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Rowlands, Ingrid J., Beesley, Vanessa L., [Janda, Monika](#), [Hayes, Sandra C.](#), Obermair, Andreas, Quinn, Michael A., Brand, Alison, Leung, Yee, McGuire, Lesley, & Webb, Penelope M.
(2014)

Quality of life of women with lower limb swelling or lymphedema 3-5 years following endometrial cancer.
Gynecologic Oncology, 133(2), pp. 314-318.

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<http://doi.org/10.1016/j.ygyno.2014.03.003>

1 **Quality of life of women with lower limb swelling or lymphedema 3-5 years following**
2 **endometrial cancer**

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28 **Abstract**

29 **Objective:** To quantitatively assess and compare the quality of life (QoL) of women with a
30 self-reported diagnosis of lower limb lymphedema (LLL), to women with lower limb
31 swelling (LLS), and to women without LLL or LLS following treatment for endometrial
32 cancer.

33 **Methods:** 1399 participants in the Australian National Endometrial Cancer Study were sent a
34 follow-up questionnaire 3–5 years after diagnosis. Women were asked if they had
35 experienced swelling in the lower limbs and, if so, whether they had received a diagnosis of
36 lymphedema by a health professional. The 639 women who responded were categorised as:
37 Women with LLL ($n = 68$), women with LLS ($n = 177$) and women without LLL or LLS ($n =$
38 394). Multivariable-adjusted generalized linear models were used to compare women's
39 physical and mental QoL by LLL status.

40 **Results:** On average, women were 65 years of age and 4 years after diagnosis. Women with
41 LLL had clinically lower physical QoL ($M=41.8$, $SE=1.4$) than women without LLL or LLS
42 ($M=45.1$, $SE=0.8$, $p =.07$), however, their mental QoL was within the normative range
43 ($M=49.6$; $SE= 1.1$ $p =1.0$). Women with LLS had significantly lower physical ($M= 41.0$,
44 $SE=1.0$, $p = .003$) and mental QoL ($M=46.8$; $SE=0.8$, $p <.0001$) than women without LLL or
45 LLS (Mental QoL: $M=50.6$, $SE=0.8$).

46 **Conclusion:** Although LLL was associated with reductions in physical QoL, LLS was related
47 to reductions in both physical and mental QoL 3-5 years after cancer treatment. Early referral
48 to evidence-based lymphedema programs may prevent long-term impairments to women's
49 QoL.

50 **Keywords:** endometrial cancer; lymphedema; lower-limb swelling; quality of life

INTRODUCTION

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Secondary lymphedema is an accumulation of fluid in body tissues resulting from damage to the lymphatic system. The condition is relatively common after cancer treatment: around one fifth of women will develop upper limb lymphedema (ULL) following breast cancer [1], and up to one third of women report either lower limb swelling or a diagnosis of lower limb lymphedema (LLL) following gynecological cancer treatment [2-5]. People affected by lymphedema following cancer treatment can experience changes in the appearance (e.g., swelling) and function of their upper or lower limb(s); other symptoms include heaviness, aching, tingling, numbness, and pain [4, 6], which may contribute to reduced quality of life (QoL) [5, 7, 8]. While the negative impact of ULL on women's QoL following breast cancer treatment is well known [9-12], comparatively fewer studies have examined the QoL of women with LLL following gynecological cancer treatment.

Treatment (e.g., surgery, lymph node removal, adjuvant pelvic radiation therapy) and patient factors (e.g., obesity) common to gynecological cancer are also strong risk factors for secondary LLL [2, 3, 13, 14]. Women who experience the physical symptoms of LLL, occurring in the legs, feet and groin, may have reduce mobility and independence, contributing to feelings of isolation, distress and hopelessness, increasing pressure on social and intimate relationships [5, 7]. Much of the existing research on LLL following gynecological cancer treatment has focused on short-term QoL outcomes, and results are largely based on small studies [7]. In addition, although endometrial cancer is the most common form of gynecological cancer in developed countries [15], few studies have examined the QoL of women with LLL several years following their endometrial cancer treatment [16].

