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Article:

Christensen, Jan, Ipsen, Thomas, Doherty, Patrick orcid.org/0000-0002-1887-0237 et al. (1 more author) (2016) Physical and social factors determining quality of life for veterans with lower-limb amputation(s) : a systematic review. *Disability and rehabilitation*. pp. 2345-2353. ISSN 0963-8288

<https://doi.org/10.3109/09638288.2015.1129446>

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1 **ABSTRACT**

2

3 **Purpose:** Most veterans live for many years after their war-related traumatic lower-
4 limb amputation, which is why understanding which factors influence health-related
5 quality of life (HRQoL) remains important to their long-term management. The
6 objective of this study was to perform a review of the literature to summarise any
7 evidence on the physical and social determinants for HRQoL in veterans with uni- or
8 bilateral lower-limb amputation(s).

9 **Method:** MEDLINE, EMBASE, PEDro, CINAHL, Scopus and Cochrane databases
10 were searched systematically for eligible studies. Inclusion criteria were: traumatic
11 lower-limb amputation(s), HRQoL outcome and veterans. Physical and social factors
12 that influence HRQoL were extracted.

13 **Results:** The literature search identified 2073 citations, leading to the inclusion of ten
14 studies in the systematic review. Physical activity level, sport participation, level of
15 amputation, back pain, years of education, as well as duration and severity of
16 phantom pain were found to be determining factors for HRQoL among veterans with
17 lower-limb amputation.

18 **Conclusions:** The identified physical and social determinants were similar to those
19 found in civilian traumatic amputees. More high quality research designs,
20 interventions and complex statistical analyses are warranted to identify the physical
21 and social factors that influence the HRQoL of veteran amputees.

22

23 INTRODUCTION

24

25 In 2005 an estimated 1.6 million people lived with the loss of a limb in the USA and
26 at the end of 2013 there were 1,558 traumatic war-related amputations registered due
27 to military operations in Iraq and Afghanistan ^{1,2}. A twenty-four-year follow-up study
28 on veteran amputees with traumatic lower-limb amputations revealed increased
29 mortality rates compared to the general population (21.9% vs. 12.1%) ³. Many veteran
30 amputees, however, live for many years after their war-related traumatic lower-limb
31 amputation ³, highlighting the importance of understanding the quality of life (QoL)
32 of survivors. Health-related quality of life (HRQoL) reflects an overall sense of well
33 being comprising the emotional, physical and social aspects of a person's life ⁴.

34 HRQoL after amputation is therefore an important short- and long-term outcome
35 measurement for patients with lower-limb amputations ⁵.

36 Veterans with lower-limb amputations due to war-related activities are typically
37 young men in good physical shape with a military mind-set. Therefore, the underlying
38 physical and social determinants of HRQoL may differ in veteran amputees compared
39 to civilians. Identification of specific determinants in veterans with traumatic
40 amputation(s) may provide crucial information for planning rehabilitation
41 interventions for veterans with lower-limb amputation(s). Even though HRQoL is an
42 important and relevant outcome, not much is known about the underlying physical
43 and social factors that influence HRQoL in veterans with lower-limb amputation.

44 Both vascular and traumatic lower-limb amputees showed decreased HRQoL ⁶⁻⁹, the
45 determining factors being: increasing age ⁹⁻¹¹, higher unemployment ⁹, more phantom
46 pain ^{9, 12}, more residual limb pain ⁹⁻¹¹, higher depression levels ¹⁰ and lower physical
47 function ¹⁰⁻¹³, but these findings are not specific for veteran amputees.

48 It is unknown whether the above-mentioned determinants are the same for veteran
49 amputees. As a result, the objective of this study was to systematically review the
50 literature concerning the relationship between physical and social determinants and
51 HRQoL in veterans with uni- or bilateral lower-limb amputation(s).

52 **Methods**

53

54 **Protocol and registration**

55 After initially screening a large volume of studies for relevance and eligibility, we
56 registered and published a protocol for our systematic review in PROSPERO, an
57 international database of prospectively registered systematic reviews in health and
58 social care, no. CRD42014014437.

