences)) (Reference No: 5201400124). No ethical approval was required for the Scottish part of the study.

## Measurements used in Papers I–IV

### **Assessment of subjective experience**

#### *Clinical–sociodemographic questionnaire*

Characteristics and medical history regarding lymphedema were provided by the participants via hard copy surveys or a website link. The questionnaires are described in greater detail in Papers I–IV.

#### *36-item Short-Form Health Survey*

One widely used generic HRQoL PROM is the SF-36. The SF-36 addresses generic health concepts that are not specific to age, disease, or treatments. It is designed to be used for self-report or during interviews and was developed and published in 1992. It was aimed to be used in general population surveys, clinical research, or clinical practice (45). Sullivan et al. (79) translated the SF-36 into Swedish and adapted it for Swedish conditions. They used the general Swedish population to test it for construct validity, replicating the same psychometric tests as used in the United States. To ensure the clinical validity of the SF-36, Persson et al. (80) 3 years later conducted further validity tests in an elderly female population, and further investigate criterion validity, another study was performed in the general Swedish population in the same year (81). The SF-36 consists of 36 items, 35 of which are divided into eight domains: Physical Functioning (ten items), Role–Physical (four items), Bodily Pain (two items), General Health (five items), Vitality (four items), Social Functioning (two items), Role–Emotional (three items), and Mental Health (five items). A single additional item assesses change in health status during the past 12 months. The scoring system ranges from 0 to 100, with a higher score signifying higher HRQoL. The instrument also includes two sum scores for Physical Health (physical component summery, PCS) and Mental Health (mental health component summery, MCS). The SF-36 is a generic HRQoL instrument that is valid and reliable, and is frequently used in studies worldwide (45, 81).

#### *The Functional Assessment of Cancer Therapy Scale-General*

The FACT-G scale is a self-report PROM designed to investigate HRQoL in patients with cancer diagnosis. The development and validation of the general component of the FACT-G with 33 items (version 2) took place from October 1987 through February 1992 in the United States (82). Patients with different kinds of



cancer diagnosis and also other chronic diseases were involved in the development of the instrument (82). Work to improve the instrument continued, resulting, in 1996, in the FACT-G (version 3) scale (83). Later, version 4 of the FACT-G was evaluated, which is a 27-item combination of general items concerning cancer treatment, divided into four subscales: Physical Well-being (seven items), Functional Well-being (seven items), Social/Family Well-being (seven items), and Emotional Well-being (six items) (84). Every item is assessed on a 5-point Likert scale ranging from 0 = “Not at all” to 4 = “Very much.” The FACT-G also computes a total score (maximum =108). A higher score indicates a higher HRQoL. The FACT-G scale is considered to be an acceptable indicator of patient well-being as long as the overall response rate for each item is >80% (82, 84).

#### *Visual analogue scale*

Visual analogue scales are a self-report device that have been used for several decades and mostly for measuring pain; however, other subjective experiences e.g., symptoms such as nausea, fatigue, and dyspnea have also been measured by VAS (85). Johansson et al. (86) used a VAS in a randomized intervention study in breast cancer patients with ULL. In that study, the VAS was used to measure the patients’ experience of tension and heaviness before and after conservative lymphedema treatment. In Papers II and IV, the subjective experience of lymphedema symptoms in the affected limb was scored by each patient on a 100 mm horizontal VAS. Patients were asked to evaluate their average, mild, and worst experience of tension and heaviness during the past week. The endpoints were “no discomfort” (0 mm) and “worst imaginable discomfort” (100 mm) (87, 88). Because the VAS measurements were repeated the initial scores were made available to the patient at the second and third measurement (89).

### **Assessment of objective volume measure**

#### *Cylinder form formula*

In the RP sample in Sweden (Papers II and IV), the volume of the extremities was calculated on each occasion using the formula for a cylinder form, with circumferential measurements taken at 4 cm intervals and the contralateral arm/leg serving as control (90). This method has been assessed as valid in patients with LLL (91). Sander et al. (92) found strong inter-rater and intra-rater reliability for both water displacement method and geometric volumes in women with ULL.

#### *Truncated cone method*

In Australia and Scotland (Papers II and IV), the volume of the extremities was calculated on each occasion using the truncated cone method, with circumferential

measurements taken at 4 cm intervals and the contralateral arm/leg serving as control (93, 94). This method has been assessed as reliable and valid (93).

#### *Water displacement method*

In the LS sample in Sweden (Papers II and IV), the volume of the extremities was measured with the water displacement method (95). Bednarczyk et al. (1993) carried out a validity test for this method with a computerized limb volume measurement system and found a high correlation coefficient ( $r=0.992$ ) (96). At each measurement occasion each, extremity was submerged in a container with water and the displaced water was weighed on a balance to the nearest 5 g (corresponding to 5 ml) (94).

## Development and psychometric testing of the LyQLI

In developing a new instrument which is an abbreviated form of the SLQOLI, we used the kappa results from the reliability test of the SLQOLI (75). Participants included in that study were 100 consecutively selected patients from each of the Lymphedema Units at Skåne University Hospital (50) in Lund, and the Bräcke diakoni Rehabcenter Sfären (50), Stockholm, Sweden. Fifty-eight patients completed the SLQOLI twice (75).

Our intention was to reduce the total number of items while keeping as much as possible of the original structure. We also wanted to examine whether it was necessary to include all three question options with respect to the 61 items.

Factor analysis (1, 97, 98) was used to analyze the correlations among items in response to the first question option and was first performed for each domain separately. Because some items were phrased in similar ways across the emotional and social domains, a factor analysis was also performed with these two domains merged. Spearman's rank correlation coefficients ( $r_s$ ) were used to examine correlations between responses to the three question options.

The results from the factor analysis were then examined by the two authors (P.K. and K.J.) who reduced, merged, and where necessary, carefully renamed the items. The reduction process and the results were then presented to a lymphedema professional group who were asked to check and share their experience of their patient's relation to lymphedema and HRQoL. The outcome of this process was a 45-item PROM, the LyQLI.

## **The Lymphedema Quality of Life Inventory**

The LyQLI is a self-report questionnaire that assesses HRQoL in patients with lymphedema (Appendix). It consists of 45 items. Forty-one of the items are divided into three multi-item domains: physical (twelve items), psychosocial (16 items) and practical (13 items). Each item assesses the impact of lymphedema on the person's HRQoL during the last 4 weeks on a 4-point Likert scale where 0 = none; 1 = a little bit; 2 = somewhat; and 3 = a lot. The scores are presented as mean scores in each domain, from 0 to 3, with a higher mean score indicating more impact on HRQoL. The questionnaire also includes four global questions, of which item 44 assesses the overall experience of lymphedema and item 45 assesses the overall quality of life, both scored on a 4-point Likert scale ranging from 0 = very bad, to 3 = very good. A higher score indicates higher HRQoL.

### **Testing of validity and reliability**

In developing the LyQLI, the testing of validity and reliability was conducted using the CL sample (Paper I). Systematic disagreement between the two test occasions was evaluated using the relative position (99). In test–retest, the cumulative frequencies for each item from the second test were plotted against the cumulative frequencies from the first test and the points were combined to receiver operating characteristic (ROC) curves (99). Deviations from the diagonal line indicated systematic changes. The Wilcoxon signed rank test was used to test whether the relative position of the measure of disagreements within each domain differed statistically significant from zero ( $p < 0.05$ ).

#### *Reliability*

Test–retest reliability was evaluated for each of the three domains based on the intraclass correlation coefficient (ICC) together with a 95% confidence interval, using two-way random effect models with absolute agreement. Test–retest reliability was evaluated by calculating possible systematic changes in the domain scores. For each domain, the differences in score between the two test occasions were calculated and tested using Student's *t*-test. Cronbach's alpha coefficients were calculated to estimate the internal consistency of each of the three domains.

#### *Validity*

Concurrent validity was assessed using Spearman's rank correlation coefficients ( $r_s$ ) (77) to assess the correlation between the scores of the three domains of the LyQLI and the scores of the two sum scores PCS and MCS in the SF-36 (100). Possible floor and ceiling effects in the items were studied by examining skewness characteristics.

## Testing of responsiveness and sensitivity

Since a PROM needs to be sensitive and responsive to changes, further psychometric analyses were made using the RP and LS samples and the RL population (Paper II). Two methods were used to evaluate responsiveness: internal responsiveness, which measures the ability to detect changes over a pre-specified time frame, e.g., before and after an intervention, and external responsiveness, which compares a measurement to a corresponding clinical measurement to detect important clinical changes (3).

Mean values, range and standard deviation (SD) were calculated for the total limb volume and excess volume. Baseline differences in total limb volume and excess volume between the RP sample and the LS sample were calculated using independent *t*-test. Mean values and SDs were calculated for the LyQLI responses in the three domains. Paired *t*-test was used to detect significant differences at baseline and 1 month after intervention. For the VAS measurements, mean values at baseline and post-intervention were calculated.

### *Floor and ceiling effects*

Floor and ceiling analysis was conducted by calculating the number of participants with possible minimum (= 0) and possible maximum (= 3) scores in both interventions in each domain, and as a total for the 41 items.

### *Responsiveness*

To determine internal responsiveness, effect size was calculated as the standardized response mean (SRM). The SRM is used to calculate the variation in changes (1) and is widely used to evaluate responsiveness using the formula  $SRM = \text{response mean} / \text{response SD}$  (3, 74). According to Cohen (101), the categorization of used is:  $<0.50$  = small;  $0.50\text{--}0.79$  = moderate, and  $>0.80$  = large. The SRM for each domain and global items 44 (overall experience of lymphedema) and 45 (overall quality of life) was calculated in both interventions. To evaluate external responsiveness, Pearson's correlation coefficient was used. Changes in LyQLI responses before and 1 month after the intervention were correlated to changes in experience of tension and heaviness in the RP sample and, to the reduction of limb volume in the affected limb in the LS sample. The correlations ( $r$ )  $<0.30$  were considered low;  $0.30\text{--}0.49$ , moderate; and  $>0.50$ , strong (101).

### *Sensitivity*

Sensitivity was analyzed by calculating the differences in baseline response between the RP and the LS samples in each domain, using the independent *t*-test. Further investigation was conducted using box plots of the baseline response from RP and LS samples and the RL population.

# Methods used to investigate health-related quality of life in persons with lymphedema

## Cross-sectional study

In Paper III, Mann-Whitney U-test and chi-square test were used to evaluate the differences between the participants and the dropouts, for continuous and categorical data, respectively. Mean scores for the items in the three domains of the LyQLI were calculated. In order to detect and analyze the participants who reported high impact from lymphedema on HRQoL, the mean score of 2.0 was chosen as a cut-off point, since the answers “none” and “a little” indicate a low impact whereas “somewhat” and “a lot” indicates a high impact of lymphedema on HRQoL.

The distributions of the domain scores tended to be skewed; therefore, non-parametric statistical tests were performed. Spearman’s correlation coefficients were used to analyze the correlations between the scores from the three domains and the continuous variables age, and years with lymphedema. Correlations ( $r$ )  $<0.30$  were considered to be low;  $0.30$ – $0.49$  moderate; and  $>0.50$  strong according to Cohen (101). Kruskal-Wallis test was used to analyze differences in the domain scores for the categorical variables *gender*, *cause of lymphedema*, *work status*, and *main part of body* affected by lymphedema. For every participant we found the corresponding SF-36 value for the Swedish population, based on gender and age (5-year intervals). The actual SF-36 values were compared with the population values by means of the Wilcoxon signed rank test. The norms for the general Swedish population ( $n=8,850$ ) were assessed in Sweden in 1991–1992 (79). The results from the FACT-G were calculated as descriptive data.

## Longitudinal study

In Paper IV, mean values and SD were calculated for the LyQLI responses in the three domains. The percentage of participants that experienced high domain score ( $\geq 2.0$ ) in one or more of the three domains at baseline and after 1, 3, 6, and 12 months were calculated. Mean values, ranges and SD were calculated for the total limb volume of the affected limb as well as for the excess volume. For the VAS measurements, mean values for the first and last day of the RP and 6 months afterwards were calculated in mm. To handle missing LyQLI forms, VAS measurements, and volume measurements, single imputation methods were used for the follow-ups at 3, 6, and 12 months. The last and next imputation was used in participants with available assessments before and after the missing assessment. Last-observation-carried-forward (LOCF) imputation was used in participants with

no further assessments (102). These methods allowed the same number of participants, from baseline to the last follow-up measurement.

The Mann-Whitney test was used to detect significant baseline differences in the affected limb volume and excess volume, between the RP and the LS samples. To detect and analyze differences in LyQLI responses in the three domains from baseline to the 12-month follow-up, Wilcoxon signed rank tests were performed. The Wilcoxon sign rank test was also used to detect differences in experience of tension and heaviness, measured using VAS up to 6 months, and changes in affected limb volume and excess volume until the 12-month follow-up.

To detect which concerns most affected the participants' HRQoL and determine whether that would change after the interventions, the responses were analyzed using 20 items with the highest mean score, identified in Paper III. The responses were dichotomized into low or high impact on HRQoL and the same cut off point was used as in Paper III. The percentage of participants who estimated a high impact on HRQoL in the 20 items, at baseline and after 12 months was calculated. The differences between baseline and 12 months were calculated as a percentage.



# Results

## Development and psychometric testing of the LyQLI

### Development of the LyQLI

In Papers I and II, a PROM which were the shortened version of the SLQOLI was developed and tested for validity, reliability, responsiveness, and sensitivity.

In the first phase in Paper I the PROM was developed. Results from the Spearman's rank correlation coefficient test revealed high correlations between responses to the first question option concerning HRQoL and the two other question options ( $r_s > 0.60$  for all four domains). Therefore, the second and third question option were considered redundant and were removed.

