

## The humanistic and economic burden of chronic wounds: A systematic review

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**Abstract**

Chronic wounds are a health problem that have devastating consequences for patients and contribute major costs to healthcare systems and societies. To understand the magnitude of this health issue, a systematic review was undertaken. Searches were conducted in MEDLINE, EMBASE, EBM Reviews and Cochrane library, CINAHL, EBSCO, PsycINFO, and Global Health databases for articles published between 2000 and 2015. Included publications had to target adults ( $\geq 18$  years of age), state wound chronicity ( $\geq 3$  weeks) and/or label the wounds as chronic, complex, hard-to-heal, or having led to an amputation. The review excluded studies that did not present data on generic health-related quality of life and/or cost data, case studies, randomised controlled trials, economic modelling studies, abstracts and editorials. Extracted data were summarised into a narrative synthesis, and for a few articles using the same health-related quality of life instrument, average estimates with 95% confidence intervals were calculated. Thirty articles met the inclusion criteria. Findings revealed that health-related quality of life was lowest for physical pathologies, and based on average estimates were scores most inferior in the domain physical role for both patients with chronic wounds and for those with wound-related amputations. The cost burden was mainly attributed to amputations for patients also comorbid with diabetes, where the cost for hospitalisation ranged from US\$ 12,851 to 16,267 (median) for this patient group. Patients with chronic wounds have poor health-related quality of life in general and wound related costs are substantial. Development and implementation of wound management strategies that focus on increasing health-related quality of life and effectively reduce costs for this patient group are urgently needed.

**Introduction**

Chronic wounds, hard-to-heal or difficult-to-heal wounds/ulcers, are defined as wounds that do

not heal properly during an amount of time that normally should be sufficient for healing.<sup>1</sup> There is no pre-established consensus for the duration of chronicity,<sup>2</sup> and the wounds are often managed as a comorbidity of other conditions.<sup>3</sup> Chronic wounds have significant humanistic and economic burdens, both at an individual (e.g. quality of life)<sup>4</sup> and a societal level (e.g. healthcare costs).<sup>1, 5-7</sup> The humanistic burden, often presented as health-related quality of life (HRQoL), reflects specific dimensions of health (e.g. physical and psychological),<sup>8</sup> and is assessed in health economic studies to understand and estimate the burden of patients suffering from a condition or disease.<sup>8</sup> Chronic wounds are also associated with major economic burdens, comprising of direct (medical and health care costs) and indirect costs (productivity losses, e.g. sick leave and early retirement) to the society.<sup>1, 5-7</sup> Treatment costs for chronic wounds are substantial and are estimated to account for approximately 1-3% of the total healthcare expenditure in developed countries.<sup>1, 5, 7</sup> However, this is probably an underestimation since more recent studies report even greater costs.<sup>6</sup> For example, Wales was estimated to have a chronic wound prevalence of 6% in the year 2012-2013, corresponding to 5.5% of National Health Service expenditure,<sup>6</sup> and in the United Kingdom as a whole, the cost associated with wound management was estimated to be £4.5-5.1 billion in 2012.<sup>9</sup> In the United States it is reported that over 6.5 million patients with wounds cost the health care system US\$ 25 billion annually.<sup>7</sup>

The humanistic and economic burden of chronic wounds is underappreciated and growing due to an ageing population, and earlier development of chronic illnesses such as diabetes, etc.<sup>7</sup> A recent systematic review explored the cost-of-illness for chronic wounds but did not specify how chronicity in the included studies was defined, nor explored the humanistic burden, which is crucial to understand the magnitude of the problem.<sup>10</sup>

No previous systematic review has assessed both the humanistic and economic burden of chronic wounds. This systematic review with a definition for chronicity (duration  $\geq 3$  weeks) aimed to explore the impact of chronic wounds on HRQoL for patients and their caregivers and to explore the economic impact of the condition measured as cost-consequences to society.