Furthermore, definitions of what constitutes lymphedema and how to best measure and diagnose it vary (especially at the very early stage). Some people may have symptoms

76 suggestive of LLL following their cancer treatment but will not be diagnosed by a health
77 professional [17]. Studies of breast cancer survivors suggest that arm problems/swelling,
78 which may be undiagnosed ULL, may contribute to reductions in women's QoL [18-20]. The
79 severity of symptoms of lymphedema may also be an important factor influencing QoL [21,
80 22]. However, there are no studies comparing the impact of diagnosed lower limb
81 lymphedema (LLL) and lower limb swelling without a diagnosis of lymphedema (LLS) on
82 the QoL of women treated for endometrial cancer. The aim of this study was, therefore, to
83 examine the QoL of women treated for endometrial cancer 3-5 years previously, comparing
84 those with and without self-reported secondary LLL or LLS.

85 **METHODS**

86 The cohort of women in this study participated in the *Australian National*
87 *Endometrial Cancer Study (ANECS)*, an Australia-wide, population-based, case-control study
88 conducted between 2005 and 2007 [23]. Briefly, 2231 Australian women aged 18–79 years,
89 who were newly diagnosed with endometrial cancer during this period, were invited to
90 participate. Of these, 1497 (67%) agreed to take part and 1399 were confirmed as eligible and
91 completed a telephone interview with a research nurse. Interviews were conducted around the
92 time of diagnosis to collect information on potential predisposing factors for endometrial
93 cancer.

94 Three to five years after their initial interview, women were asked to complete a
95 follow-up mail survey to collect self-report data regarding lymphedema, physical and mental
96 QoL, other aspects of their current lifestyle and supportive care needs [24]. Of the 1399
97 original ANECS participants, 116 had died. Of the remaining 1283 women, 639 (49.8%)
98 refused to participate, could not be contacted or were too unwell, leaving 644 (50.2%)
99 women who returned a completed follow-up survey. Of these, 639 provided valid data for the
100 questions assessing lymphedema and had not been diagnosed with this condition prior to their

101 diagnosis of endometrial cancer. The study was approved by the Human Research Ethics
102 Committees at the QIMR Berghofer Medical Research Institute and all participating
103 hospitals.

104 **Measures**

105 *Lymphedema.* A series of questions, with satisfactory face validity, from another
106 Australian study of women with gynecological cancer [13] was used to categorize women
107 into three groups. Women were asked, “Since being treated for endometrial cancer, have you
108 experienced swelling in your legs, feet or groin?” Women who responded “No” were
109 categorized as “without lymphedema or lower limb swelling” (Without LLL or LLS; n=394).
110 Women who responded “Yes” to this question were asked if they had ever been told by a
111 doctor or health professional that they had lymphedema. Those women who responded “No”
112 were categorized as “Lower limb swelling only” (LLS; n=177), while those women who
113 responded “Yes”, were categorized as “Diagnosed lower limb lymphedema” (LLL; n=68).

114 Women were also asked if anyone had mentioned the possibility of developing
115 lymphedema to them when they were diagnosed or treated for endometrial cancer. Women
116 who responded “Yes” were asked to report who mentioned it, and when this was mentioned
117 (before, during or after treatment). Women in the LLL and LLS groups were asked further
118 questions about the severity of their swelling in the last month (no symptoms, mild, moderate
119 or severe) and the level of difficulty performing daily tasks as a result of swelling (no
120 difficulty, mild, moderate or severe).

121 *Clinical variables.* Information on tumor stage at diagnosis, treatment type (surgery,
122 chemotherapy, radiotherapy, brachytherapy, other), and number of lymph nodes examined
123 was abstracted from the diagnostic histopathology reports and medical records of consenting
124 women.