As a result of the factor analysis and the expert-based reduction, the four domains (physical, emotional, social, and practical) were reduced to three (physical, psychosocial, and practical). The number of items in the domains were reduced in all four domains and the emotional and social domains were merged to one, renamed the "psychosocial domain." The open-ended item was removed. In total, the number of items was reduced from 188 to 45. A small modification in the sequence of the items on the last page was made and the scales in the two items with 10-point Likert-type scales were converted to 4-point Likert scales.

The lymphedema professional group judged the abbreviated scale to have good content and face validity, resulting in the shortened LyQLI (Appendix).

The second phase in Paper I included psychometric testing of the new PROM. In total, 131 patients agreed to participate, 129 (98%) completed test 1 and out of those 126 (97%) completed test 2 in test-retest (Table 1). Median time between the two completed tests was 10 days (range 1–144 days; 25th to 75th percentile: 7–14 days). Median time to complete the form was 6 (range 5–11) minutes.



## **Psychometric testing of the LyQLI**

In Paper II, the psychometric testing of the LyQLI continued. Participants in the RP sample (n=18) and the LS sample (n=50) fulfilled the criteria and completed the LyQLI before and 1 month after the intervention (Table 1).

### *Reliability*

The mean relative position (99) in the physical domain was -0.059, versus -0.031 in the psychosocial and -0.035 in the practical domain. The results indicate a small, but statistically significant, change in reporting between tests 1 and 2 in the test-retest analysis, with lower scores for each domain at test 2. All three mean differences differed significantly from zero. This difference was also found for the overall quality of life items 44 and 45. The ICC in the physical and psychosocial domains was 0.88 ( $p < 0.01$ ), versus 0.87 and in the practical domain ( $p < 0.01$ ). Cronbach's alpha was 0.88, 0.92, and 0.88, respectively, for the three domains.

### *Validity*

Altogether 131 participants completed test 1, and 129 also completed the SF-36 (Paper I). There were four (3%) missing values in each of the PCS and MCS. The correlation coefficient between the physical and practical domain in the LyQLI and PCS in the SF-36 was moderate; the correlation coefficient between the physical and psychosocial domains in the LyQLI and MCS was low, and the correlation coefficient between the practical domain and MCS was moderate. These results provide evidence of concurrent validity of the LyQLI.

### *Floor and ceiling effects*

The results in Paper I reveal a tendency towards a small floor effect. Results in Paper II, show minimum (= 0) and maximum (= 3) scores of 34% and 15%, respectively, at baseline and of 44% and 6% post-intervention in the RP sample. In the LS sample, the corresponding scores were 22% and 26% at baseline and 40% and 8% after the intervention.

### *Responsiveness*

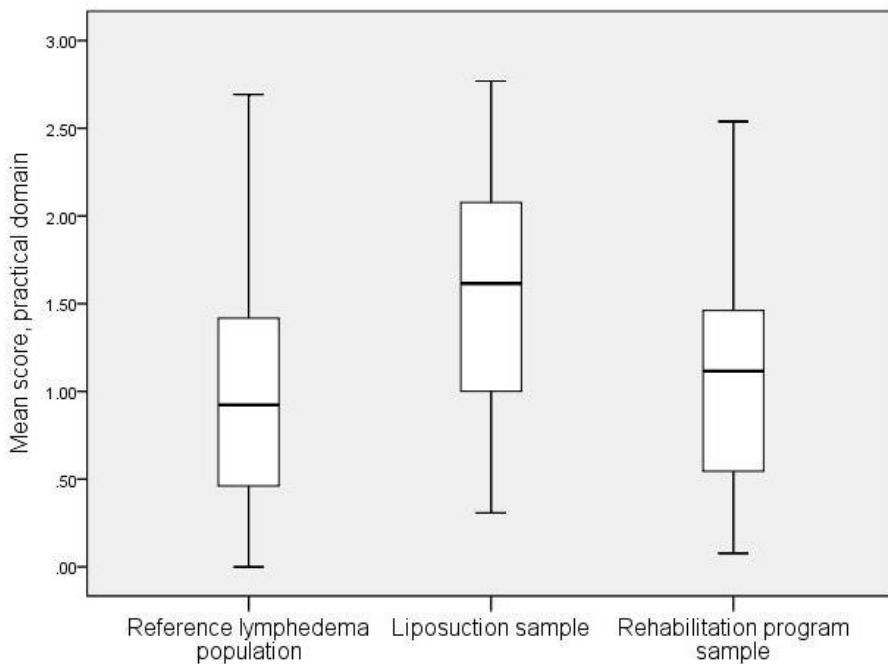
The results for internal responsiveness (Paper II) in the three domains show that, for the RP sample, the SRM was large ( $> 0.80$ ) in the psychosocial domain, moderate ( $< 0.80$ ) in the physical domain, and small ( $< 0.50$ ) in the practical domain. In the LS sample, the SRM values were mostly higher: large ( $> 0.80$ ) in the psychosocial and practical domains, and moderate ( $< 0.80$ ) in the physical domain (101).

The results for external responsiveness (Paper II), show that the correlation between decrease in LyQLI responses and decrease in average tension and least tension in the RP sample varied from low ( $r < 0.30$ ) to strong ( $r > 0.50$ ) (101), with significant

results in least tension in the physical and psychosocial domains. The correlation with experiences of heaviness was smaller (data not shown). The correlation between affected limb volume reduction and increase in HRQoL in the LS sample was low ( $r < 0.30$ ) (101). Some participants with a large limb volume reduction rated their HRQoL lower after the intervention, while some participants with a small reduction reported higher HRQoL.

### *Sensitivity*

The independent *t*-test showed differences between LyQLI baseline responses in the two samples (RP and LS) within the physical ( $p = 0.194$ ), psychosocial ( $p = 0.141$ ), and practical ( $p = 0.036$ ) domains. To report the sensitivity test, the results from the box plots calculations in the practical domain are shown in Figure 4.



**Figure 4**  
Differences in mean scores at baseline in the practical domain of the Lymphedema Quality of Life Inventory (LyQLI) between the three lymphedema samples: The reference lymphedema (RL) population, liposuction (LS) sample, and rehabilitation program (RP) sample

# Health-related quality of life in persons with lymphedema

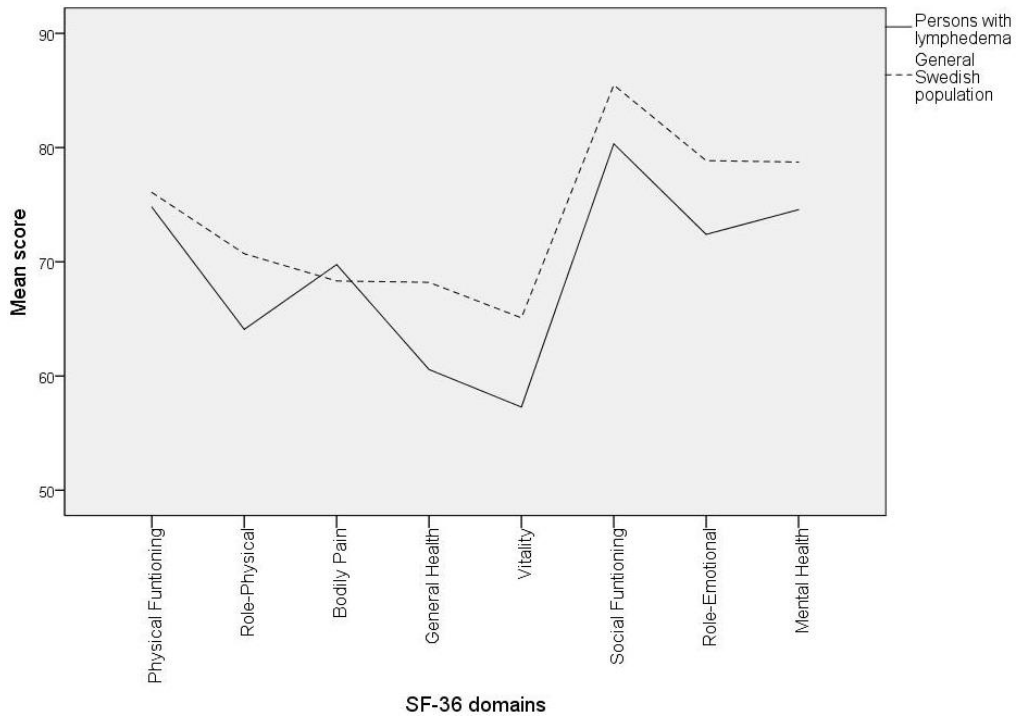
## Cross-sectional study

In Paper III, the participants (n=129) experienced an impact from lymphedema on HRQoL in all three domains of the LyQLI, with the mean score of  $\leq 1.14$ . Twenty-five participants (20%) had a mean score of  $\geq 2.0$  in at least one of the three domains. Out of these 25 participants, 17 had LLL and eight had ULL, 22 were female and three were male, and 17 had secondary and eight had primary lymphedema. Fifteen were employed. Nine of them worked full-time and six worked part-time. Ten participants were unemployed or retired.

The results show that the impact on HRQoL decreased with age, which was significant in the psychosocial domain ( $p=0.028$ ). Participants with LLL reported more lymphedema impact on HRQoL compared to participants with ULL or head/neck lymphedema, which difference was significant in the practical domain ( $p=0.002$ ). Participants who worked part-time reported more impact of the disease on HRQoL, with significance in the practical domain ( $p=0.005$ ) and a tendency to be significant in the physical domain ( $p=0.051$ ), compared to those who worked full-time.

### *Quality of life compared to the general Swedish population*

The results for participants (n=129) who completed the SF-36 were compared with the norms for the general Swedish population (n=8,850) (79) (Paper III). The results show that the persons with lymphedema had significantly lower scores in three domains of the SF-36, General Health ( $p=0.006$ ), Vitality ( $p=0.002$ ), and Social Functioning ( $p=0.025$ ). Figure 5 shows the domain scores in a linear diagram.



**Figure 5**  
 Mean scores in the eight domains of the 36-item Short Form Health Survey (SF-36) for the persons with lymphedema (n=129) compared with the general Swedish population (n=8,850).

*Health-related quality of life in cancer*

The participants (n=79) who had lymphedema secondary to cancer treatment answered the FACT-G. The total sum score was 88 (SD 16.6), with the maximal possible sum score being 108.

## Longitudinal study

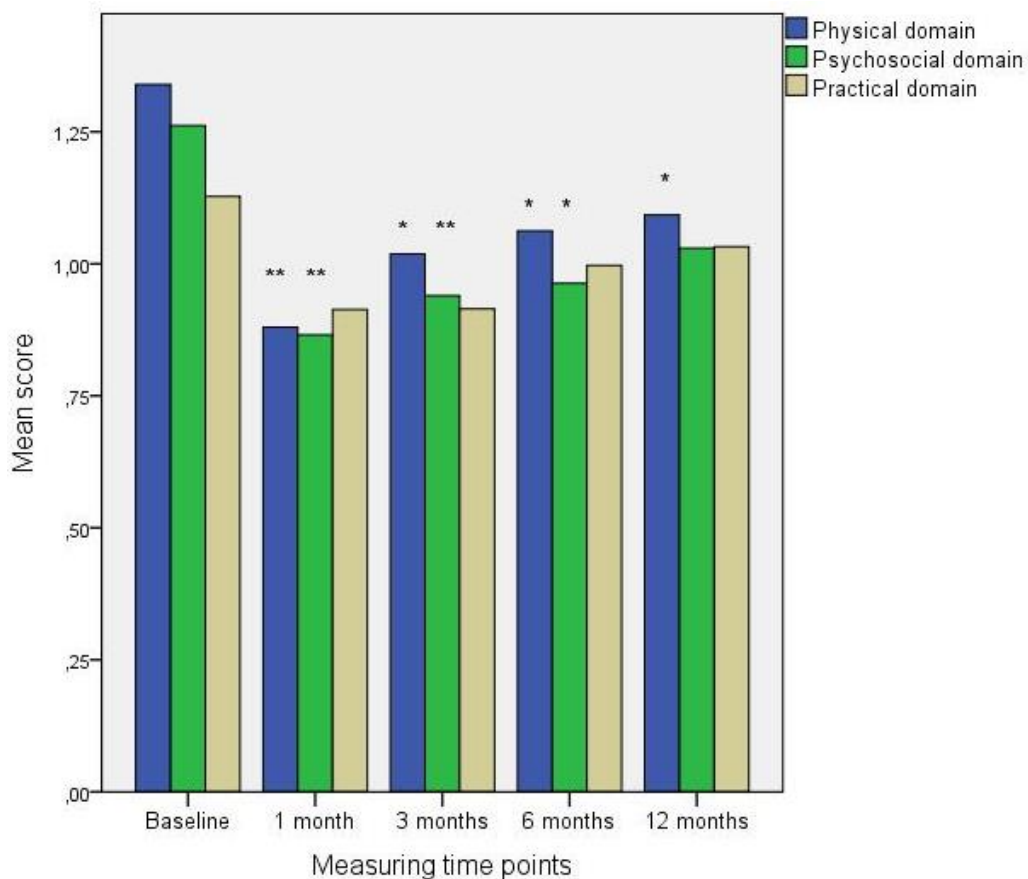


Lymphedema before and after 2 weeks of conservative treatment. © Imke Wallenius

### *Rehabilitation program*

The results show that the LyQLI scores decreased significantly compared to baseline, indicating improved HRQoL, in the physical ( $p=0.003$ ) and psychosocial domains ( $p=0.002$ ) 1 month after the program and these results remained stable up to 6 months for the psychosocial domain ( $p=0.012$ ) and 12 months for the physical domain ( $p=0.024$ ). The scores in the practical domain also decreased, but not significantly (Figure 6). At baseline, 21% of the participants scored  $\geq 2.0$  in at least one of the three domains, which indicates a high impact on HRQoL. At 1 month had this decreased to 11%, but it increased again to 28% at the 12-month follow-up. The 20 items with the highest impact on HRQoL and the changes in impact, from baseline to the 12-month follow-up, are shown in Table 2.