## **Materials and methods**

### **Search strategy and selection criteria**

This systematic review followed the PRISMA statement,<sup>11</sup> and systematic searches were carried out in the MEDLINE, EMBASE, EBM Reviews and Cochrane library, Cumulative Index to Nursing and Allied Health Literature (CINAHL, EBSCO), PsycINFO and Global Health databases during April 2016.<sup>12</sup> The search was limited to articles published between January 2000 and December 2015. Search strategies were created in collaboration with dermatology- and wound-specialist and medical research librarians.<sup>12</sup>

Studies targeting adults  $\geq 18$  years of age having chronic wounds specified by wound duration ( $\geq 3$  weeks), or labelled as chronic, complex, hard-to-heal or having led to an amputation were included. Wounds that failed to heal within three weeks were considered chronic, as ulcers not reducing in size after four weeks are probable to become chronic.<sup>13</sup> Since there is no pre-established consensus for chronicity and when a wound generally is considered as chronic a duration of  $\geq 3$  weeks was deemed appropriate to capture hard-to-heal wounds across various wound aetiologies.<sup>2</sup>

HRQoL articles had to report data obtained from a generic instrument (e.g. The MOS 36-item Short-Form Health Survey (SF-36), SF-12, SF-6D and EuroQol-5D (EQ-5D)), and for economic burden studies, cost data had to be presented. Only peer-reviewed, full-text publications in

English were included.

The review excluded large non-chronic wounds (e.g. surgical wounds and skin tumours that due to size and malignity require a longer time to heal), and solely disease-specific HRQoL studies, case studies, randomised controlled trials, economic modelling studies, abstracts, or editorials.

The included publications were imported to Endnote X7©, and duplicates were removed. Two reviewers independently screened the titles and abstracts to identify studies with potential for inclusion, and full-text copies of relevant articles were obtained and assessed for eligibility for final inclusion. Discrepancies in assessment were resolved by discussion between the reviewers, with reasons for exclusion noted.

### **Data extraction**

Data extraction was done independently by two reviewers and documented in extraction forms inspired by the Joanna Briggs Extraction Form for Economic Evaluations.<sup>14</sup> The methodological quality was assessed by using the Joanna Briggs Institute (JBI) Critical Appraisal Tool: Checklist for Prevalence studies, which is mainly developed for prevalence data but also applicable for quality of life data such as HRQoL,<sup>15, 16</sup> and Drummond and Jefferson's Checklist for Economic Evaluation<sup>17</sup> for cost articles. HRQoL- and cost data were reviewed separately and key findings were summarised. The results were presented as a descriptive narrative synthesis including pooled-analyses for HRQoL outcomes when homogeneity allowed (i.e. when data were uniform enough to enable comparisons).

### **Statistical analysis**

No formal meta-analysis was performed due to the large heterogeneity (probably due to different kind of wounds, severity and method of evaluation etc.) between studies. For HRQoL, weighted average with corresponding 95% confidence interval (CI) was calculated for SF-36 domains separately for chronic wounds and amputation groups. Weighted mean and corresponding standard deviation were calculated by  $\sum_i^T n_i m_i / \sum_i^T n_i$  and  $\sqrt{\left[ \sum_i^T (n_i - 1) (s_i)^2 / \left( \sum_i^T n_i - T \right) \right]}$ , respectively, where  $n_i$  is the sample size of study group  $i$ ,  $m_i$  is the mean of study group  $i$ ,  $s_i$  is the standard deviation of study group  $i$ , and  $T$  is the number of studies. For missing standard deviation values corresponding to a SF-36 domain, we used largest available standard deviation in the group of studies to enable weighted standard deviations.<sup>18</sup> Subgroup analyses were conducted for chronic wounds (excluding amputation groups due to lack of control group and less than three studies in total) when control groups were present (see supplementary Figure 1). No formal statistical comparisons was performed for the subgroup analysis of SF-36 domain scores in order to avoid misleading conclusions as recommended in the Cochrane Handbook for systematic reviews.<sup>19</sup> A value of  $p < 0.05$  was considered statistically significant and data analyses were conducted in Stata software version 14.0 (StataCorp LLC, College Station, Texas, USA). Currencies extracted from the included cost articles were converted into US\$ with the appropriate exchange rate for the respective cost year. Costs were adjusted for inflation by using the average consumer price index (CPI)<sup>20</sup> for each country and purchasing power parity (PPP)<sup>21</sup> for the year 2015 to enable comparability. When information for cost year was missing, the year of the data collection was as assumed to be the cost year.