59

60 **Eligibility criteria**

61 To be included in our review studies had to examine veterans with uni- or bilateral
62 transtibial, knee joint, transfemoral, hip joint or trough pelvic bone amputation(s)¹⁴
63 and they had to study HRQoL factors. Randomised controlled trials, quasi-
64 randomised controlled trials, controlled trials, cohort studies, and cross-sectional
65 studies were accepted. No language, publication date or publication status restrictions
66 were imposed.

67

68 **Search**

69 The following databases were searched on 28 September 2014: National Library of
70 Medicine (MEDLINE), Physiotherapy Evidence Database (PEDro), Cumulative
71 Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica
72 dataBASE (EMBASE), Scopus, Cochrane Central Register of Controlled Trials,
73 Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of
74 Effect. The search matrix consisted of a combination of lower-limb amputation and
75 veterans, with synonyms and indexed terms. Supplementary Table S1 provides an

76 example of a search matrix used in MEDLINE. Reference lists in the studies
77 identified were also screened to include any additional studies of relevance.

78

79 **Study selection**

80 First, two reviewers (JC, TI) independently screened for eligible studies by title and
81 abstract. Next, the eligible studies were compared and differing opinions discussed.
82 Finally, the two reviewers independently performed the process again on full text
83 articles.

84

85 **Data collection process**

86 JC and TI extracted data from the trials independently. A standardised form was used
87 to collect descriptive data on the study populations, level of amputation, inclusion
88 criteria, time since amputation and physical and social factors for HRQoL. Data and
89 figures were crosschecked.

90

91 **Assessment of risk of bias in individual studies**

92 The National Institutes of Health (NIH) Quality Assessment Tool for Observational
93 Cohort and Cross-Sectional Studies was used to rate the methodological strength and
94 risk of bias for the eligible studies ¹⁵. The two reviewers discussed any disagreements
95 concerning the study selection process, including bias, to reach consensus. A third
96 reviewer arbitrated where necessary.

97

98 **Quality of evidence**

99 Grades of Recommendation, Assessment, Development and Evaluation (GRADE)
100 was used to assess the overall quality of evidence ¹⁶ based on the following five

101 factors: risk of bias, indirectness, inconsistency, imprecision and publication bias. The
102 body of evidence identified for each outcome was rated as high, moderate, low or
103 very low quality.

104 **RESULTS**

105

106 **Study selection**

107 The literature search identified 2073 citations, 1005 of which were duplicates (figure
108 1). The remaining 1068 unique articles were screened for eligibility by title and
109 abstract, resulting in 29 potential articles for full-text review, 23 of which were
110 excluded. During the full-text reading an additional two studies were identified and
111 included after undergoing the same selection process (Dougherty 1999, 2001),
112 resulting in ten articles for our systematic review. Supplementary Table S2 lists the
113 characteristics of the studies that were excluded.

114

115 *Insert figure 1 about here*

116

117 **Synthesis of results**

118 A descriptive analysis of the data was undertaken due to the heterogeneity of the
119 studies. Physical and social factors that influence HRQOL will be presented
120 separately.

121

122 **Characteristics of included studies**

123 Table 1 presents the title, design, participants, inclusion criteria, primary outcome,
124 and main findings of the included studies.

125

126 *Insert table 1 about here*

127

128 **Quality assessment and risk of bias in included studies**

129 Figure 2 shows the quality assessment and risk of bias summary of the included
130 studies.

131

132 *Insert figure 2 about here*

133

134 **Factors influencing HRQoL**

135 Ten cross-sectional studies investigating determining factors for HRQoL were
136 included and divided into three groups: Studies directly investigating determinants of
137 HRQoL, studies comparing veterans to the normal population and studies comparing
138 veterans to other veterans.