The results from the volume measurements show that the affected limb volume as well as the excess volume decreased significantly ( $p<0.001$ ) directly after the intervention. By 6 months post-intervention, the volume had increased again (Table 2 of Paper IV). The results from the VAS measurements show that six participants experienced neither tension nor heaviness in the affected limb. For the rest, the mean score decreased after 1 month, indicating less discomfort. After 6 months, the impact increased again, except for *heaviness-worst* (Table 2 of Paper IV).



**Figure 6**  
 Scores of participants in the rehabilitation program (RP) (n=18) in the three domains of the Lymphedema Quality of Life Inventory (LyQLI). The Figure show changes in scores from baseline to the 12-month follow-up. A decrease in score indicates increase in health-related quality of life (HRQoL). \*p<0.05; \*\*p<0.01

**Table 2**

The 20 items with the most impact on health-related quality of life (HRQoL) identified by the Lymphedema Quality of Life Inventory (LyQLI), and the percentage of participants (n=18) who reported a high impact on HRQoL before, and 1 and 12 months after, the rehabilitation program (RP). The items are presented in descending order, from highest increase in HRQoL to the lowest increase among these 20 items.

	Lymphedema-related concerns and problems, with high impact on HRQoL	Somewhat / a lot of impact on HRQoL			Percentage increase in HRQoL
		Percentage of participants			Baseline – 12-month follow-up
		Baseline	1-month follow-up	12-month follow-up	
20	Paying constant attention to my condition	72	33	39	46
18	Not being able to do the things I used to enjoy	50	33	28	44
27	Concerns about negative changes in my appearance	44	39	28	36
33	Having less energy to do activities (e.g. personal, normal daily or employment)	47	28	33	30
36	Traveling long distances by car, train, plane etc.	47	28	33	30
13	Feelings of frustration/feeling annoyed	61	39	44	28
10	Feeling physically aware of my lymphedema all the time	67	39	50	25
14	Feeling anxious about whether or not the lymphedema will get worse	67	50	50	25
15	Embarrassed by lymphedema/compression garments	44	33	33	25
38	Limitations in hot weather/sun	78	44	61	22
1	Pain/aches due to my lymphedema	56	33	44	21
3	A feeling of heaviness due to my lymphedema	56	39	44	21
16	Negative changes in how I see myself	56	41	44	21
37	Finding clothes and shoes that are comfortable and attractive, the right size and type of material	61	39	50	18
30	Normal daily activities (e.g. doing housework, sports- and hobby activities)	33	22	28	15
2	Discomfort due to my lymphedema	61	33	56	8
6	Swelling/tightness due to my lymphedema	78	56	72	8
11	Feeling a loss of strength in the swollen part of my body	61	33	56	8
9	Movement difficulties due to my lymphedema	44	22	44	0
39	The constant self-care I need to do to stop my lymphedema from getting worse	56	50	67	-16

Items 1-12 relate to the physical domain, 13–28 to the psychosocial domain, and 29–41 to the practical domain

## Liposuction

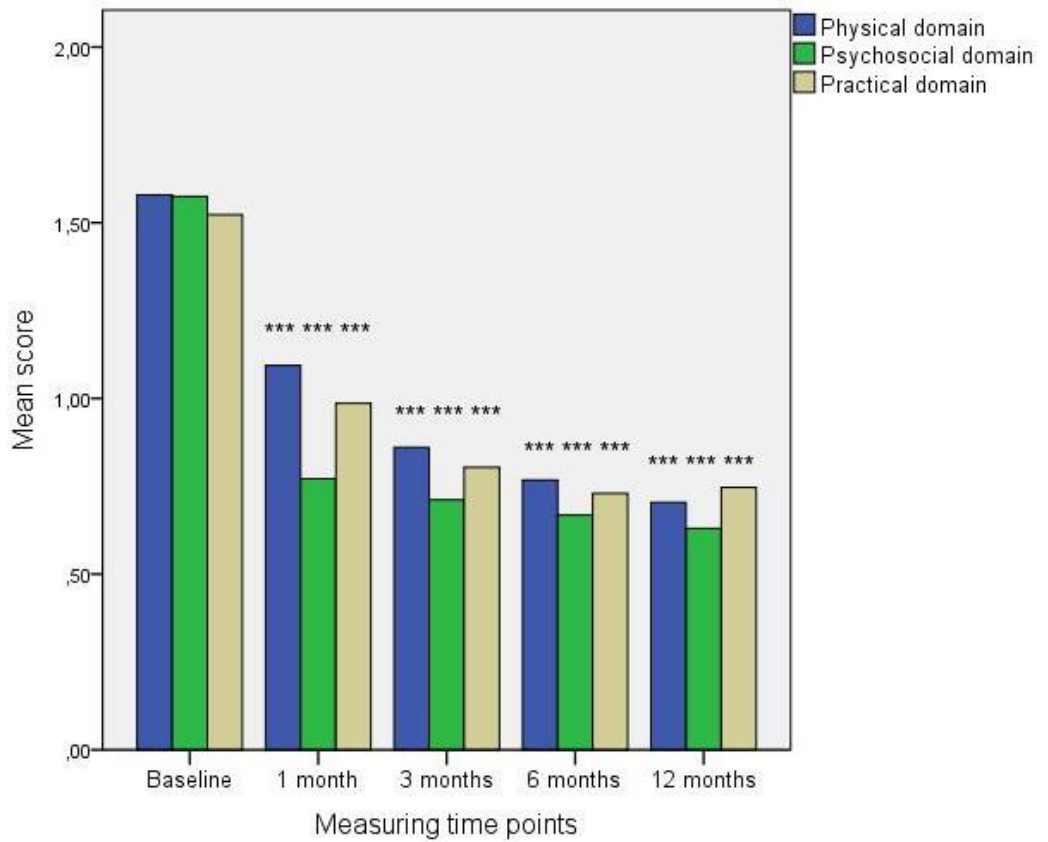


Preoperative excess volume of 3,170 ml (upper figure) before liposuction (LS). Post-operative excess volume of -10 ml at follow-up 2 years after surgery, i.e., the treated arm is somewhat smaller than the unaffected one. © Håkan Brorson

The results show that the LyQLI-scores decreased significantly ( $p < 0.001$ ) compared to baseline in all three domains, indicating improved HRQoL. These results remained stable up to the 12-month follow-up (Figure 7). At baseline, 45% of the participants scored  $\geq 2.0$  in at least one of the three domains, which indicates a high impact on HRQoL. At 1 month, this had decreased to 19%, and it continued to decrease to 5% by the 12-month follow-up. The 20 items with highest impact on HRQoL and the change of impact from baseline to the 12-month follow-up are shown in Table 3.

The results from the volume measurements show a significant decrease in the affected limb volume as well as the excess volume ( $p < 0.001$ ). The largest decrease was seen between baseline and follow-up at 1 month. However, the reduction in excess volume continued up to 12-month follow-up (Table 4 of Paper IV). To analyze a potential correlation between the changes in HRQoL in the three domains and the reduction in volume in the affected limb at the 12-month follow-up, scatterplots were used. The results show that the increase in HRQoL had a low correlation ( $< 0.3$ ) to the reduction in volume in the affected limb (101).





**Figure 7**  
 Scores of participants in the liposuction (LS) sample (n=57) in the three domains of the Lymphedema Quality of Life Inventory (LyQLI). The Figure show changes in scores from baseline to the 12-month follow-up. A decrease in score indicates a increase in health-related quality of life (HRQoL). \*\*\*p<0.001

**Table 3**

The 20 items with the most impact on health-related quality of life (HRQoL) identified by the Lymphedema Quality of Life Inventory (LyQLI), and the percentage of participants (n=57) who reported a high impact on HRQoL before, and 12 months after liposuction (LS). The items are presented in descending order, from highest increase in HRQoL to the lowest increase among these 20 items.

Lymphedema-related concerns and problems, with high impact on HRQoL		Somewhat / a lot of impact on HRQoL		Percentage increase in HRQoL
		Percentage of participants		Baseline – 12-month follow-up
		Baseline	12-month follow-up	
6	Swelling/tightness due to my lymphedema	89	12	86
14	Feeling anxious about whether or not the lymphedema will get worse	75	11	85
3	A feeling of heaviness due to my lymphedema	91	18	82
18	Not being able to do the things I used to enjoy	56	12	78
30	Normal daily activities (e.g. doing housework, sports- and hobby activities)	42	9	78
2	Discomfort due to my lymphedema	79	18	77
9	Movement difficulties due to my lymphedema	61	14	77
13	Feelings of frustration/feeling annoyed	66	16	76
33	Having less energy to do activities (e.g. personal, normal daily or employment)	46	11	76
27	Concerns about negative changes in my appearance	63	16	75
16	Negative changes in how I see myself	70	18	74
10	Feeling physically aware of my lymphedema all the time	84	23	73
11	Feeling a loss of strength in the swollen part of my body	58	16	72
15	Embarrassed by lymphedema/compression garments	72	23	68
1	Pain/aches due to my lymphedema	54	18	67
20	Paying constant attention to my condition	55	18	67
37	Finding clothes and shoes that are comfortable and attractive, the right size and type of material	91	39	57
39	The constant self-care I need to do to stop my lymphedema from getting worse	68	30	56
36	Traveling long distances by car, train, plane etc.	63	30	52
38	Limitations in hot weather/sun	79	44	44

Items 1-12 relate to the physical domain, 13–28 to the psychosocial domain, and 29–41 to the practical domain



# General discussion

The overall aim of this thesis was to develop a reliable, valid, responsive, and sensitive, lymphedema-specific HRQoL PROM and evaluate how persons with lymphedema experience the impact of the disease on HRQoL. The main results are discussed below.

## Development and psychometric testing of the LyQLI

Face- and content validity (1) were examined during the development procedure of the original PROM, in Australia. When our group adapted the LQOLI to Swedish conditions, face and content validity as well as criterion and cross-cultural validity were tested on the Swedish PROM, the SLQOLI (75). Further tests of the face, content, and criterion validity were performed on the developed PROM, the LyQLI (Paper I). Criterion validity (1) was performed through concurrent validity. The correlation between the three LyQLI domains and the two sum scores, PCS and MCS, in the SF-36, was low to moderate, which confirmed the concurrent validity (Paper I). We have, within this thesis, continued the validation process of the LyQLI (1).

When evaluating test–retest reliability (repeatability) we found a small systematic change, in all three domains, towards higher HRQoL in the second test (Paper I). Since the mean time between the two tests was 10 days, the proposed time gap of approximately 2 weeks was achieved. As previously mentioned, the gap was expected to be short enough for the condition to be stable and long enough to prevent recall (1). Possibly, the tendency to report higher HRQoL can be explained by the “expectations effect” and the desire to please the researcher. Also, the participants may have felt attentive and felt that they were seen by the researcher (103). Since the difference was found also in the overall experience of lymphedema and overall quality of life items 44 and 45, the change may also be explained by the fact that the investigation was performed during spring, with nicer weather and the prospect of vacations giving a more positive outlook (Paper I).

Further evaluation of the repeatability gave an estimated ICC of  $>0.87$  in all three domains, which can be considered good (1, 104). To measure internal consistency,

Cronbach's alpha coefficient was used. Cronbach's alpha in the physical and practical domain was 0.88, which is considered good. In the psychosocial domain, it was 0.92, which is considered excellent. The results confirm that the LyQLI is reliable and can be used in group comparisons (1, 104).

To evaluate responsiveness, which is an important property for a PROM intended to be used in longitudinal studies (1, 105), two methods were used. Internal responsiveness, which measures the ability to detect changes over a pre-specified time frame, and external responsiveness, which compares a PROM measurement to a corresponding clinical measurement (3). The results for internal responsiveness (Paper II) in the three domains show that, for the RP sample, the SRM was small to large; in the LS sample, the SRM values were moderate to large. This is considered to be an acceptable internal responsiveness (1, 101).

The external responsiveness was evaluated in two different calculations (Paper II). In the RP sample, the correlation between improvements in experienced tension/heaviness in the affected limb, measured with a VAS, was calculated, as were the improvements in HRQoL in the three LyQLI domains. We chose the experience of tension/heaviness to be used in the RP sample because this is subjective measure that is a well-known complaint in lymphedema (86). The correlations for tension were moderate to large, which indicates a good external responsiveness (101).

In the LS sample, the correlation between the reduction in volume in the affected limb and improvements in HRQoL in the three good domains, was calculated. We chose to evaluate the external responsiveness in the LS sample by testing the correlation between reduced volume in the affected limb and HRQoL, as the reduction in limb volume/excess volume post-LS is known to be high. We assumed that the volume reduction would influence HRQoL (37, 38, 94). However, the correlations were low all three domains. In this thesis, the correlation was also analyzed at the 12-month follow-up. However, our findings were the same, namely, that the correlation between the increase in HRQoL and the reduction in volume was low (101). These results agree with other studies in which the subjective experience of improvements did not correspond to the objective measurements of volume reduction which may indicate that limb volume is not the main concern among lymphedema patients (43, 106, 107). On the other hand, Brorson et al. found a correlation between reduction in excess volume in women with ULL and a number of scores in the Psychological General Well-Being index, the NHP, and the Hospital Anxiety Depression Scale (HADS) (37).

We used independent *t*-test and box plots to evaluate sensitivity of the LyQLI. The analysis showed that the LyQLI was able to discriminate between different patients groups. Especially the items in the practical domain had high sensitivity. Sensitivity is related to reliability, therefore, a sensitive PROM will most likely be reliable (1).