## Results

A total of 5,570 publications were identified, and after scanning titles/abstracts, 5,298

publications were excluded due to not meeting the inclusion criteria (not chronic wounds, no generic HRQoL data or no cost data). After adding two articles from manual searches, 274 articles were viewed in full-text, of which 244 did not meet the inclusion criteria. Finally, 30 articles (one article presented both HRQoL and costs data) were included in the systematic review (Figure 1).

*Insert Figure 1 here*

In the included articles, 16 labelled the wound as chronic or hard-to-heal, and five studies stated a wound duration longer than three weeks, but did not label the wounds chronic/hard-to-heal.

Eight studies assessed amputations, and one study presented both chronic wounds and amputations.

The majority of the included HRQoL articles (n=17) presented acceptable sample sizes for HRQoL studies.<sup>22</sup> However, methods for sampling were often based on convenience or poorly described. Seven articles had appropriate sampling methods and most studies (n=18) described study participants and settings in detail, and measured HRQoL by validated methods. With regards to the Drummond and Jefferson's Checklist, several non-applicable items for cost-of-illness evaluations were excluded in the quality assessment. All included cost studies stated the research question (n=11), most studies presented the economic importance of the study (n=10), few studies presented details of study participants (n=3), and only one study discussed the productivity impact. More than half of the studies presented the quantity of resource use separated from the unit costs (n=7), most studies provided currency and price data (n=9), and approximately half of the studies presented details of currency and price adjustments for inflation



conversions (n=5). Eight studies stated a time horizon for costs, one study incorporated discounting, and no study justified the choice of discount rate nor gave an explanation for non-discounted costs. A sensitivity analysis was presented in only one study. The majority of studies answered their research question (n=10) and all studies provided a conclusion.

*Insert Table 1 here*

The HRQoL articles consisted of nine cross-sectional studies, six case-control studies, two observational studies, one quasi-experimental study, and one study assessed a measurement tool for HRQoL and one pilot study. Two studies (using SF-36 and EQ-5D) failed to report standardised domain scores which impeded comparability to other studies applying the same instrument.<sup>23,24</sup> In one study, only wound duration specific subgroup data could be extracted due to lack of chronicity information for the rest of the sample (mixed wounds of unknown duration).<sup>25</sup>

Nine different instruments were used to measure HRQoL (five studies used more than one instrument). SF-36, the most frequently used instrument was used in half of the studies.

Six studies presented aggregated utility values from different HRQoL instruments; Nottingham Health Profile (NHP),<sup>26</sup> SF-36,<sup>25</sup> EQ-5D,<sup>27</sup> Ferran's and Power's Quality of Life Index (QLI),<sup>28</sup> EQ-5D Visual Analogue Scale (VAS),<sup>27,29</sup> WHOQOL-bref.,<sup>30</sup> and Numerical Rating Scale (NRS).<sup>27</sup> One study evaluated a disease specific instrument for patients with chronic wounds by comparing domain scores from three different HRQoL tools.<sup>27</sup>

Patients with chronic wounds most frequently reported lower HRQoL scores in the domains related to physical pathologies i.e. role physical, physical functioning, equivalent to mobility