139

140 *Studies directly investigating determinants of HRQoL*

141 Two studies investigated the factors that influence HRQoL^{17, 18}. A significant negative
142 relationship was found between severity of phantom pain and three Short Form-36
143 Healthy Survey (SF-36) domains: physical functioning, general health and physical
144 component scale¹⁷. No R or R-squared values for the correlations of variability were
145 stated. Findings also showed a significant negative relationship between duration of
146 phantom pain and physical functioning, bodily pain, mental health and physical
147 component scale. Furthermore, 61% of the amputees reported vertebral column pain.
148 The presence of either vertebral pain or neck pain was significantly associated with
149 lower scores on the subscales for bodily pain, vitality, social functioning, mental
150 health, physical component scale and mental component scale¹⁷.

151 Participants who suffered from thoracic pain had significantly lower scores on the

152 physical function subscale, general health, vitality, social function, mental health,
153 physical component scale and mental component scale ¹⁷.
154 In another study, poor physical HRQoL was positively associated with the presence of
155 phantom movement, low back pain, transfemoral amputation and a lower Barthel
156 Index score ¹⁸. No R or R-squared values for the correlations of variability were
157 stated. Amputees who had received educational services represented a higher
158 percentage of veterans with a good physical HRQoL (40 cases, 87.0%) compared
159 with others (66 cases, 69.5%), ($p=0.02$). Likewise, a good mental HRQoL was
160 significantly higher among veterans who received additional education (41 cases,
161 89.1%) compared to those who had not since the amputation (65 cases, 68.4%),
162 ($p=0.01$).

163 *Studies comparing veterans to the normal population*

164 Two studies compared veteran amputees to a normal population ^{19,20}.
165 Significant between-groups differences were found on the SF-36 subscale physical
166 functioning, with no differences observed on any other subscales ¹⁹. Forty-three
167 percent of the veterans reported still walking, 78% used a wheelchair as primary
168 transportation, 70% were employed and 91% were married. No determining factors
169 were reported.
170 Significant between-group differences on all SF-36 subscales were reported for
171 amputees with an additional major long-bone fracture of the lower extremity, burns
172 covering >20% of the body, or a chest, abdominal, face or head wound, compared to
173 the normal population ²⁰. All amputees with additional injury were employed, 93%
174 were married, 82% had children and 21% received psychological care. For the group
175 of amputees without an additional injury no significant between-group difference was
176 observed when compared to the normal population. Ninety-eight percent of the

177 amputees without additional injury were employed and married, 84% had children
178 and 50% received psychological care. No determining factors were reported in either
179 of the two groups.

180

181 *Studies comparing veterans to other veterans*

182 Six studies compared veteran amputees to another veteran population²¹⁻²⁶.

183 No differences in the prevalence of depression, posttraumatic stress disorder and brain
184 injury were found between groups or type of limb loss, but an increasing prevalence
185 of chronic back pain with more limbs amputated was found^{21, 22}.

186 Patients from the Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF)
187 group had a better function compared to the Vietnam War group²². Employment was
188 reported as 77% for the Vietnam War group and 60% for the OIF/OEF group. No
189 significant difference in HRQoL was observed between groups, but 55% of patients in
190 the Vietnam group rated their HRQoL as excellent/very good while 70% in the
191 OIF/OEF group did.

192 The OIF/OEF group had a higher level of function, four out of eleven reporting
193 participation in high-impact activities versus none in the Vietnam War group
194 ($p=0.018$)²³. QoL was similar between groups, with excellent, very good and good
195 QoL reported for 69% of the Vietnam War group and 73% of the OIF/OEF group
196 ($p=0.85$). Other health factors were non-significant.

197 In another study the OIF/OEF group reported better QoL compared to the Vietnam
198 War group²⁴. Those with unilateral lower-limb loss reported their amputation had the
199 highest effect on their current life (amputation impact rank = 7.5 ± 2.7 , $p < 0.05$)
200 compared with multiple limb loss (7.1 ± 3.1).