125 *Demographic and personal variables.* Marital status, education, employment status,
126 area of residence (urban, rural or remote) and comorbidities (e.g. hypertension, heart disease,
127 rheumatoid arthritis) and common medications prior to diagnosis was self-reported and
128 collected at the initial survey. At follow-up, the woman's current age, comorbidities and
129 weight were also collected. Comorbidities at follow-up were combined with those at the
130 initial survey to form one overall comorbidity score and weight was used to calculate body
131 mass index (kg/m^2) [coded as underweight/normal (<25), overweight (25-29.9), obese (≥ 30)].
132 The question, "Is there someone available to you whom you can count on to listen to you
133 when you need to talk?" was used as a proxy for current level of social support (categorized
134 as: none/little, some and all of the time).

135 *Quality of life.* The Medical Outcomes Study Short Form-12 (SF-12) Health Survey
136 was used to assess physical and mental QoL [25]. The scale is made up of eight subscales
137 (physical functioning, bodily pain, general health, physical and emotional role limitations,
138 vitality, social functioning, and mental health), which are combined to form two summary
139 scores - physical and mental QoL. Scores range from 0 to 100 and higher scores indicate
140 better QoL. To assess the clinical significance of the findings and to enable comparison with
141 US studies, SF-12 scores were standardized ($M = 50$, $SD = 10$) using US general population
142 norms so that a score of 40 and 60 represent one standard deviation (SD) below and above
143 the US population mean on this scale, respectively, suggesting clinically meaningful
144 differences in QoL [26]. The SF-12 has acceptable internal consistency [27], which was also
145 demonstrated in this study with Cronbach's alpha = 0.87 for the physical QoL summary
146 score, and alpha = 0.82 for the mental QoL summary score.

147 **Statistical Analysis**

148 The characteristics (measured at diagnosis) of women who completed the follow-up
149 survey and those who did not (including those who had died) were compared using χ^2 tests

150 for categorical variables, in order to check for participation bias. Following this, unadjusted
151 and multivariable-adjusted generalized linear models compared overall physical and mental
152 QoL and subscale scores of women with LLL, women with LLS and women without LLL or
153 LLS. Pairwise comparisons using a Bonferroni adjustment were conducted when there was a
154 significant main effect for the lymphedema classification variable. For unadjusted models, we
155 also calculated effect sizes (Cohen's *d*) to assess the magnitude of the difference in QoL
156 outcomes between the groups and to make comparisons with other studies. A standardized
157 mean difference of 0.30 to 0.80 reflects a moderate, and more than 0.80, a large effect [28].

158 All models were adjusted for current age, BMI, social support and stage of disease at
159 diagnosis and NSAID use in the 5 years prior to diagnosis as these variables were either
160 associated with the outcome or explanatory variable. Other potential demographic, personal
161 and clinical confounders (outlined above) were evaluated but not retained because they did
162 not change age-adjusted parameter estimates by more than 10%, nor alter interpretation of the
163 results.

164 Additional analyses combining the LLL and LLS groups assessed (i) the relationship
165 between the severity of swelling in the last month (no/mild symptoms versus moderate/severe
166 symptoms) and physical and mental QoL; and (ii) whether this relationship varied according
167 to symptom group by adding a group by severity interaction to the model. All statistical
168 analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

169 RESULTS

170 Compared to women who did not complete the follow-up survey (n=755),
171 respondents to the lymphedema questions (n=639) were more likely to be middle-aged (75%
172 aged 50-69 years) and slightly better educated (52% attended technical college or had a
173 university degree) and less likely to be obese (43%) (all $p<0.05$). Clinical characteristics were

174 similar between respondents and non-respondents. Respondents were on average 4 years
175 post-diagnosis at time of completing the survey.