and/or the physical summary component (PSC).<sup>26, 31-40</sup> The similar and comparable domains, vitality (SF-36) and energy (NHP)<sup>32</sup>, also presented inferior scores for patients with chronic wounds.<sup>26, 34, 35, 39, 41</sup> For emotional- and mental health domains, four studies reported lower HRQoL scores for patients with chronic wounds,<sup>31, 35, 36, 40</sup> while five studies did not find any statistical difference when compared to controls.<sup>34, 37-39, 42</sup> Four studies with control groups reported significantly lower scores for patients with chronic wounds in the domains of bodily pain and pain/discomfort.<sup>26, 35, 39, 40</sup> Eight studies were homogenous enough to enable calculations of pooled estimates of HRQoL for patients with chronic wounds and amputations (Table 2)).<sup>33-36, 39-41, 43</sup> The estimates showed that patients with amputation had inferior scores in most domains, except for the domain role physical, pain and social function where patients with chronic wounds had lower scores. Further, in the subgroup analysis, five studies incorporated patients with chronic wounds and control groups. The box plots (n = 5) showed lower mean scores for chronic wound patients in all SF-36 domains when compared to the control groups. (Supplementary Figure 1). However, these scores should be interpreted with caution due to small sample sizes, large differences in study designs, and heterogeneity in participant characteristics.

*Insert Table 2 here*

*Insert Figure 2 here*

Long wound duration and/or large wound size were correlated to poorer HRQoL scores in three studies.<sup>25, 37, 40</sup> Three studies specifically assessed pain and HRQoL for patients with chronic wounds, and showed that patients with chronic wounds and severe pain reported even lower HRQoL in several domains compared to patients with wounds experiencing less pain.<sup>24, 30, 31</sup> One

study compared patients with amputation and patients with chronic wounds, with significantly poorer scores in the domain bodily pain presented for the latter.<sup>33</sup> An association between pain and lower HRQoL was also supported by two other studies reporting improvements in the domain bodily pain and subsequent increases in overall HRQoL after wound healing for patients with chronic wounds.<sup>29, 40</sup>

None of the included HRQoL studies addressed or assessed the caregivers' perspective and their HRQoL.

*Insert Table 3 here*

Eleven cost-of-illness studies assessing patients with chronic wounds were found for the cost data. Participants were identified through hospital- and patient records, Diagnosis Related Group (DRG) codes, International Classification of Diseases (ICD) codes, health insurance companies, wound clinics and national disease specific registers. The study settings captured costs from inpatient, outpatient, community and primary care perspectives e.g. hospitals, wound centres and foot care teams.<sup>44-46</sup> Cost data in this section were converted into annual costs when possible to enable a better overview.

Diabetes related amputations reported the largest proportion of costs for chronic wounds,<sup>38, 45, 47, 48</sup> a cost largely associated with additional inpatient days when hospitalised compared to non-diabetic patients.<sup>45, 48</sup> Cost for hospitalisation for diabetes related amputations ranged from US\$ 12·851<sup>49</sup> to 16·267<sup>47</sup> (median) per patient admitted. Davis *et al.*<sup>49</sup> estimated that 9·3% of the total cost for diabetes-related hospital admissions was related to amputations. One study presented diabetes related amputation costs from a societal perspective, including both direct- and indirect

costs, estimated at US\$ 33·499 in year 2002 (total annual cost per patient).<sup>38</sup> Long treatment times after amputation e.g. rehabilitation, outpatient costs and other additional long-term care also contributed to substantial costs related to amputations.<sup>38, 48</sup>

Cost for leg ulcers were assessed in five studies in primary care, outpatient and community settings (one study covered both in- and outpatient settings). Leg ulcers presented considerably lower costs than amputations, with costs that ranged from US\$ 449<sup>50</sup> to 2·307<sup>51</sup> annually per patient for primary- and outpatient care, and between US\$ 13·334<sup>46</sup> and 13·761<sup>44</sup> from a societal perspective. Wound treatment costs (e.g. medical equipment and consumables) were considerable for chronic wound management across all study settings.<sup>38, 44, 48, 50</sup> One study compared wound treatment costs for in- and outpatients in hospital settings, and reported no difference for the cost for wound treatment, but detected a lower cost for consumables for the non-hospitalized patients.<sup>52</sup> Large ulcer size, and more severe ulceration<sup>38, 44, 50</sup> with subsequent longer treatment duration (>6 months) (nurse visits for wound dressings and drug prescriptions from physicians, e.g. analgesics and antibiotics),<sup>44, 50, 51</sup> were associated with higher costs. Two studies presented more than doubled costs for patients having larger and more than one wound, when compared to smaller ulcers with shorter healing times.<sup>44, 50</sup> Having several chronic wounds was found to be more cost enlarging due to longer work time for nurses and the utilisation of more wound care products.<sup>38, 44</sup> Pain severity was another cost-contributing factor related to an increased consumption of analgesics for pain management.<sup>46</sup> One large study assessing costs for chronic wounds from a Medicaid service claim database concluded that hospitalisation made up the larger proportion compared to physician visits and prescription costs.<sup>53</sup> Three studies assessed indirect costs,<sup>38, 44, 46</sup> and reported costs for early retirement,<sup>38, 44</sup> temporary work disability,<sup>38, 44</sup> and productivity losses due to wound dressings (but failed to