If most persons had felt a great impact of lymphedema on HRQoL and reported the maximum value, there might have been a ceiling effect. On the other hand, if most individuals had experienced little or no impact and rated the minimum value, there might have been a floor effect. This would have resulted in a PROM that was less sensitive. In the LyQLI there is a tendency towards a small floor effect. However, to have null scores in a lymphedema-specific PROM may be necessary to cover all possible symptoms and concerns a person with lymphedema may experience; otherwise, differences between groups of persons may be difficult to detect, which may result in low sensitivity (1). To our understanding the most important issue when measuring impact from a disease would be the ability to find all those persons with a lot of problems and concerns. Since we did not find any ceiling effects in the LyQLI, the PROM will be sensitive enough for this clinically very important group.

## Health-related quality of life in study participants

One of the aims of the thesis was to investigate HRQoL in persons with lymphedema regardless of which body part was affected and by what cause.

In Paper III, which was a cross-sectional study performed in two lymphedema clinics in different sites in Sweden, the main results show that 80% of the participants perceived a small impact from the disease on HRQoL. This result is interesting, since several studies have shown the opposite (55, 56, 59, 62, 69, 108, 109). However, 20% had a high impact on HRQoL, defined as one or more domains in the LyQLI with a score  $\geq 2.0$ . Results in Paper III (Table 3) show how heterogeneous this group was. This indicates how complex the impact of lymphedema can be and that it is not straightforward to estimate a person's HRQoL depending on personal characteristics, such as gender, age, time with lymphedema, or body affected. These results are similar to a study conducted by Lee et al., which observed that the person's experience of HRQoL did not correlate to the severity of the lymphedema (110). Persons with lymphedema are individuals with different problems and concerns related to the edema, and should be treated accordingly by health care.

However, when we compared the different subgroups, we found that participants with lymphedema in the lower limbs and genital region reported greater impact of the lymphedema on HRQoL than those with ULL or head and neck lymphedema. We have not found other studies in which different patient groups are compared in the same way as in the present study, probably because other lymphedema-specific PROMS are body part-specific. Our results also indicate that the impact may decrease with age. This can be explained by findings showing that, over time, individuals adapt to the illness, e.g., by making self-care a part of normal life (111,

112). There may also be other explanations and we need to further investigate problems and concerns that are specific to younger persons. We also found that persons who worked part-time experienced more impact on HRQoL than those working full-time. One explanation for this may be that they worked part-time because of impairments from the lymphedema. These results are in accordance with other studies (22, 113).

In Paper III, we compared the SF-36 scores of our participants with lymphedema to scores from the general Swedish population. The results showed that the persons with lymphedema had lower overall HRQoL, and the HRQoL was significantly lower in General Health, Vitality, and Social Functioning. Interesting to note is that the scores in the domain Bodily Pain were equal across the two samples. This result is comparable to Hoffner et al. who investigated HRQoL, using the SF-36, in women with ULL undergoing LS. They found that at baseline, these women had the same score in the domain Bodily Pain as the general Swedish population (58). In Paper III (Table 2), which shows the mean scores in each item in the LyQLI, pain had a relatively low mean score (= 1.03), indicating a low impact on HRQoL. On the other hand, when analyzing the impact of individual items on the participants (Tables 2 and 3) more than 50% of the participants in both the RP and the LS samples rated that pain had high impact on HRQoL, at baseline. After both interventions, the number of participants that had high impact from pain had decreased, and after 12 months, the improvement was 21% in the RP sample and 67% in the LS sample.

The issue that lymphedema may cause pain has been discussed, and the answers go in opposite directions. Lee and Chang (10) describe primary lymphedema as painless, at least initially, but add that pain can occur later, probably because of distension and swelling of the deep lymphatic system. Agarwal et al. argue that pain related to primary lymphedema is a problem that has been neglected (114). Chachaj et al. studied physical discomfort and pain in women with ULL compared to women without lymphedema and found that the women with ULL were more disabled and had significantly more pain (61). In their pilot study Jeong et al. (115) investigated pain and shoulder dysfunction in women with ULL after breast cancer treatment. The women were divided into three groups, no pain, pain with normal ultra sound (US), and pain with abnormal US. Thirty-nine percent had pain with an abnormal US. The diagnoses were, e.g., supraspinatus tear, biceps tenosynovitis, or acromioclavicular arthritis. These findings point to the importance of a correct diagnosis, so that not all pain will be attributed to the lymphedema. However, 32% had pain and normal US, suggesting that lymphedema possibly could be one of the origins of pain in this group (115).

## Health-related quality of life after rehabilitation program or liposuction

In Paper IV, two different interventions were evaluated using the LyQLI. The results show that both a conservative treatment (RP) and a surgical treatment (LS) were able to improve the participants' HRQoL. Since participation in the respectively study group was not randomized the results have been presented separately. We found differences between the two samples at baseline. In the LS sample the participants seemed to be younger, and the percentage of primary lymphedema and LLL was higher. The excess volume and the total volume in the affected limb were significantly larger in the LS sample and these patients also had had their lymphedema for a longer time. The LS sample also rated lower HRQoL at baseline compared to the RP sample, even though the difference was significant only in the practical domain. The percentage of the participants who had a high impact on HRQoL at baseline in one or more domains was 21% in the RP and 45% in the LS sample.

### **Changes after the rehabilitation intervention**

The results show a significant increase in HRQoL 1 month after the intervention in all three domains, and this improvement remained in the physical domain for up to 12 months of follow-up (Figure 6).

One of the reasons for the improvements could be that the participants in the RP sample were treated by a multidisciplinary team. D'Egidio et al. (116) argued that a multidisciplinary approach can help to repair and maintain impaired physical and psychosocial health, and in that way increase HRQoL. During the RP, the participants were treated both individually and in groups. The majority of the patients with lymphedema who were treated at the clinic at the same time as the study sample were cancer survivors with a long history of lymphedema, who had participated in an RP before. To meet and listen to other patients' experiences can be an important aspect of inpatient treatment (22). Other reasons for the increase in HRQoL may be that the RP included different kinds of exercises, which are known to increase quality of life (27, 117).

Both the excess volume and the affected limb volume were significantly reduced by the last day of the RP, but after 6 months, the edema began to deteriorate again (Table 2 of Paper IV). Similar results were seen in the VAS measurements. This findings may explain the increase in HRQoL at 1 month, and decrease in HRQoL at 12 months. On the other hand, when we analyzed the correlation between increased HRQoL and reduction in limb volume in the LS sample (Table 3 of Paper



II) the correlation was considered low (101), indicating that volume is of minor importance in relation to HRQoL.

Even though the majority of the participants in Paper IV had relatively low domain scores, 21% had at least one domain score  $\geq 2.0$ . These results are similar to the results in Paper III (Table 3 of Paper III). One month after the RP, the number of participants who experienced high impact decreased to 11%, which implies that the intervention improved HRQoL also in those participants with a number of problems and concerns. However, after 12 months the participants again reported increased impact of lymphedema on HRQoL. One explanation for this could be the lack of regular follow-ups. After the RP, the participants were expected to perform self-care and find out-door treatments by themselves. It is important that the compression garments are right both in compression class and in fitting, and for this regular visits are need. Depending on where the person lives, it can be hard to find a lymph therapist or a physiotherapist with adequate knowledge in the field.

When we analyzed the percentage changes in individual items (Table 2), the improvements of items in the psychosocial domain seemed to be most stable up to 12 months of follow-up. It is possible that all the information the patients were given and also the meeting with fellow patients, made them feel more secure and self-confident. The impact in items like *paying constant attention to my condition, not being able to do the things I used to enjoy, and concerns about negative changes in my appearance* changed from high impact to low impact in more than 40% of participants, and after 12 months the improvements were still >35%.

Three items within the practical domain, with high impact >40% at baseline but a decrease in impact to half after 1 month, followed by another increase again at the 12-month follow-up, were: *discomfort due to my lymphedema, feeling a loss of strength in the swollen part of my body, and movement difficulties due to my lymphedema*. These results may stress the importance of exercise for these participants and indicate that we, as health professionals, must put more effort into helping them to find the right sort of exercises. This also stresses the importance of follow-ups. Why did the participants HRQoL decrease again, and how can we better support this kind of patient?

Other items had high impact at baseline, and did not change so much at the follow-ups. This was particular the item: *the constant self-care I need to do to stop my lymphedema from getting worse*, in which 56% of the participants reported high impact. After 1 month, the impact had decreased a little, but by the 12-month follow-up it had increased again (Table 2). The negative impact of self-care on HRQoL has also been reported in other studies (26, 118). Since the time needed for performing self-care probably was the same after the rehabilitation, the impact would also been the same. However, by the 1-month follow-up the impact on HRQoL had decreased, perhaps because the participants felt encouraged directly

after the RP. The findings that so many felt that self-care impacts HRQoL highlights the importance of adequate and evidence based information, so we do not burden patients with unnecessary do's and don'ts.

One way to improve HRQoL can be to inform and educate persons with lymphedema about the disease and individualize the care in order to ease the burden as much as possible. In a literature review, Ostby and Armer (119) searched for studies evaluating adherence to self-care and self-management in women with ULL after breast cancer. They found e.g., that a person's perceptions of self-efficacy led to possibility to manage self-care. They confirmed that education is important and should include items such as lymphedema risks, patient-centered strategies, and motivational components (119). One qualitative study including interviews and focus groups, and aimed to identify factors that could ease the burden in managing self-care in patients with complex chronic diseases (111), reported that the patients had to use a variety of personal, social, and health care resources to ease the burden. The authors suggested that the burden of self-care could be lessened by turning self-care into a daily routine (111).

## **Changes after liposuction**

Our results for the LS sample show a significant increase in HRQoL 1 month after the intervention, and the improvement persisted up to 12 months in all three domains (Figure 7). At baseline, 45% of the participants experienced high impact on HRQoL in at least one of the domains. The number decreased after the intervention and during the following months, and at the 12-month follow-up only 5% had high impact on HRQoL. During the same period, the excess volume and the volume in the affected limb decreased, indicating a correlation. However, when calculating the Spearman's correlation coefficient, the result showed a low correlation (101) at both 1 and 12 months. When examining the results of individual participants (Paper II), we noticed that some participants with a large volume reduction rated low HRQoL, and vice versa. Similar results were found in a study by Yang et al., in which the patients' subjective report of improvement did not correlate with the objective reduction in excess volume (43).

We analyzed the percentage of participants in the LS sample who experienced high impact on HRQoL in 20 selected items (Table 3) at baseline and 12 months. Our findings were that in 13 out of 20 items the improvement was >70%. In two items from the physical domain, *swelling/tightness due to my lymphedema* and *a feeling of heaviness due to my lymphedema*, the improvements were high, and at the 12-month follow-up only 10% of the participants experienced high impact in these two concerns/problems. This was probably due to the almost total reduction in excess volume (Table 4 of Paper IV), easing the weight of the limb. Two other items in the

physical domain, *discomfort due to my lymphedema* and *movement difficulties due to my lymphedema*, in which the improvements were high, may also be related to the reduction in limb volume.

Other items that had high impact at baseline and then improved greatly were, feeling *anxious about whether or not the lymphedema will get worse*, *not being able to do the things I used to enjoy* and *feelings of frustration/feeling annoyed*, in the psychosocial domain. These improvements may not relate directly to the edema itself, but to the care that is usually included in LS, e.g., regular follow-ups with new compression garments, volume measurements, and other support from the professionals (120-122).

One item, in the practical domain, in which 90% of the participants experienced high impact at baseline, was: *finding clothes and shoes that are comfortable and attractive, the right size and type of material*. After 12 months, the result had improved, but 40% still reported high impact. One reason for this may be that LS is rarely performed on the feet (121), so even though the volume of the affected limb had been reduced, the foot might still have been swollen, with the problem of finding suitable shoes remaining.

## Strengths and limitations

In Papers I and II, we used several statistical methods to evaluate the psychometric properties of the LyQLI, which we believe is a strength of this thesis. When we started to develop and test the LyQLI we were not aware of any standards such as the COSMIN checklist (2). However, during our research we realized that the tests we have performed corresponded to six out of nine boxes in the COSMIN checklist, and that most items in these boxes could be positively answered by us (2). Even though we evaluated the most important components of research methodology, we did not always use the proposed statistical method. For example, we used ICC to evaluate test–retest reliability, while the checklist proposed using the weighted Kappa method for ordinal data (2). This could be considered a limitation of the thesis.

However, to our knowledge there is no consensus nor is there a uniform approach to evaluating ordinal data like Likert scales. Traditionally in HRQoL studies the statistics used to analyze data from HRQoL PROMs are often parametric, treating the data as continuing or at least as normally distributed (58, 64, 72, 97). To investigate which is the preferable method Donneau et al. analyzed responses from the generic PROM EORTC QLQ-C30, version 2, which uses a 4-point Likert scale, with methods for both longitudinal quantitative and longitudinal ordinal data (123).

The two treatments were compared and the results showed that both statistical methods revealed similar statistically significant differences. They concluded that the two statistical methods in this context were exchangeable (123). We did not use the proposed method to analyze responsiveness (2). Instead of employing ROC analysis, we used SRM, a well-used method recommended by Fayers and Machin (1).

When developing the LyQLI, the intention was to develop a PROM with potential to be used in persons with lymphedema, regardless of body part affected or of the cause of lymphedema. On the other hand, we also wanted to make a strategic selection, including patients with LLL, and ULL or head and neck lymphedema, based on frequency of patients presenting with these conditions at the clinics. The intention with this was to “create” a so-called “reference lymphedema (RL) population.” This methodology resulted in only 4% of participants in Papers I and III with lymphedema in the head and neck region. Consequently, the evaluation of validity and reliability, as well as examination of HRQoL in this patient group, may be limited.

