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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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ABSTRACT

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

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

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

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

INTRODUCTION

In 2005 an estimated 1.6 million people lived with the loss of a limb in the USA and at the end of 2013 there were 1,558 traumatic war-related amputations registered due to military operations in Iraq and Afghanistan ^{1,2}. A twenty-four-year follow-up study on veteran amputees with traumatic lower-limb amputations revealed increased mortality rates compared to the general population (21.9% vs. 12.1%) ³. Many veteran amputees, however, live for many years after their war-related traumatic lower-limb amputation ³, highlighting the importance of understanding the quality of life (QoL) of survivors. Health-related quality of life (HRQoL) reflects an overall sense of well being comprising the emotional, physical and social aspects of a person's life ⁴. HRQoL after amputation is therefore an important short- and long-term outcome measurement for patients with lower-limb amputations ⁵. Veterans with lower-limb amputations due to war-related activities are typically young men in good physical shape with a military mind-set. Therefore, the underlying physical and social determinants of HRQoL may differ in veteran amputees compared to civilians. Identification of specific determinants in veterans with traumatic amputation(s) may provide crucial information for planning rehabilitation interventions for veterans with lower-limb amputation(s). Even though HRQoL is an important and relevant outcome, not much is known about the underlying physical and social factors that influence HRQoL in veterans with lower-limb amputation. Both vascular and traumatic lower-limb amputees showed decreased HRQoL ⁶⁻⁹, the determining factors being: increasing age ⁹⁻¹¹, higher unemployment ⁹, more phantom pain ^{9, 12}, more residual limb pain ⁹⁻¹¹, higher depression levels ¹⁰ and lower physical 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).

Methods

Protocol and registration

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

Eligibility criteria

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

Search

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

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

Study selection

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

Data collection process

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

Assessment of risk of bias in individual studies

The National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used to rate the methodological strength and risk of bias for the eligible studies¹⁵. The two reviewers discussed any disagreements concerning the study selection process, including bias, to reach consensus. A third reviewer arbitrated where necessary.

Quality of evidence

Grades of Recommendation, Assessment, Development and Evaluation (GRADE) was used to assess the overall quality of evidence¹⁶ 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.

RESULTS

Study selection

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

Insert figure 1 about here

Synthesis of results

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

Characteristics of included studies

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

Insert table 1 about here

Quality assessment and risk of bias in included studies

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

Insert figure 2 about here

Factors influencing HRQoL

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

Studies directly investigating determinants of HRQoL

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

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

physical function subscale, general health, vitality, social function, mental health, physical component scale and mental component scale¹⁷. In another study, poor physical HRQoL was positively associated with the presence of phantom movement, low back pain, transfemoral amputation and a lower Barthel Index score¹⁸. No R or R-squared values for the correlations of variability were stated. Amputees who had received educational services represented a higher percentage of veterans with a good physical HRQoL (40 cases, 87.0%) compared with others (66 cases, 69.5%), ($p=0.02$). Likewise, a good mental HRQoL was significantly higher among veterans who received additional education (41 cases, 89.1%) compared to those who had not since the amputation (65 cases, 68.4%), ($p=0.01$).

Studies comparing veterans to the normal population

Two studies compared veteran amputees to a normal population^{19, 20}. Significant between-groups differences were found on the SF-36 subscale physical functioning, with no differences observed on any other subscales¹⁹. Forty-three percent of the veterans reported still walking, 78% used a wheelchair as primary transportation, 70% were employed and 91% were married. No determining factors were reported. Significant between-group differences on all SF-36 subscales were reported for amputees with an additional major long-bone fracture of the lower extremity, burns covering >20% of the body, or a chest, abdominal, face or head wound, compared to the normal population²⁰. All amputees with additional injury were employed, 93% were married, 82% had children and 21% received psychological care. For the group of amputees without an additional injury no significant between-group difference was observed when compared to the normal population. Ninety-eight percent of the

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

Studies comparing veterans to other veterans

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

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

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

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

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

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

Quality of evidence and risk of bias across studies

As stated in the protocol and the methods section the present review aimed to include randomised controlled trials, quasi-randomised controlled trials, controlled trials, cohort studies and cross-sectional studies; however, due to limited evidence base only cross-sectional studies were included in this systematic review. GRADE was used to evaluate the quality of the body of evidence for determining factors for HRQoL. Only two of the included studies were designed to directly investigate factors determining HRQoL; however, when data was available, relevant factors for HRQoL were included in the present review. All of the included studies were cross sectional and the majority of them had relatively small sample sizes, which means publication bias cannot be assessed or ruled out. Results varied considerably 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*

DISCUSSION

Summary factors that influence HRQoL

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

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

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

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

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

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

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

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

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

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

Limitations

The findings in this review are limited to veterans with traumatic lower-limb loss. The review included studies that did not primarily focus on factors that influence HRQoL. As a result, some factors that affect HRQoL may have been ignored and data unreported in those articles. Because the total body of evidence was not very large, we nonetheless included these studies to obtain the data that was available on the reported determinants.

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

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

CONCLUSIONS

Implications for practice

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

Insert Implication for Rehabilitation Box about here

Implications for research

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

Future research

As a result of the involvement in Iraq and Afghanistan, health care systems are facing long-term future challenges in caring for veterans³¹. To manage these challenges, there is an urgent need to identify and study the factors that influence HRQoL to be able to meet veterans' rehabilitation needs and to prevent the increased mortality rate 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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- 483

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