describe how this was assessed).<sup>46</sup> The latter study also assessed but did not calculate or report costs for the patients' productivity losses since "only a few participants in the study were still working".<sup>46</sup>

## **Discussion**

This systematic review attempted to have a clear definition for chronicity of wounds even though there is no pre-established consensus, to ensure the inclusion of only chronic wounds. The review reveals a poorer HRQoL for patients with chronic wounds, and that wound related costs are considerable. The inferior HRQoL observed for patients with chronic wounds is worst for physical pathologies, and are similar or markedly lower in some domains when compared to HRQoL for other chronic conditions e.g. chronic obstructive pulmonary disease and cardiovascular diseases.<sup>54,55</sup> Pain and reduced mobility were reported as the main problem areas for patients with wounds, which underlines the urgent need for improvements in those domains to alleviate the most negative impacts of the condition.<sup>56</sup> It should also be noted that HRQoL may differ between participants due to what wound treatment patients received, if any additional complications were present as well as the current stage of the wound healing trajectory. For example, decreases in HRQoL are often associated with an advancement in the severity of the wound.<sup>38</sup>

No publication assessing HRQoL for informal caregivers of patients with chronic wounds was identified in the review, impeding a more comprehensive exploration of the humanistic and economic burden of chronic wounds.

For costs, diabetes related amputations presented the greatest costs. These were attributed to lengthy hospital stays and long-term costs e.g. rehabilitation and outpatient treatments. In

comparison to patients admitted for heart failure, the median cost per hospitalisation were larger for diabetes related amputations (US\$ 12,851 to 16,267 vs. US\$ 10,454 for heart failure),<sup>57</sup> indicating that amputation costs are similar to other major public health scourges. The substantial cost for diabetes related amputations shows the importance of preventing chronic wounds from developing into a severe state where amputation is unavoidable. Previous research suggests that cost-saving preventions for amputations should be early and incorporate a comprehensive wound management strategy.<sup>58</sup> Appropriate interventions and management for wounds can lower the risk of amputation by 47% to 72% depending on strategy (e.g. education, multidisciplinary approaches, wound monitoring, vascular surgery interventions, and the use of therapeutic foot wear)<sup>58-60</sup> with cost reductions from US\$ 85,000 up to 1,100,000 per year and intervention.<sup>59</sup> The review revealed that costs for leg ulcers were lower than for amputations and predominantly related to community- and primary care. Although presenting lower costs than amputations, the cost for leg ulcers will accelerate when wounds persist for many years. The work time of nurses and costs for dressing materials are considered the main cost causative components for leg ulcers, which suggests that reduced working time and dressing frequencies would lower costs for leg ulcers.<sup>61</sup> This could be achieved by early detection of changes in the wound that result in worsening conditions, and subsequently providing prompt treatment before the wound requires more extensive care.<sup>58</sup> To enable timely identification of such changes in wounds, extended wound monitoring is fundamental, while to avoid adding costs for nurses work time, technology based interventions such as tele monitoring could be a solution.<sup>62</sup> Other preventive and cost-effective treatments for leg ulcers when the underlying cause is venous insufficiency are compression therapies<sup>63, 64</sup> and vascular surgery.<sup>64</sup> Few articles in the current review addressed indirect costs. A plausible reason for this might be

that chronic wounds often occur in patients above retirement ages.<sup>44</sup> However, a previous study reported substantial indirect costs related to work absenteeism among patients with wounds.<sup>65</sup> Hence, capturing indirect costs are important to comprehensively assess the economic burden of chronic wounds.