Deng et al. (23) created a PROM especially for persons with lymphedema in the head and neck region after cancer treatment. Their PROM includes items common to most persons with lymphedema, but also more specific items, e.g., eating, swallowing, and talking problems, items which are absent in the LyQLI. The lack of specific head and neck-associated items may be a limitation of the LyQLI. On the other hand, most items in the psychosocial domain e.g., *concerns about negative changes in my appearance, negative changes in how I see myself, and embarrassed by lymphedema/compression garments*, and in the practical domain e.g., *normal daily activities (e.g., doing housework, sports- and hobby activities)* and *the constant self-care I need to do to stop my lymphedema from getting worse*, may have an impact also on persons with head and neck lymphedema. For this reason, different instruments may be required for the evaluation of HRQoL in patients with lymphedema in the limbs compared to the head and neck region. Alternatively, using the LyQLI together with a shorter tool with head and neck-specific items, such as talking, salivation, and swallowing, may also be sufficient. Disease-specific PROMs ought to include symptoms (1). Since symptoms differ depending on where in the body the lymphedema occurs, including all lymphedema symptoms would make a PROM too comprehensive, and would lead to inclusion of several symptoms that many persons do not experience at all. This may increase the time to complete it. When we shortened the PROM, the median time to complete it decreased from 30 to 6 minutes, which we considered to be a strength of the LyQLI.

The tests for responsiveness and sensitivity were evaluated in participants with LLL or ULL (Paper II). When we designed the study, we intended to test the internal responsiveness of the LyQLI in an intervention, with great results in volume

reduction (LS). A further aim was to test external responsiveness by correlating the change in HRQoL to the change in lymphedema volume, and also to experience of tension and heaviness. For this reason, we only included persons with lymphedema in the limbs, in whom it was possible to measure volume. A strength of this thesis is that the LyQLI had been used in different lymphedema samples and in both cross-sectional and longitudinal studies. However, a limitation may be the relatively small study sample. Further limitations are the skewed age- and gender distribution, with older women over-represented. A strength may be that there were few missing items and also few drop-outs. To further ensure the reliability of the longitudinal study and to follow the results over time the LOCF was used for imputation (102). Another strength is that the three countries involved demonstrated the possibility of using the LyQLI in international studies.

## Ethical considerations

Before a study involving human beings is performed it has to be approved by an ethics research committee in accordance to the Helsinki Declaration (78). This declaration became Swedish law on 1 January 2004 (124), since which date, a potential participant must be provided with adequate information about a study and its potential consequences for the persons involved. The researcher has to obtain their written approval before they can be included in the study and they can withdraw at any time without giving any reason.

In the present thesis, participants were included in three different study samples and ethical approval was obtained for the Swedish and Australian parts of the study. In Scotland, the researcher had an agreement regarding distribution of PROMs in connection to surgery without extra ethical approval needed. However, the participants are always asked for informed consent. This kind of arrangement seems to simplify the research process. On the other hand, there is a risk that participants will be inundated with questionnaires. It is important to bear in mind that, whereas the primary purpose of medical research is to generate new knowledge, this goal should never take priority over the rights and interests of the individual study participant (78).

Considering this specific HRQoL PROM, the LyQLI, there are items in it, e.g., about sexuality, and finance, that could be embarrassing to answer and might therefor generate internal drop-outs. However, in the present thesis this was not the case. The PROM is relatively comprehensive, which can be a burden for the participant. For this reason, it was important to remind the participants of their possibility to withdraw from the study.

# Conclusions

The aim of this study was to reduce the 188-item SLQOLI to a shortened, clinically useful instrument and test it for reliability and validity. The LyQLI is shorter containing 45 items, and the median time to complete it is 6 minutes. The PROM now is available for use in Sweden. The results from the cross-sectional study (Paper III) and the longitudinal study (Paper IV) reveal its applicability.

The statistical properties of the LyQLI have been properly tested and analyzed and the PROM is valid and reliable for use in cross-sectional studies in persons with lymphedema regardless of the affected body part. The LyQLI demonstrates good test–retest reliability and internal consistency reliability and moderate face and concurrent validity.

The sensitivity and internal responsiveness of the instrument is good, but external responsiveness is low to moderate. The LyQLI is responsive and sensitive enough to be used in longitudinal studies in persons with lymphedema in the limbs.

Primary findings of this thesis are that the participants experienced lower overall HRQoL, measured using the SF-36, compared to the general Swedish population. On the other hand, most participants reported a low impact of lymphedema on HRQoL, with 20% experiencing a high impact. In some subgroups, such as in persons with LLL, younger persons, persons working part-time, and persons with large lymphedema dominated by adipose tissue, the impact were higher, which is important for the health care system to recognize.

Treatment with conservative rehabilitation in moderate lymphedema, or LS combined with CCT in severe lymphedema, increases HRQoL in the persons with LLL or ULL. The improvements were found across all three domains of the instrument. The results persisted in the physical domain for up to 12 months post-RP and in the physical, psychosocial, and practical domains post-LS. In the LS sample, the HRQoL even continued to increase up to the 12-month follow-up. At baseline, 45% of the participants in the LS sample experienced high impact of their lymphedema on HRQoL, but after 12 months no more than 5% still had that experience, which shows the effectiveness of this treatment.



# Future research

In its current structure, the LyQLI can be used to evaluate HRQoL in clinical trials, before and after interventions, in persons with lymphedema in the upper or lower limbs. However, further studies are needed to evaluate the external responsiveness, since we judge it to be low to moderate. Before using it to evaluate interventions in persons with lymphedema in other parts of the body e.g., in the genitals, breast, trunk, and head and neck regions, further tests of the LyQLI's responsiveness and sensitivity should be performed in these groups.

In future research to improve the LyQLI, a shorter form may be helpful. Since the LyQLI is fairly comprehensive, including 45 items, it can be a burden for study participants to complete, with risks of drop-out. In our research, approximately the same 20 items had the highest impact on HRQoL in different patient samples. This clinical analysis, together with confirmatory factor analysis may be a way to decide which items and how many dimensions (factors) should be included in a shorter PROM (1).

To further improve the shorter PROM, it may be suitable to correlate its items to the ICF categories which were included in the Lymphedema Core Sets (51). When the LyQLI was developed no such core sets were available. However, when going through the items of the LyQLI and the two Lymphedema Core Sets, we noted that the similarity is notable, and almost all the common categories from the two core sets are represented in the LyQLI in one way and or another. To include the categories may even further simplify the international use of the shorter LyQLI.

More studies should be performed to investigate the impact of lymphedema on HRQoL, especially in younger persons, persons with head and neck lymphedema, and persons with LLL and genital lymphedema but also in persons who want to work full time, but struggle to because of the lymphedema. More effort and research is needed to identify, understand, and support these groups with severe lymphedema-related problems. Research, preferably using qualitative interviews, will lead to a better understanding of their suffering.

In this thesis, RP improved HRQoL, but after 1 year the impact of the disease on HRQoL had again increased. More research is needed to find out why this happened, and what we as professionals in health care can do to optimize HRQoL in persons with lymphedema, when LS is not an option.





# Clinical implications

In the clinic, the LyQLI may be used by healthcare professionals to establish each patient's needs and problems and thus make it possible to individualize his or her support. The patient can complete the PROM at home before the visit or fill in the form together with the health professionals and this can serve as a beginning to further education and treatments. Once the patient has defined in which way he or she is affected by the lymphedema, it is easier to determine which concerns and problems he or she needs support with. Together the patient and the health care professional can use the LyQLI to find measurable goals for exercise and self-care, and thus increase the patient's HRQoL.

The results of this thesis show that performing self-care can be burdensome and can impact HRQoL. For this reason, it is important to decide together with the patient which parts of self-care are necessary in order to maintain good health, and which parts are redundant. How comprehensive can the self-care be, without high impact on HRQoL?

The answers in the LyQLI can also be used to evaluate HRQoL after a period of treatment (both indoor and outdoor), for patients with lymphedema in their limbs, after different follow-up periods.



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# Appendix



# Lymphedema Quality of Life Inventory (LyQLI)

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This questionnaire is concerned with the way lymphedema may affect your quality of life and activities of daily living.

You may have experienced very mild lymphedema, moderate or severe symptoms. You may have lived with your symptoms for a short or long period of time.

**Please answer these questions only as they concern your lymphedema**

The questionnaire consists of three parts

- Physical
- Psychosocial
- Practical

Please think about your Lymphedema and your Quality of Life during **the past four weeks**. When it comes to questions that depend on seasons, think about the **past year**.

For each question circle the answer that best matches your experiences. **Try to answer all questions. If a question does not seem to apply to you, please circle the choice that says "None"**

<b>Physical concerns due to lymphedema</b>		<b>How much do these concerns affect your quality of life?</b>			
<b>1</b>	Pain/aches due to my lymphedema	None	A little bit	Somewhat	A lot
<b>2</b>	Discomfort due to my lymphedema	None	A little bit	Somewhat	A lot
<b>3</b>	A feeling of heaviness due to my lymphedema	None	A little bit	Somewhat	A lot
<b>4</b>	Pins and needles/numbness due to my lymphedema	None	A little bit	Somewhat	A lot
<b>5</b>	Burning sensation/heat due to my lymphedema	None	A little bit	Somewhat	A lot
<b>6</b>	Swelling/tightness due to my lymphedema	None	A little bit	Somewhat	A lot
<b>7</b>	Skin problems due to my lymphedema	None	A little bit	Somewhat	A lot
<b>8</b>	Difficulty sleeping due to my lymphedema	None	A little bit	Somewhat	A lot
<b>9</b>	Movement difficulties due to my lymphedema	None	A little bit	Somewhat	A lot
<b>10</b>	Feeling physically aware of my lymphedema all the time	None	A little bit	Somewhat	A lot
<b>11</b>	Feeling a loss of strength in the swollen part of my body	None	A little bit	Somewhat	A lot
<b>12</b>	Infection (e.g. cellulitis, erysipelas)	None	A little bit	Somewhat	A lot

<b>Psychosocial concerns due to lymphedema</b>		<b>How much do these concerns affect your quality of life?</b>			
<b>13</b>	Feelings of frustration/feeling annoyed	None	A little bit	Somewhat	A lot
<b>14</b>	Feeling anxious about whether or not the lymphedema will get worse	None	A little bit	Somewhat	A lot
<b>15</b>	Embarrassed by lymphedema/compression garments	None	A little bit	Somewhat	A lot
<b>16</b>	Negative changes in how I see myself	None	A little bit	Somewhat	A lot
<b>17</b>	Feeling discouraged	None	A little bit	Somewhat	A lot
<b>18</b>	Not being able to do the things I used to enjoy	None	A little bit	Somewhat	A lot
<b>19</b>	Concerns about when to seek medical attention	None	A little bit	Somewhat	A lot
<b>20</b>	Paying constant attention to my condition	None	A little bit	Somewhat	A lot
<b>21</b>	Concerns about how my lymphedema affects my existing relationships	None	A little bit	Somewhat	A lot
<b>22</b>	Concerns about how lymphedema could affect new relationships	None	A little bit	Somewhat	A lot
<b>23</b>	Negative changes in my feelings about intimacy/sexuality	None	A little bit	Somewhat	A lot
<b>24</b>	Feeling uncomfortable/embarrassed while doing sports and hobbies	None	A little bit	Somewhat	A lot
<b>25</b>	Feeling uncomfortable/embarrassed when attending social activities with friends and at work	None	A little bit	Somewhat	A lot
<b>26</b>	Having to ask for help in different situations	None	A little bit	Somewhat	A lot
<b>27</b>	Concerns about negative changes in my appearance	None	A little bit	Somewhat	A lot
<b>28</b>	Having to answer questions about my lymphedema	None	A little bit	Somewhat	A lot

<b>Practical concerns due to lymphedema</b>		<b>How much do these concerns affect your quality of life?</b>			
<b>29</b>	Personal activities of daily living (e.g. dressing, combing hair, foot care)	None	A little bit	Somewhat	A lot
<b>30</b>	Normal daily activities (e.g. doing housework, sports- and hobby activities)	None	A little bit	Somewhat	A lot
<b>31</b>	Employment activities	None	A little bit	Somewhat	A lot
<b>32</b>	Learning to do things differently	None	A little bit	Somewhat	A lot
<b>33</b>	Having less energy to do activities (e.g. personal, normal daily or employment)	None	A little bit	Somewhat	A lot
<b>34</b>	Financial costs of managing my lymphedema (e.g. clothes, shoes, treatments, garments)	None	A little bit	Somewhat	A lot
<b>35</b>	Finding well-functioning compression garments (e.g. stockings, sleeves, gloves)	None	A little bit	Somewhat	A lot
<b>36</b>	Traveling long distances by car, train, plane etc.	None	A little bit	Somewhat	A lot
<b>37</b>	Finding clothes and shoes that are comfortable and attractive, the right size and type of material	None	A little bit	Somewhat	A lot
<b>38</b>	Limitations in hot weather/sun	None	A little bit	Somewhat	A lot
<b>39</b>	The constant self-care I need to do to stop my lymphedema from getting worse	None	A little bit	Somewhat	A lot
<b>40</b>	Obtaining information about how to manage my lymphedema	None	A little bit	Somewhat	A lot
<b>41</b>	Being prepared for emergencies (e.g. always having a script for antibiotics)	None	A little bit	Somewhat	A lot

**42.** In terms of your lymphedema, has this been a typical four week period for you?  
**Yes ( ) No ( )**

**43.** If you answered "No" to the question above, has this period been (tick one)

**Much Worse ( ) Worse ( ) Better ( ) Much Better ( ) than usual**

**44.** Please think about how your lymphedema has affected you in the past four weeks and circle the number below that best matches your experience with lymphedema.