176 Table 1 shows that overall 11% of women reported a physician diagnosis of LLL, and
177 28% reported LLS. Women with LLL were more likely to have a diagnosis of advanced
178 cancer; to have had more than 15 lymph nodes at initial surgery removed and to have had
179 adjuvant radiation and/or chemotherapy compared to women without LLL or LLS; however,
180 these groups did not differ with respect to their body size. In contrast, women with LLS had
181 similar clinical and treatment characteristics to women without LLL or LLS, but they were
182 more likely to be obese and to have other comorbidities than both women with LLL and
183 women without LLL or LLS (all $p < 0.05$).

184 Most women with LLL or LLS reported leg swelling in the last month (78%), but
185 swelling was more often reported as “severe” by those with LLL (15% vs. 2% respectively, p
186 < 0.001). Similarly, somewhat more women with LLL reported difficulty performing daily
187 tasks as a result of swelling than women with LLS, but this difference was not statistically
188 significant (21% vs. 15%, with moderate to severe difficulty, respectively, $p = 0.5$).

189 Adjusted mean scores for physical and mental QoL summary scales and subscales are
190 shown in Table 2. Overall physical and mental QoL of all women treated for endometrial
191 cancer was within the normative range. However, women with LLL had clinically lower
192 levels of overall physical QoL, scoring more than half a SD below the mean (effect size =
193 0.34), and they also scored significantly lower on three of the eight subscales (physical
194 functioning, physical role limitations, and social functioning,) than women without LLL or
195 LLS (all $p < 0.05$). Women with LLL scored lowest on the physical functioning subscale,
196 suggesting that they had difficulty participating in moderate activities or climbing several
197 flights of stairs. Women with LLS had significantly lower overall physical and mental QoL
198 and significantly lower scores for all 8 subscales than women without LLL or LLS. Effect

199 sizes comparing women with LLS to women without LLL or LLS were moderate (0.43-0.60)
200 for both physical and mental subscale scores.

201 Comparisons between the LLL and LLS groups showed no significant differences on
202 physical QoL and mental QoL, although women with LLS tended to score lower on the
203 mental health subscale. When these groups were combined, women who reported
204 experiencing “moderate/severe” swelling in the last month had significantly lower overall
205 physical QoL ($M= 37.5, SE = 1.6$) than women who reported only mild/no swelling ($M=$
206 $44.3, SE = 1.1, p<0.01$), however, there was no association for mental QoL. These results did
207 not vary when women with LLL and LLS were considered separately.

208 DISCUSSION

209 We examined the QoL of women who self-reported having secondary LLL or LLS
210 following their treatment for endometrial cancer and compared this to women without LLL or
211 LLS. Overall, 39% of women experienced either LLL (11%) or LLS (28%); these overall
212 estimates are consistent with other studies of self-reported LLL following endometrial cancer
213 [2, 3]. Although physical and mental QoL of the total sample of women with endometrial
214 cancer was within the normative range [29-31], women with LLL or LLS had lower QoL
215 scores. Specifically, women with LLL had meaningful reductions in their physical QoL
216 relative to women without LLL or LLS, adding to existing evidence of the negative impact of
217 lymphedema on women’s physical well being [7, 16]. Mental QoL did not differ significantly
218 between these groups of women and this may be due to the timing of the follow-up survey
219 and women’s access to treatment. On average, women with LLL were diagnosed 1-3 years
220 previously so the majority had been living with the condition for several years [32]. It is
221 possible that intervention and management of the condition facilitated positive emotional
222 adjustment, however, other personal, social and medical factors may also explain these
223 findings and this warrants further research attention [33, 34].

224 Women with LLS had similar physical QoL to women with LLL, and had
225 significantly lower physical QoL than women without LLL or LLS. However, in contrast to
226 women with LLL, women with LLS had significantly lower mental QoL than women who
227 were asymptomatic and effect sizes suggested a moderate difference between the groups.
228 Similarly, the score for mental QoL was approaching half a SD below US population norms,
229 suggesting subclinical levels of distress among women with LLS that should be monitored.
230 Other studies of women with breast [18] and various cancers [35] have also found that those
231 with undiagnosed symptoms are more likely to have reduced long-term QoL than those who
232 have received a formal diagnosis of lymphedema. Notably, a US study of more than 1200
233 women with breast cancer found that women with arm symptoms without diagnosed ULL,
234 had lower mental well-being on the SF-36 QoL questionnaire, than women without arm
235 symptoms. In contrast, women with diagnosed ULL had similar mental health to women
236 without ULL [18]. People who have symptoms following their cancer treatment and who
237 remain undiagnosed, may find it difficult to cope without an explanation of their symptoms
238 and appropriate treatment advice from health professionals [18, 33].