201 For those with unilateral lower-limb loss in the Vietnam War group, the highest effect
202 for injury to the non-amputated lower limb (mean combat injury rank = 5.4 ± 3.1)²⁴.
203 There was no difference in self-reported health status among veterans with lower-limb
204 amputations as 81.9% in the Vietnam War group and 84.8% in the OIF/OEF group
205 reported excellent to good health²⁵. In the OIF/OEF group, 52% were significantly
206 more likely to do low- and high-impact activities compared 20% in the Vietnam War
207 group. No difference was observed between groups regarding total pain but mental
208 health was worse in the OIF/OEF group.
209 Veterans who participated in sports had higher favourable physical subscale scores on
210 SF-36²⁶. Furthermore, veterans with more proximal amputations remained more
211 symptomatic (e.g. phantom sensation and phantom pain). Overall, 93% of veterans
212 were married and 90% reported back pain.

213

214 **Quality of evidence and risk of bias across studies**

215 As stated in the protocol and the methods section the present review aimed to include
216 randomised controlled trials, quasi-randomised controlled trials, controlled trials,
217 cohort studies and cross-sectional studies; however, due to limited evidence base only
218 cross-sectional studies were included in this systematic review.

219 GRADE was used to evaluate the quality of the body of evidence for determining
220 factors for HRQoL. Only two of the included studies were designed to directly
221 investigate factors determining HRQoL; however, when data was available, relevant
222 factors for HRQoL were included in the present review. All of the included studies
223 were cross sectional and the majority of them had relatively small sample sizes, which
224 means publication bias cannot be assessed or ruled out. Results varied considerably
225 concerning physical activity, some studies identifying it as a determining factor for

226 HRQoL and others failing to find a relationship between the two. The authors of the
227 present review rate the body of evidence to be of very low quality for each of the
228 identified determinants for HRQoL among veterans with lower-limb amputation(s).

229 Table 2 presents the individual ratings in a GRADE profile.

230

231 *Insert table 2 about here*

232 **DISCUSSION**

233 **Summary factors that influence HRQoL**

234 The identified HRQoL determinants for veteran amputees included: higher physical
235 activity, years of education, higher phantom pain severity, duration of phantom pain,
236 level of amputation and back pain.

237 Higher physical activity level and years of education were positively associated with
238 better physical and mental HRQoL¹⁷.

239 Higher phantom pain severity is a predictor of lower scores on SF-36 subscales for
240 physical functioning, general health and for the physical component scale¹⁷. Phantom
241 pain is often reported to be a determining factor for HRQoL and veteran amputees
242 with phantom pain have poorer HRQoL compared to civilian amputees without
243 phantom pain^{12,27}. For veteran amputees, the duration of phantom pain is associated
244 with worse physical functioning, bodily pain, mental health and a lower score on the
245 physical component scale¹⁷. Higher proximal level of amputation is associated with
246 more bodily pain²⁶ and lower HRQoL^{18,20}.

247 Civilians with lower-limb amputation(s) often report back pain^{17,18,28-30}. For veterans
248 with lower-limb amputation(s), back pain is associated with lower scores on the
249 subscales for bodily pain, vitality, social functioning, mental health and on the
250 physical component and mental component scales¹⁷. Furthermore, back pain is
251 associated with poor physical HRQoL¹⁸.

252 This systematic review only included studies that examined veterans with lower-limb
253 amputation(s). This group is primarily younger men in relatively good physical shape
254 before the amputation. With this in mind, the authors did not hypothesise that a
255 civilian population necessarily would have the same determining factors for HRQoL
256 as veterans. Nevertheless, many of the factors identified in this present review were

257 not unique to the veteran amputee as they were likewise reported among civilian
258 amputees. These more general determinants include: age, number of comorbidities,
259 level of amputation, time since amputation, residual stump pain, phantom limb pain,
260 social support, employment status and depressive symptoms^{9, 10}.

261 It was not possible to state how much of the variation in HRQoL was due to the
262 identified factors. Neither R nor R^2 was reported in the studies included in the present
263 review. For civilian amputees the eight known determinants: age, time since
264 amputation, phantom limb pain, employment status, use of prosthesis, comorbidities,
265 use of assistive devices and residual limb pain explained up to 50.8% of the variance
266 observed in physical HRQoL⁹. Depression in civilian patients accounted for 30% of
267 the variance observed in HRQoL, with six other factors accounting for an additional
268 18% of the observed variance¹⁰.