**0**

**1**

**2**

**3**

**Very bad**

**Very good**

**45.** Taking all parts of your life into consideration, how would you describe your quality of life in the past four weeks? Please circle the number below that best matches your overall quality of life.

**0**

**1**

**2**

**3**

**Very bad**

**Very good**

**Thank you for your time completing this questionnaire!**





Paper I





# Lymphedema Quality of Life Inventory (LyQLI)-Development and investigation of validity and reliability

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## Abstract

**Purpose** The purpose of this study was to reduce the 188-item Swedish Lymphedema Quality of Life Inventory (SLQOLI) to an abbreviated, clinically useful version (phase 1) and to test it for reliability and validity (phase 2).

**Methods** In phase 1 correlation analysis, factor analysis, content validity assessment and expert panels were used to reduce the number of items in SLQOLI to 45 items, which was named, Lymphedema Quality of Life Inventory (LyQLI). In phase 2, LyQLI was sent to 200 patients with lymphedema. 126 patients completed the questionnaire twice to determine stability of the instrument over time. SF-36 was sent to the patients once, correlations between the three domains in LyQLI and the two sum scores Physical Health (PCS) and Mental Health (MCS) in SF-36 were used to assess concurrent validity.

**Results** The 188-item SLQOLI was reduced to 45-item LyQLI. Four domains were reduced to three: physical, psychosocial and practical. Reliability estimates using ICC for the physical and psychosocial domains were 0.88 ( $p < 0.01$ )

and 0.87 ( $p < 0.01$ ), for the practical domain 0.87 ( $p < 0.01$ ). Cronbach's alpha coefficients for the three domains were 0.88, 0.92 and 0.88, respectively. The physical domain correlated highly significantly with PCS, psychosocial highly significantly with MCS and practical equally highly significantly to both PCS and MCS. Using skewness coefficients, small floor effects in the items were found.

**Conclusion** The shorter LyQLI demonstrated good reliability and validity with potential use to assess quality of life in clinic settings and in further cross-sectional studies of patients with lymphedema.

**Keywords** Health-related quality of life · Lymphedema · Disease-specific instrument · Reliability · Validity

## Introduction

Lymphedema (LE) is defined as swelling of one or more parts of the body because of impairments in lymph transport

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capacity based on malfunction or malformation of the lymphatic system. Without adequate treatment, LE can result in complications such as massive edema, lymphangitis/cellulitis, impaired limb function, psychosocial disability and even malignant complications [1–4]. LE is most often a chronic condition which requires lifelong treatment including conservative treatment such as daily wrapping with non-elastic bandages and/or compressive garments, manual lymphatic drainage, intermittent pneumatic [2–5] and in some cases surgical treatment [6] or lymphatic venous anastomosis [7].

LE can be classified as primary or secondary LE. The etiology of primary LE is not well known; however, in children nearly all LE is classified as primary [1]. Secondary LE is much more frequent [3]. It can result from obstruction or disruption of the lymphatic system, which can occur as a consequence of malignancy, surgery, radiation therapy, trauma, inflammation, or infections such as filariasis. The resulting mechanical insufficiency can lead to accumulation of fluid in the interstitial tissues [8]. In Western societies, the most common cause of secondary LE is cancer treatment [3]. LE has been described as one of the most significant survivorship impairments after the surgical treatment of breast cancer. Apart from breast cancer, secondary LE also has been reported as a consequence of treatment for several solid tumors, including melanoma, head and neck, gynecological and genitourinary malignancies and sarcomas [8].

Traditionally, LE has been viewed as a relatively unimportant complication of essential life-saving treatment for cancer. However, recently it has been shown that it can cause physical symptoms such as pain and discomfort, impaired physical and social functions and emotional effects and is now recognized as a complex problem that can strongly influence patients Health-Related Quality of Life (HRQL). Patients with LE may experience depression and some report that coping with LE is more distressing than coping with the cancer itself [9]. Therefore, LE may have severe consequences in terms of the patient's functional, mental, practical and social aspects of life [9–11].

This paper uses the concepts health, Quality of life and HRQL to explore the problems that patients with LE encounter. The World Health Organization (WHO) definition of Health was signed in 1946, and in 1993 WHO put forward a definition of quality of life linked to health “The perception by individuals 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” [12]. To distinguish between quality of life in its more general sense and the requirements of clinical medicine and clinical trials, the term HRQL is used [13]. HRQL can be defined in many different ways, but in 1992 an international Board of Advisors in south Caroline stated a consensus that four fundamental dimensions including physical, mental/psychological and social health, as well as global perceptions

of function and well-being, were essential to any HRQL instrument. They also stated study participants to be the primary source in any HRQL investigation, if possible [14].

A number of questionnaires have been used to assess HRQL in patients with LE, with most instruments being either generic or cancer specific. Several researchers have focused on HRQL in patients after breast cancer treatment. They have used cancer-specific instruments such as “EORTC QLQ-BR23” [15] and “Functional Living Index-Cancer” [16] or generic instruments such as Medical Outcome Study-36 item short form (SF-36) [17–19] and the “Nottingham Health Profile Part 1” (NHP-1) [20, 21]. The researchers found that breast cancer patients with LE were more disabled, experienced poorer HRQL and had increased psychological distress compared to survivors without LE [22–25], but they also often found that these instruments were not sensitive enough [26]. A few studies had examined HRQL in patients with non-cancer-related LE. Bogan et al. [4] used a qualitative approach and found that people with non-cancer-related LE in lower limbs score their HRQL as low. Studies with quantitative approaches often used generic instruments with similar results, but they also concluded that the lack of disease-specific approach is a problem [9, 27].

In recent years, there has been more interest in developing LE-specific HRQL tools. The “Upper limb lymphedema 27” (ULL-27) is specially designed and validated for assessing HRQL in patients with upper limb LE [28]. The “Lymphedema functioning, disability and health questionnaire” (Lymph-ICF) also focuses on upper limb LE. It was tested for reliability and validity in Belgium [29]. Augustin et al. [30] developed and validated a disease-specific HRQL questionnaire for patients with LE in lower limbs (FLQA-I) using a German sample. In UK, Keeley et al. [31] have designed and validated an assessment tool “Lymphedema quality of life” (LYMQOL) that consists of two questionnaires, one for patient with upper limb edema and one for lower limb edema; the second focuses on chronic edema in general.

Due to the special symptoms and problems of the patients with LE, it is important to use a questionnaire developed especially for this group [9]. The only disease-specific HRQL instrument that assesses HRQL in patients with different kinds of LE that is tested for validity and reliability thus far is the Swedish Lymphedema Quality of Life Inventory (SLQOLI) [32], originally developed and tested for validity in Australia, presented at the Australian Lymphology Association 5th biennial conference Brisbane, Australia, 2004. When adapted for use with Swedish patients, content and face validity was assessed by a panel of experts ( $n = 11$ ) and patients with different types of LE ( $n = 16$ ). During this process, three items were added.

The SLQOLI consists of 61 perceived concerns (items) structured as four domains: physical, emotional, social and

**Table 1** Swedish Lymphedema Quality of Life Inventory consists of three questions each having four answer alternatives

How much do these concerns affect your quality of life?	No effect	A little	A bit	A lot
How many changes have you had to make in your everyday life because of these concerns?	No changes	Few	Some	Many
How difficult have these changes been for you?	Not difficult	Some	Very	Extremely

practical concerns (Table 1). Respondents are asked to think about these concerns over the past 4 weeks and respond to three questions: “How much do these concerns affect your quality of life?”, “How many changes have you had to make in your everyday life because of these concerns?” and “How difficult have these changes been for you?” Responses to these questions are structured as a 4-point Likert scale ranging from 0 (no effect on HRQL) to 3 (a large effect on HRQL). The questionnaire also includes four items about general HRQL: two of them are structured as a 10-point Likert-type scale and one is an open-ended item.

Test–retest reliability of the questionnaire was assessed using 58 Swedish patients with LE and demonstrated moderate reliability and was judged to be valid [32]. However, the instrument was lengthy, creating a burden for patients to complete. The time needed to complete the form varied from 15 min to 2 h and 40 min (median = 30 min). Therefore, it was deemed appropriate to develop and test an abbreviated instrument based on the SLQOLI for use in both clinical and research settings. The aim of this study was first to reduce the SLQOLI to an abbreviated, clinically useful version while at the same time trying to keep the original structure (phase 1) and then test it for reliability and validity (phase 2).

## Methods

### Phase 1

#### *Development of the abbreviated SLQOLI*

Results from the reliability testing of the SLQOLI were used for the item reduction phase of the study. Subjects included 50 consecutive patients from each of the LE Units at Skåne University Hospital, Lund and the Red Cross Hospital, Stockholm, Sweden. Fifty-eight patients completed the SLQOLI twice [32].

We examined whether it was necessary to include all three questions with respect to the 61 items.

Factor analysis, a principal component analysis followed by varimax rotation, was used to analyze the correlations among items in response to the first question. Spearman’s rank correlation coefficients ( $r_s$ ) [33] were used to examine correlations between responses to the three questions. Factor analysis was performed first on each domain separately. Because some items were phrased in similar ways across the

emotional and social domains, a factor analysis was also performed with these two domains merged.

Results of the factor analysis were examined by two physiotherapists with long clinical practice and experience within the lymphology area, considered to reduce, merge and if relevant also to carefully rename the items. The reduction process and the results were presented to a LE expert group, including four physiotherapists, four enrolled nurses, two occupational therapists and a social worker with extensive experience working with patients with LE and knowledge of questionnaire design. Nine of the expert group members were also lymph therapists. All were asked to check and relate their experience of their patient’s relation to lymphedema and quality of life.

The outcome of phase 1 was a 45-item LyQLI.

### Phase 2

#### *Reliability and validity testing of the abbreviated scale*

A consecutive sample of 200 outpatients (100 per study site) was selected from the registers of the LE Units at Skåne University Hospital, and from the Red Cross Hospital, Solna, Sweden. Adults, 18 years and older, diagnosed with LE for at least 6 month, and who understood Swedish verbally and in writing, were included.

Strategic selection was used to recruit the following subgroups: secondary LE in the upper limbs/head and neck ( $n = 80$ ), secondary LE in the lower limbs/genitalia ( $n = 60$ ) and primary LE ( $n = 60$ ). The selection is consistent with the incidence of LE patients at both clinics.

Patients’ with secondary upper limbs LE had to have volume differences of 10 % or more [34]. Cases of lower limb edema that had developed secondary to medical conditions such as cardiovascular and renal disease, venous thrombosis and end-stage recurrent malignancy, patients with mental disease and in-door patients involved in intensive LE treatment during the test period were excluded. In Sweden, intensive LE treatment is often performed in periods of 1–3 weeks, depending on the severity of the LE. Treatments include: daily wrapping with non-elastic bandages, manual lymphatic drainage, skin care, physical training, intermittent pneumatic [2–5].

**Procedure** The 45-item LyQLI (Appendix) was mailed to the patients, along with a consent form, a demographic

questionnaire and the SF-36. All persons gave their informed consent prior to the inclusion, and they were informed that identity details should be omitted. A reminder letter was sent after 1 week to patients who had not responded. Directly after the first response was received, the questionnaire was sent again to achieve no more than a 2-week time gap between the two tests. It was expected that the time gap would be long enough to avoid memory effects. No additional treatment should be given within this time frame to interfere with stability over time testing. If the patient did not reply to the second test, a reminder was sent after 1 week. Patients who still did not respond to the second test were contacted by telephone, to make sure that they had received the questionnaire. The test period was April–June 2012.

An additional nine patients answered the LyQLI while attending the LE Unit in Solna and the length of time for completion of the instrument was recorded.

**Statistical analysis** Systematic disagreement between the two tests occasions was evaluated using the relative position (RP) [35]. For each item, the cumulative frequencies from the second test were plotted against the cumulative frequencies from the first test; the points were combined to ROC curves [35]. Deviations from the diagonal line were signs of systematic changes. The ROC curves belonging to the same domain were plotted with one diagram for each domain. The Wilcoxon signed rank test was used to test whether the disagreements measures RP within each domain differed statistically significant from zero ( $p < 0.05$ ).

Test–retest reliability was evaluated for each of the three domains using the Intraclass Correlation Coefficient (ICC) together with a 95 % confidence interval, using two-way random effect models with absolute agreement. We pre-determined that patients with more than five missing responses were considered dropouts and their data would not be used. We further determined that for respondents with fewer than five missing response, a mean score for each domain for each patient would be imputed missing values. Test–retest reliability was evaluated by calculating possible systematic changes in the domain scores. For each domain, the differences in score between the two test occasions were calculated and tested using student's  $t$  test. Cronbach's alpha coefficients were calculated to estimate the internal consistency of each of the three domains.

Concurrent validity was assessed using Spearman's rank correlation coefficients ( $r_s$ ) [36] to assess concordance of scores of the three domains of LyQLI and the scores of the two sum scores Physical Health (PCS) and Mental Health (MCS) in the SF-36 [18]. Possible floor and ceiling effects in the items were studied by examining skewness characteristics. A skewness value close to zero was used to indicate that there was neither a floor nor a ceiling effect.

IBM SPSS Statistics 20 was used for statistical analysis and significance values of  $<0.05$  were pre-set to indicate statistical significance.

The study was approved by the Research Ethics Committee, Lund University, Sweden, Dnr 2012/146 in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

## Results

### Phase 1

#### *Development of the abbreviated SLQOLI*

Results from the Spearman's rank correlation coefficient tests revealed high correlations between responses to the first question concerning HRQL and the two other questions about these items ( $r_s > 0.60$  for all four domains, see Table 2). Therefore, second and third questions were judged to be redundant and were removed.