239 Consistent with studies of women with ULL following breast cancer [21, 22], women
240 with recent moderate to severe swelling had lower overall physical QoL, but there was no
241 association between the extent of swelling and mental health. Health care factors, such as the
242 quality of provider-patient communication about lymphedema appear important for well-
243 being following cancer, [6, 36] and may better predict long-term mental health outcomes.
244 Researchers have reported that people living with lymphedema after cancer have difficulties
245 finding a health professional who can diagnose and treat the condition [6], and who can also
246 provide adequate information and ongoing support [9, 13, 36]. Women who have had their
247 lymph nodes removed and who have pre-existing conditions, which may place them at

248 higher risk of swelling (e.g., obesity, diabetes, heart conditions), may benefit from
249 information and communication about lymphedema.

250 Women with LLL differed from women with LLS on health-related characteristics
251 (e.g. were less likely to be obese and to have comorbidities) and on clinical characteristics
252 (e.g., greater stage of disease and more likely to have had adjuvant treatment). Thus, reduced
253 QoL among women with LLS may be related to having edema or other health conditions (e.g.
254 lipedema, heart conditions) rather than having undiagnosed LLL. Obesity was also strongly
255 associated with reduced physical QoL, and slightly attenuated the association between LLS
256 and physical QoL. Because health professionals may find it difficult to diagnose LLL among
257 women who are overweight or obese, QoL reductions in women who are obese and who have
258 LLS may be explained by differences in health care.

259 Similar to other studies using mailed surveys [37, 38], we had a relatively low
260 response rate (50%) and, therefore, the findings may not relate well to the larger population
261 of women with endometrial cancer. Women who were older and better educated were less
262 likely to respond to the lymphedema questions and because these characteristics are also
263 associated with better mental QoL among women [39, 40], our data may overestimate the
264 levels of distress. In addition, this was a cross-sectional study and because we did not have a
265 measure of QoL at diagnosis, we could not determine whether reduced QoL was directly the
266 result of the LLL or LLS or of pre-existing disparities in QoL. QoL trajectories may also
267 differ for the LLL and LLS groups and future research should longitudinally examine QoL
268 changes. Furthermore, we may have overestimated the number of symptomatic women if
269 women chose not to respond because they felt that they were no longer burdened by disease.
270 On the other hand, because we only asked women about swelling following their cancer
271 diagnosis, it is possible that some women were incorrectly classified as not having LLL.
272 Similarly, while most women will develop symptoms of lymphedema within the first year

273 following their cancer treatment [8, 32], others may be diagnosed several years later and our
274 analysis will not have captured these women.

275 In conclusion, we show that both LLL and LLS may limit the physical QoL of long-
276 term endometrial cancer survivors, and the mental QoL of women who report experiencing
277 swelling but who are not diagnosed with LLL. Thus, the emotional and physical well-being
278 of women with lymphedema-like symptoms could be managed better through early referral to
279 evidence-based lymphedema intervention programs, such as those of exercise training,
280 bandaging or elevation [8, 41, 42]. Ongoing health care attention may be particularly
281 important given the enormous personal and social costs associated with lymphedema [7, 8].