269 Due to poor reporting in the ten eligible studies, this review was unable confidently
270 quantify the extent of contribution for most of the identified factors for veterans.

271 Generally, the included studies had small sample sizes, some did not provide long-
272 term outcomes and all of them showed shortcomings in the methodological quality,
273 not to mention a medium to high risk of bias. Based on GRADE, the quality of
274 evidence for each of the identified determinants is very low due to the study design,
275 indirectness of the research question in some of the studies, the inconsistency of
276 findings between studies and due to the probability of publication bias, table 2.

277 Notwithstanding the above findings, the very low grade reflects that the authors
278 suspect that the determinants identified in the studies may vary substantially from the
279 ones identified in the current review. Good methodological studies with larger sample
280 sizes are urgently needed to better understand the factors that influence HRQoL in
281 veterans with lower-limb amputation.

282 **Limitations**

283 The findings in this review are limited to veterans with traumatic lower-limb loss. The
284 review included studies that did not primarily focus on factors that influence HRQoL.

285 As a result, some factors that affect HRQoL may have been ignored and data
286 unreported in those articles. Because the total body of evidence was not very large,
287 we nonetheless included these studies to obtain the data that was available on the
288 reported determinants

289 Two of the studies in the present review were conducted over ten years ago and may
290 not reflect modern service provision and outcomes. In recent years prosthetics have
291 improved, which has possibly had an impact on HRQoL.

292 Used to assess the quality and risk of bias in the studies in this review, the NIH
293 Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies is
294 based on a subjective assessment but bolstered by NIH guidelines and supplemented
295 by an evaluation based on consensus.

296 **CONCLUSIONS**

297 **Implications for practice**

298 This systematic review identified physical activity level, sport participation, level of
299 amputation, back pain, years of education, as well as duration and severity of
300 phantom pain as determining factors for HRQoL among veterans with lower-limb
301 amputation. When considering interventions aimed at improving HRQoL, clinical and
302 rehabilitation teams are well placed to promote physical activity and sport but should
303 also take into account the level of amputation, the extent of back pain and the severity
304 of phantom pain.

305

306 *Insert Implication for Rehabilitation Box about here*

307

308 **Implications for research**

309 A key recommendation from this review is that HRQoL studies involving veterans
310 should adopt a higher level of reporting for correlation and regression analyses.
311 Systematic reviews are only as good as the data they collate and the study types they
312 include, which suggest that more high quality research designs, interventions and
313 complex statistical analyses are warranted to identify which physical and social
314 factors influence HRQoL.

315 **Future research**

316 As a result of the involvement in Iraq and Afghanistan, health care systems are facing
317 long-term future challenges in caring for veterans³¹. To manage these challenges,
318 there is an urgent need to identify and study the factors that influence HRQoL to be
319 able to meet veterans' rehabilitation needs and to prevent the increased mortality rate
320 among veterans due to cardiovascular disease^{3,32}. For example, clinical trials can

321 play a part in determining the effectiveness of interventions aimed at improving
322 HRQoL, while registry and audit data sets can help determine if routine practices in
323 amputee centres produce the desired effects.

324 **Declaration of interest**

325 The authors declare no conflict of interest. This study was funded by the Danish
326 Defence Agreement 2013-2017.

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484 **TABLE AND FIGURE CAPTIONS**

485 **Figure 1:** Flowchart showing systematic literature search, screening of studies, full
486 text reading, and studies included in review with number and reasons of study
487 exclusion at each stage.

488 **Figure 2:** Quality assessment and risk of bias summary based on the “Quality
489 Assessment Tool for Observational Cohort and Cross-Sectional Studies”: review
490 authors' judgements about quality assessment and risk of bias for each included study.

491 **Table 1:** Characteristics of included studies

492 **Table 2:** GRADE profile for Health Related Quality of Life determinants