As a result of the factor analysis and the experience based reduction, the four domains (physical, emotional, social and practical) were reduced to three (physical, psychosocial and practical). In the physical domain, the number of items was reduced from 17 to 12 (Fig. 1). For the emotional and social domains, the number of items was reduced from 26 to 16 and the two domains were merged to one, relabeled the psychosocial domain (Fig. 2). The practical domain was reduced from 18 to 13 items (Fig. 3), and the open-ended item was removed because responses indicated that the item did not provide new information. In total, the number of items was reduced from 188 to 45. A small modification in the sequence of the items at the last page was made, and the two items with 10-point Likert-type scale response options were changed to a 4-point Likert scale to avoid confusion.

The LE expert group and the social worker judged the abbreviated scale to have good face validity and the new questionnaire, with vertically arranged items on an A4 paper to be an improved format resulting in the abbreviated Lymphedema Quality of Life Inventory (LyQLI) (see Appendix).

### Phase 2

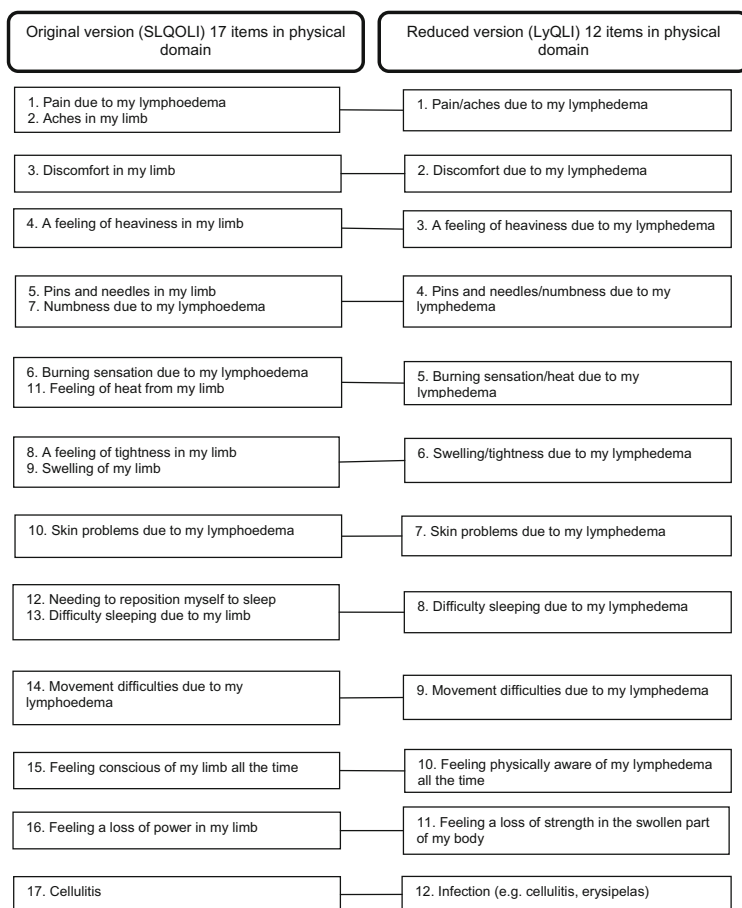
#### *Reliability and validity testing of the abbreviated scale*

Two hundred questionnaires were mailed to patients. One patient notified that she no longer had a LE and was excluded because she did not fulfill inclusion criteria. One hundred and thirty-one patients agreed to participate of them 126 patients (97 %) completed test 1 and test 2, and their characteristics are shown in Table 3. Seventy-three

**Table 2** Frequency distributions of the correlations between the first question and the two others (Table 1)

Domain	$r_s = 0.60-0.69$	$r_s = 0.70-0.79$	$r_s = 0.80-0.89$	$r_s = 0.90-1.00$	Total <sub>s</sub> 0.6-1.00
Physical (%)	12	41	20	26	100
Emotional (%)	6	28	44	16	100
Social (%)	0	20	25	55	100
Practical (%)	0	11	56	33	100

**Fig. 1** Items in the physical domain that remained were reworded or were merged

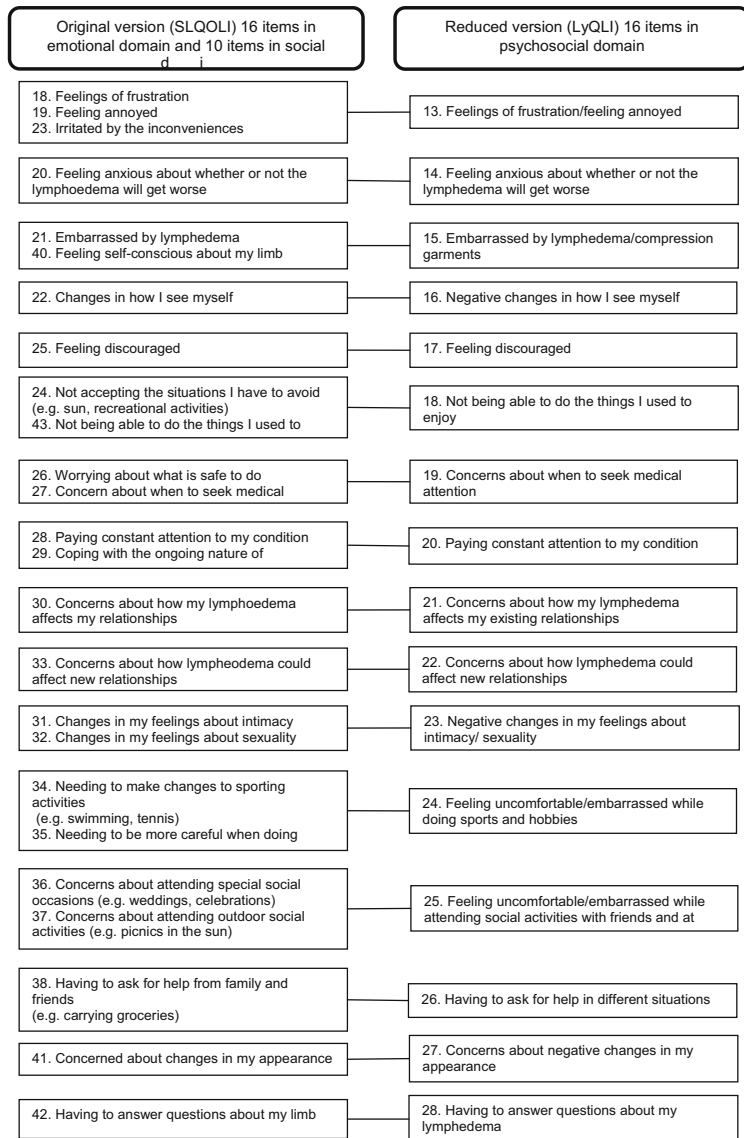


patients did not complete the two questionnaires for different reasons shown in Fig. 4. Characteristics for these dropouts are shown in Table 3. Median time between the two completed tests was 10 days (range = 1-144 day, 25th to 75th percentile: 7-14 days). Median time to complete the form was 6 min (range = 5-11).

There were few internal missing values. At the initial testing time, the maximum number of missing values for physical/psychosocial/practical domains was 4, 1 and 2, respectively; and for the retest responses, the number of missing values for these three domains was 3, 2 and 5. For all 41 items, the percentage of missing items for the



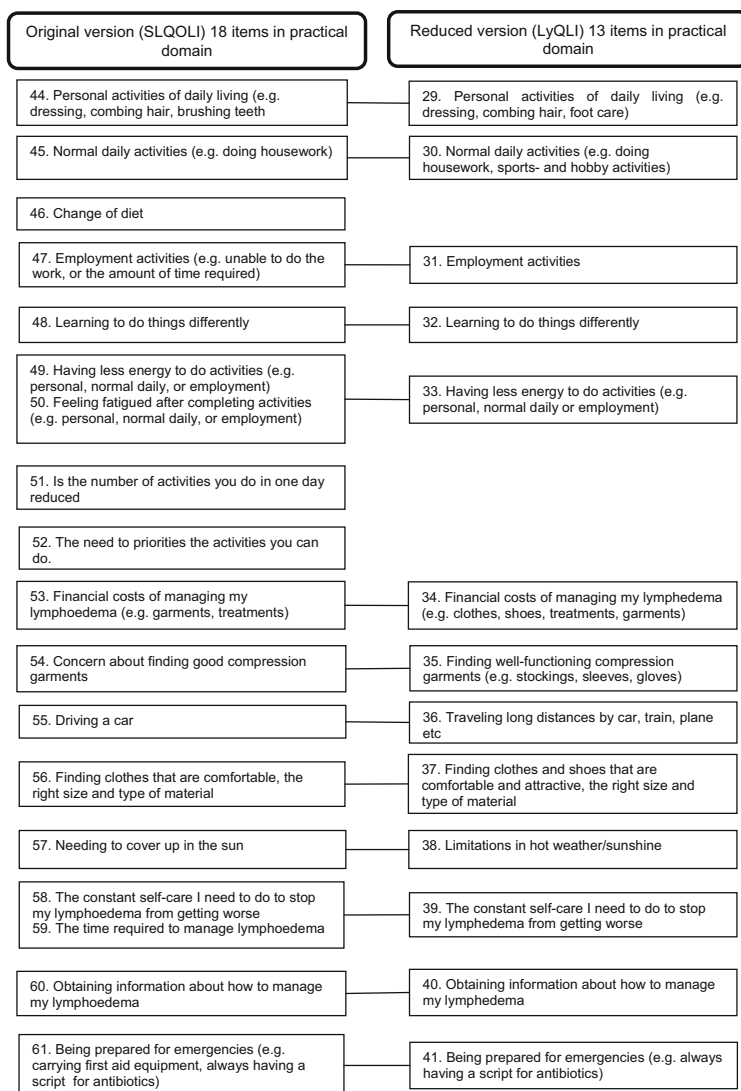
**Fig. 2** Items in the emotional and social domains that remained were reworded or were merged into the psychosocial domain



patients varied between 0 to 14.6 % for both tests, 25th to 75th percentile: 0.0–0.2 % for test 1 and 0.0–0.0 % for test 2. For these patients, the mean score was imputed. Given the small number of internal missing values, there were no missing domain scores.

Systematic disagreements between test 1 and test 2 were calculated using the disagreement measure RP and are illustrated by receiver characteristic curve (ROC) for items belonging to the same domain (Figs. 5 6 7) [35]; the mean RP in the physical domain was  $-0.059$ , in the psychosocial

**Fig. 3** Items in the practical domain that remained were reworded, reduced or merged



−0.031, and in the practical −0.035. For all three domains, a small systematic statistical significant change was seen toward higher HRQL.

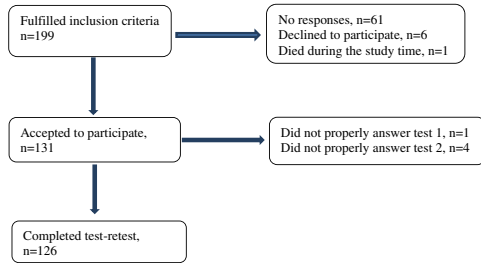
Assessment of responses indicated that there was a statistically significant change in reporting between tests one and two, with lower scores for each domain at test 2 (Table 4). All three mean differences differed significantly from zero. This

difference was also found for the overall quality of life items 44 and 45. In the physical and psychosocial domain, ICC was 0.88 ( $p < 0.01$ ) and in the practical 0.87 ( $p < 0.01$ ). Cronbach's alpha coefficients of 0.88, 0.92, and 0.88 were obtained for each of the three domains, respectively.

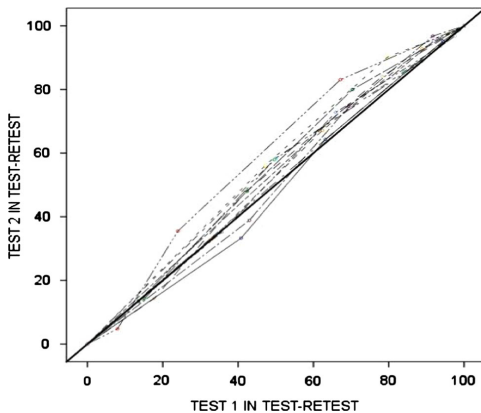
One hundred and thirty patients completed test 1, all of them except for one also completed SF-36. There were four

**Table 3** Characteristics of patients that participated ( $n = 126$ ) and dropouts ( $n = 74$ )

Characteristics	Test–retest	Dropouts
Age, years, median (range)	62 (19–92)	58 (20–91)
Year with lymphedema, median (range)	7 (0–70)	6 (0–87)
Women/men, no (%)	110/16 (87/13)	58/16 (78/22)
Lymphedema secondary/primary, no (%)	93/33 (74/26)	50/23 (68/32)
Edema of the lower limbs/upper limbs/others, no (%)	70/50/6 (55/40/5)	45/23/5 (62/31/7)

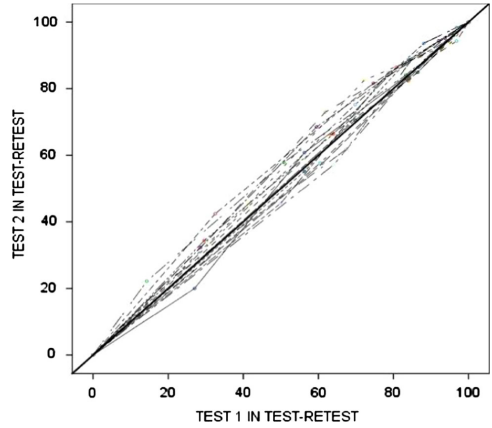


**Fig. 4** Flow chart of participants in test–retest of the Lymphedema Quality of Life Inventory

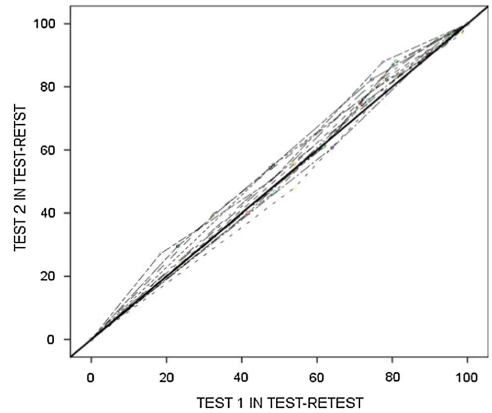


**Fig. 5** ROC curve for the physical domain, each *line* represents one item and the paired answers in test–retest on group level

(3 %) missing values in each of PCS and MSC. The correlation between the score in the three domains of LyQLI and the two sum scores PCS and MCS in SF-36 is shown in Table 5. Correlations are negative because high values in LyQLI indicate low HRQL which is the opposite for



**Fig. 6** ROC curve for the psychosocial domain, each *line* represents one item and the paired answers in test–retest on group level



**Fig. 7** ROC curve for the practical domain, each *line* represents one item and the paired answers in test–retest on group level

SF-36. Therefore, results provide evidence of concurrent validity of the LyQLI.