282 **Acknowledgements**

283 We thank all the women who participated in the study.

284 We gratefully acknowledge the cooperation of the following institutions: NSW: John Hunter
 285 Hospital, Liverpool Hospital, Mater Misericordiae Hospital (Sydney), Mater Misericordiae
 286 Hospital (Newcastle), Newcastle Private Hospital, North Shore Private Hospital, Royal
 287 Hospital for Women, Royal Prince Alfred Hospital, Royal North Shore Hospital, Royal
 288 Prince Alfred Hospital, St George Hospital; Westmead Hospital, Westmead Private Hospital;
 289 Qld: Brisbane Private Hospital, Greenslopes Hospital, Mater Misericordiae Hospitals, Royal
 290 Brisbane and Women's Hospital, Wesley Hospital, Queensland Cancer Registry; SA:
 291 Adelaide Pathology Partners, Burnside Hospital, Calvary Hospital, Flinders Medical Centre,
 292 Queen Elizabeth Hospital, Royal Adelaide Hospital, South Australian Cancer Registry; Tas:
 293 Launceston Hospital, North West Regional Hospitals, Royal Hobart Hospital; Vic:
 294 Freemasons Hospital, Melbourne Pathology Services, Mercy Hospital for Women, Royal
 295 Women's Hospital, Victorian Cancer Registry; WA: King Edward Memorial Hospital, St
 296 John of God Hospitals Subiaco & Murdoch, Western Australian Cancer Registry.

297

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 299 Research Institute); Consumer representative: L McQuire; Clinical Collaborators: NSW: S
 300 Baron-Hay, D Bell, A Bonaventura, A Brand, S Braye, J Carter, F Chan, C Dalrymple, A
 301 Ferrier (deceased), G Gard, N Hacker, R Hogg, R Houghton, D Marsden, K McIlroy, G
 302 Otton, S Pather, A Proietto, G Robertson, J Scurry, R Sharma, G Wain, F Wong; Qld: J
 303 Armes, A Crandon, M Cummings, R Land, J Nicklin, L Perrin, A Obermair, B Ward; SA: M
 304 Davy, T Dodd, J Miller, M Oehler, S Paramasivum, J Pierides, F Whitehead; Tas: P
 305 Blomfield, D Challis; Vic: D Neesham, J Pyman, M Quinn, R Rome, M Weitzer; WA: B
 306 Brennan, I Hammond, Y Leung, A McCartney (deceased), C Stewart, J Thompson.

307 **Conflict of Interest Statement**

308 The authors have declared that no conflict of interest exists.

309 **Funding**

310 The Australian National Endometrial Cancer Study was supported by the National Health and
311 Medical Research Council (NHMRC) of Australia (#339435) and Cancer Council Tasmania
312 (#403031 and 457636). The ANECS Quality of Life study and clinical data collection were
313 funded by a Cancer Australia grant. IJ Rowlands and VL Beesley and are funded by NHMRC
314 program grant (#552429), M Janda is funded by a Career Development Fellowship from the
315 NHMRC, and PM Webb is funded by Senior Research Fellowships from the NHMRC.

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431

432 Table 1: Characteristics of endometrial cancer survivors according to lymphedema status 3-5
 433 years post-cancer diagnosis (N= 639)

	Without LLL or LLS (n= 394)	LLL (n = 68)	LLS (n = 177)	
	N(%)	N(%)	N(%)	P
Current* age <i>M (SD)</i>	65.2 (8.4)	65.2 (8.3)	65.4 (9.6)	0.97
Married	273 (70.2)	51 (75.0)	108 (61.7)	0.06
Education				
High School	193 (49.0)	35 (51.5)	80 (45.2)	0.8
Technical College	144 (36.5)	22 (32.4)	70 (39.5)	
University	57 (14.5)	11 (16.2)	27 (15.3)	
Urban area of residence	244 (63.4)	43 (64.2)	115 (65.7)	0.9
FIGO Stage 1 at diagnosis	341 (86.5)	47 (70.1)	149 (84.2)	0.003
Number of nodes examined				
0	188 (49.3)	5 (7.9)	80 (46.2)	<0.001
1-14	138 (36.2)	22 (34.9)	66 (38.2)	
≥15	55 (14.4)	36 (57.1)	27 (15.6)	
Adjuvant chemotherapy	35 (9.1)	19 (28.8)	15 (8.6)	<0.001
Adjuvant radiotherapy	58 (15.1)	18 (27.3)	29 (16.4)	0.05
Adjuvant brachytherapy	60 (15.7)	17 (25.8)	29 (16.4)	0.13
Current BMI (kg/m ²)				
<24.9	135 (34.4)	24 (35.3)	31 (17.5)	<0.001
25-29.9	109 (27.7)	21 (30.9)	44 (24.9)	
>30	149 (37.9)	23 (33.8)	102 (57.6)	
Comorbidities				
Yes	148 (37.6)	28 (41.2)	86 (48.6)	0.046