Table 6 shows the distribution of skewness characteristic, whether they are not significantly different from zero and how many that is positively and negatively skewed. Results reveal a tendency toward a small floor effect.

**Discussion**

The purpose of this study was to reduce SLQOLI to develop and test a shorter instrument for use in clinical

**Table 4** Test–retest scores and differences in the Lymphedema Quality of Life Inventory ( $n = 126$ )

Domain	Test 1 mean (95 % CI)	Test 2 mean (95 % CI)	Difference mean (95 % CI)
Physical	1.13 (1.02–1.24)	1.03 (0.93–1.13)	0.10 (0.05–0.14)
Psychosocial	0.89 (0.78–1.00)	0.83 (0.73–0.94)	0.06 (0.01–0.11)
Practical	1.00 (0.89–1.11)	0.93 (0.82–1.03)	0.07 (0.02–0.13)

All factors have possible values in the interval (0, 3)

**Table 5** Correlations between the two sum scores Physical Health and Mental Health in SF-36 and the three domains in the Lymphedema Quality of Life Inventory ( $n = 129$ )

SF-36 sum score	LyQLI		
	Physical domain	Psychosocial domain	Practical domain
Physical health (PCS)	−0.578**	−0.285**	−0.533**
Mental health (MCS)	−0.389**	−0.469**	−0.510**

\*\* Correlation is significant at the 0.01 level (2-tailed)

**Table 6** Skewness characteristics

Domain	Skewness not significantly different from 0	Skewness significant positive	Skewness significant negative
Physical items ( $n = 12$ )	6	5	1
Psychosocial items ( $n = 16$ )	5	11	0
Practical items ( $n = 13$ )	4	9	0
Sum items ( $n = 41$ )	15	25	1

practice and research with less subject burden. LyQLI has been developed and the items that were retained measure physical, psychosocial and practical problems that patients with LE experience and which may affect their HRQL [9–11]. Results were consistent with opinions from the expert group and the social worker. A limitation in this study may be that we have no patient expert group looking over the final version of the questionnaire for the comprehensiveness of the items. However, the items that were retained were mostly not changed, just fewer in number. Small changes included merging two items, “pain due to my lymphedema” and “aches due to my lymphedema” into one item “Pain/aches due to my lymphedema” (Fig. 1) and “feelings of frustration” and “feeling annoyed” into “feeling of frustration/feeling annoyed” (Fig. 2). Our hypothesis was that this would make it easier for the patients, though they did not have to distinguish between two relatively equally items. The reduction was based on Spearman’s correlation coefficients and factor analyses, and reliability of the abbreviated instrument was then examined using appropriate statistics [33].

## Phase 1

### *Development of the abbreviated SLQOLI*

As a result of the correlation analysis in phase 1, the three questions pertaining to the items were reduced to one. The SLQOLI consists of 188 items and the LyQLI of just 45. One reason to only retain the question referring to HRQL was that many patients have had the LE for a long time (median = 7 years) and may have difficulties relating to items about changes in everyday life. In addition, patients with primary LE may have had the edema from birth or from very young years, with no other experience to compare.

The four domains (physical, emotional, social and practical) were reduced to three (physical, psychosocial and practical) with agreement from the expert panel to merge the emotional and social domains, although there were several items that were similar and were difficult to classify. The median time for patients to complete the abbreviated form was 6 min, compared with 30 min for the original questionnaire, providing evidence for the feasibility and practicality of the shorter questionnaire.

## Phase 2

### *Reliability and validity testing of the abbreviated scale*

Characteristics of the 126 patients who completed the two questionnaires as well as the 73 who withdrew are shown in Table 3. The two groups did not differ according to age, sex, year with LE and type of LE (secondary/primary). The interval between tests one and two was as intended (median = 10 days). It is recommended that the time gap between the repeated administrations should be long enough to prevent recalls, though short enough to ensure that clinical change has not occurred. Often, 1 or 2 weeks will be appropriate [37]. The median time for patients to complete the new form was 6 min and for the original questionnaire 30 min. The patients were recruited from outdoor units, which means that they are in contact with the clinic regularly. This may imply that they are cared for in a better way than patients having less frequent contact to the clinic. Patients seeking more contact may, on the other

hand, be those who have more severe LE. However, it may be the opposite that patients have less contact because they feel better. Thus, we estimate that patients taking part in this study are representative for LE patient with both small and large LE problems. Patients with edema developed secondary to medical conditions such as cardiovascular and renal disease, venous thrombosis, and end-stage recurrent malignancy were not included, so the study population is not representative for patients with such comorbidities.

Systematic disagreements between test 1 and test 2 were calculated using the disagreement measure RP for the three domains and for the two overall quality of life items. A minute systematic change toward increased HRQL was found for all indicators of HRQL. The mean improvement in the three domains is shown in Table 4. Because there was no intervention between the two test occasions, no improvement was expected. One explanation for the change may be that the test–retest period was set in a spring time period. In Sweden, the winter is dark and often cold. Spring brings light and warmer weather, and therefore, the patients' general quality of life may have increased.

Another explanation may be an *expectations effect*. Participants who participated in a study may have felt that some results/change was expected, with a social desirability factor prompting patients to rate their HRQL more positively the second time tested [38]. It is also possible that the time interval between tests one and two was too long and that the phenomenon being tested changed over this time period (10 days). This improvement between the two test occasions has to be taken into consideration when using the LyQLI during an intervention.

In the physical and psychosocial domain, ICC was 0.88 ( $p < 0.01$ ) and in the practical 0.87 ( $p < 0.01$ ). An ICC  $> 0.70$  is considered as good [33]. Cronbach's alpha coefficients of 0.88, 0.92 and 0.88 for each of the three domains were obtained. An alpha value 0.70–0.95 is considered to be a very good estimate of internal consistency reliability [37].

According to Fayers and Machin, concurrent validity involves assessing an instrument against the true value or if no true value is available to a *gold standard* [13]. In this study, the well-established questionnaire SF-36 was chosen because it is a widely used generic HRQL instrument both in Sweden and worldwide, with demonstrated validity and reliability [17–19]. However, because the SF-36 was not developed for this specific study population, we estimated that the sum scores for PCS and MCS in SF-36 should be at least reasonably highly correlated with the three domains in the LyQLI to confirm concurrent validity. The correlation coefficient between the physical and practical domain in the LyQLI and PCS in the SF-36 was moderate; the correlation coefficient between the physical and psychosocial domain

in the LyQLI and MCS was low, and the correlation coefficient between practical domain and MCS was moderate [39]. These results provide evidence to support the concurrent validity of the abbreviated instrument.

## Conclusion

The aim of this study was to reduce the 188-item SLQOLI to an abbreviated, clinically useful version and test it for reliability and validity. LyQLI is shorter with 45 items instead of 188. The median time to complete the form was reduced from 30 min to 6 min. LyQLI demonstrated good internal consistency reliability and face and concurrent validity. Further research to assess the sensitivity of the LyQLI is warranted. However, the instrument shows promise for evaluations of quality of life in clinical settings and in future cross-sectional studies to increase understanding and test interventions aimed at assisting patients with LE.

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The Lymphedema Quality of Life Inventory (LyQLI) © 2015, Pia Klerna. All rights reserved. Those interested in using the instrument should contact Pia Klernäs at <pia.klernas@med.lu.se>.

## Appendix “Lymphedema Quality of Life Inventory (LyQLI)”

This questionnaire is concerned with the way lymphedema may affect your quality of life and activities of daily living.

You may have experienced very mild lymphedema, moderate or severe symptoms. You may have lived with your symptoms for a short or long period of time.

**Please answer these questions only as they concern your lymphedema**

The questionnaire consists of three parts

- Physical
- Psychosocial
- Practical

Please think about your Lymphedema and your Quality of Life during **the past four weeks**. When it comes to questions that depend on seasons, think about the **past year**.

For each question circle the answer that best matches your experiences. **Try to answer all questions. If a question does not seem to apply to you, please circle the choice that says “None”**

Physical concerns due to lymphedema		How much do these concerns affect your quality of life?			
1	Pain/aches due to my lymphedema	None	A little bit	Somewhat	A lot
2	Discomfort due to my lymphedema	None	A little bit	Somewhat	A lot
3	A feeling of heaviness due to my lymphedema	None	A little bit	Somewhat	A lot
4	Pins and needles/numbness due to my lymphedema	None	A little bit	Somewhat	A lot
5	Burning sensation/heat due to my lymphedema	None	A little bit	Somewhat	A lot
6	Swelling/tightness due to my lymphedema	None	A little bit	Somewhat	A lot
7	Skin problems due to my lymphedema	None	A little bit	Somewhat	A lot
8	Difficulty sleeping due to my lymphedema	None	A little bit	Somewhat	A lot
9	Movement difficulties due to my lymphedema	None	A little bit	Somewhat	A lot
10	Feeling physically aware of my lymphedema all the time	None	A little bit	Somewhat	A lot
11	Feeling a loss of strength in the swollen part of my body	None	A little bit	Somewhat	A lot
12	Infection (e.g., cellulitis, erysipelas)	None	A little bit	Somewhat	A lot
Psychosocial concerns due to lymphedema		How much do these concerns affect your quality of life?			
13	Feelings of frustration/feeling annoyed	None	A little bit	Somewhat	A lot
14	Feeling anxious about whether or not the lymphedema will get worse	None	A little bit	Somewhat	A lot
15	Embarrassed by lymphedema/compression garments	None	A little bit	Somewhat	A lot
16	Negative changes in how I see myself	None	A little bit	Somewhat	A lot
17	Feeling discouraged	None	A little bit	Somewhat	A lot
18	Not being able to do the things I used to enjoy	None	A little bit	Somewhat	A lot
19	Concerns about when to seek medical attention	None	A little bit	Somewhat	A lot
20	Paying constant attention to my condition	None	A little bit	Somewhat	A lot
21	Concerns about how my lymphedema affects my existing relationships	None	A little bit	Somewhat	A lot
22	Concerns about how lymphedema could affect new relationships	None	A little bit	Somewhat	A lot
23	Negative changes in my feelings about intimacy/sexuality	None	A little bit	Somewhat	A lot
24	Feeling uncomfortable/embarrassed while doing sports and hobbies	None	A little bit	Somewhat	A lot
25	Feeling uncomfortable/embarrassed when attending social activities with friends and at work	None	A little bit	Somewhat	A lot
26	Having to ask for help in different situations	None	A little bit	Somewhat	A lot
27	Concerns about negative changes in my appearance	None	A little bit	Somewhat	A lot
28	Having to answer questions about my lymphedema	None	A little bit	Somewhat	A lot
Practical concerns due to lymphedema		How much do these concerns affect your quality of life?			
29	Personal activities of daily living (e.g., dressing, combing hair, foot care)	None	A little bit	Somewhat	A lot
30	Normal daily activities (e.g., doing housework, sports and hobby activities)	None	A little bit	Somewhat	A lot
31	Employment activities	None	A little bit	Somewhat	A lot
32	Learning to do things differently	None	A little bit	Somewhat	A lot
33	Having less energy to do activities (e.g., personal, normal daily or employment)	None	A little bit	Somewhat	A lot
34	Financial costs of managing my lymphedema (e.g., clothes, shoes, treatments, garments)	None	A little bit	Somewhat	A lot
35	Finding well-functioning compression garments (e.g., stockings, sleeves, gloves)	None	A little bit	Somewhat	A lot
36	Traveling long distances by car, train, plane etc.	None	A little bit	Somewhat	A lot
37	Finding clothes and shoes that are comfortable and attractive, the right size and type of material	None	A little bit	Somewhat	A lot
38	Limitations in hot weather/sun	None	A little bit	Somewhat	A lot
39	The constant self-care I need to do to stop my lymphedema from getting worse	None	A little bit	Somewhat	A lot
40	Obtaining information about how to manage my lymphedema	None	A little bit	Somewhat	A lot
41	Being prepared for emergencies (e.g., always having a script for antibiotics)	None	A little bit	Somewhat	A lot

42. In terms of your lymphedema, has this been a typical four week period for you?

Yes ( ) No ( )

43. If you answered "No" to the question above, has this period been (tick one)

Much Worse ( ) Worse ( ) Better ( ) Much Better ( ) than usual

44. Please think about how your lymphedema has affected you in the past four weeks and circle the number below that best matches your experience with lymphedema.

0 1 2 3

Very bad

Very good

45. Taking all parts of your life into consideration, how would you describe your quality of life in the past four weeks? Please circle the number below that best matches your overall quality of life.

0 1 2 3

Very bad

Very good

Thank you for your time completing this questionnaire!

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