434 *Current at the time of follow-up survey

435 *Note.* Numbers may not sum to total because some data missing

436 Table 2: Adjusted mental and physical quality of life scores among women diagnosed with endometrial cancer 3-5 years earlier: overall and by
 437 lymphedema status

SF-12 Summary and Subscales	All women with endometrial cancer ^a (n= 639)		Without LLL or LLS ^b (n= 394)		LLL ^b (n= 68)		LLS ^b (n = 177)		*Effect size	^Effect size	P#	P§	LLL vs. Without LLL or LLS	LLS vs. Without LLL or LLS	LLL vs. LLS
	M	(SD)	M	(SE)	M	(SE)	M	(SE)							
Physical QoL summary	45.1	(11.8)	45.1	(0.8)	41.8	(1.4)	41.0	(1.0)	0.34	0.54	.07	.0003	1.0		
Mental QoL summary	51.4	(9.8)	50.6	(0.8)	49.6	(1.1)	46.8	(0.8)	0.22	0.54	1.0	<.0001	.09		
General Health	45.0	(11.3)	44.8	(0.8)	43.3	(1.3)	40.2	(0.9)	0.20	0.59	.55	<.0001	.11		
Physical functioning	45.2	(11.8)	44.8	(0.8)	41.1	(1.4)	41.9	(1.0)	0.39	0.43	.03	.01	.86		
Role limitations, physical	46.3	(11.3)	46.2	(0.7)	42.6	(1.3)	41.0	(0.9)	0.43	0.66	.03	<.001	.54		
Bodily Pain	48.4	(11.2)	48.6	(0.7)	45.9	(1.3)	43.9	(0.9)	0.30	0.59	.13	<.0001	.42		
Mental health	50.8	(9.2)	50.2	(0.6)	49.3	(1.1)	46.5	(0.7)	0.18	0.53	.72	<.0001	.06		
Role limitations, emotional	48.5	(11.1)	48.0	(0.7)	45.5	(1.3)	43.2	(0.9)	0.38	0.61	.15	<.0001	.29		
Social functioning	50.2	(10.0)	49.6	(0.7)	46.6	(1.2)	46.2	(0.8)	0.45	0.53	.04	.0003	.96		
Vitality	49.1	(10.2)	48.3	(0.7)	46.8	(1.2)	44.4	(0.8)	0.26	0.60	.50	<.0001	.17		

438 Scores are standardised ($M = 50$; $SD = 10$) using normative data from the general USA population; higher scores indicate better functioning

- 439 ^a Unadjusted data
- 440 ^b Adjusted for current age, stage, BMI, NSAID, social support
- 441 * Effect size based on unadjusted data comparing women with lymphedema (LLL) to women without lymphedema or lower-limb swelling
- 442 (without LLL or LLS)
- 443 ^Effect size based on unadjusted data comparing women with lower-limb swelling only (LLS) to women without LLL or LLS
- 444 # Difference between women with LLL and women without LLL or LLS, with Bonferroni adjustment for multiple comparisons
- 445 § Difference between women with LLS and women without LLL or LLS, with Bonferroni adjustment for multiple comparisons
- 446 || Difference between women with LLL and women with LLS, with Bonferroni adjustment for multiple comparisons