Several studies assessed for eligibility in the review failed to specify wound chronicity and were therefore excluded, e.g. pressure ulcers were only labelled as: chronic” in one of the included articles since this wound type is more commonly is referred to in terms of stages of tissue loss. Introducing a specified duration/label for inclusion may have excluded relevant articles, but at the same time this approach ensured that included article were in fact focused on chronic wounds, which adds to the robustness of the findings. Including only articles in English, as well as the overrepresentation of articles from European countries, may have resulted in a reduced generalizability of the findings. Characteristics of study populations were not always clearly stated which is an important aspect given that the patients often were recruited from rather homogenous settings e.g. clinics, hospitals which also affects the generalizability. Furthermore, the participants were predominantly over 60 years of age, which possibly caused a lower HRQoL related to decreased mobility and increased probability of being comorbid in older ages.

However, the risk of developing chronic ulcers increases with age hence reflects the target study population.

For the economic burden of leg ulcers, comparing costs for ulcers of vascular and arterial aetiologies would have been valuable, but no cost study differentiated between ulcers of vascular and arterial aetiologies, prohibiting comparisons.

Large variations across the studies collecting data for HRQoL (different instruments used) and variations in the costs being assessed impeded larger scale pooled estimates for HRQoL and

feasible cost comparisons. It can be argued that including only generic HRQoL into this systematic review may have captured the impact of chronic wounds on HRQoL less adequately due to common comorbidities in this patient population.<sup>66</sup> However, information on HRQoL based on data collected by condition-specific tools prevents comparisons of HRQoL across diseases which is important for decisions that concern resource allocation.<sup>66</sup>

Methodological discrepancies for cost articles comprised wounds of various aetiology and severity levels being assessed (with subsequently different treatments), further complicated by assorted cost categories and cost-perspectives being applied. Inconsistency of evidence can also be attributed to the lack of sensitivity analyses to account for the degree of uncertainty of cost valuations (only conducted in one study), lack of presentation of detailed cost data, variation in study design and valuations of unit costs as well as costs being reported from different healthcare systems in various countries making it difficult to conduct feasible cost comparisons. For example, multiple studies did not present the sources of where data for unit costs were retrieved, and some studies assumed that all health care utilisation was related to the wound treatment. This is most likely not the case since participants may suffer from other comorbidities. Moreover, most studies presented patients with chronic wounds without a comparison group, thus making it difficult to understand the burden of chronic wounds in relation to healthy individuals and other patient groups.

In conclusion, patients with chronic wounds report low HRQoL and the condition imposes a substantial economic burden. To improve HRQoL and reduce costs for this patient group, better wound care management must be implemented. This study also detected a lack of published HRQoL data for the caregivers of patients with chronic wounds, and notes that only a few cost studies included indirect costs. Future studies need to assess HRQoL of informal caregivers and



capture productivity losses for patients with chronic wounds to comprehensively estimate the economic burden from a societal perspective.

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### **Footnotes**

CINAHL	Cumulative Index to Nursing and Allied Health Literature
DRG	Diagnosis Related Group
EBM	Evidence-based Medicine
EQ-5D	EuroQol-5D
EQ-5D VAS	VAS EuroQol-5D Visual Analogue Scale

EBSCO	EBSCO Information Services
EMBASE	Excerpta Medica dataBASE
HRQOL	Health-related quality of life
ICD	International Classification of Diseases
JBI	Joanna Briggs Institute
MEDLINE	Medical Literature Analysis and Retrieval System Online
NHP	Nottingham Health Profile
NRS	Numerical Rating Scale
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSC	Physical summary component
QLI	Ferran's and Power's Quality of Life Index
SF-36	MOS 36-item Short-Form Health Survey
SF-12	MOS 12-Item Short Form Survey Instrument
VAS	Visual Analogue Scale
WHOQOL-bref	World Health Organization Quality of Life-BREF

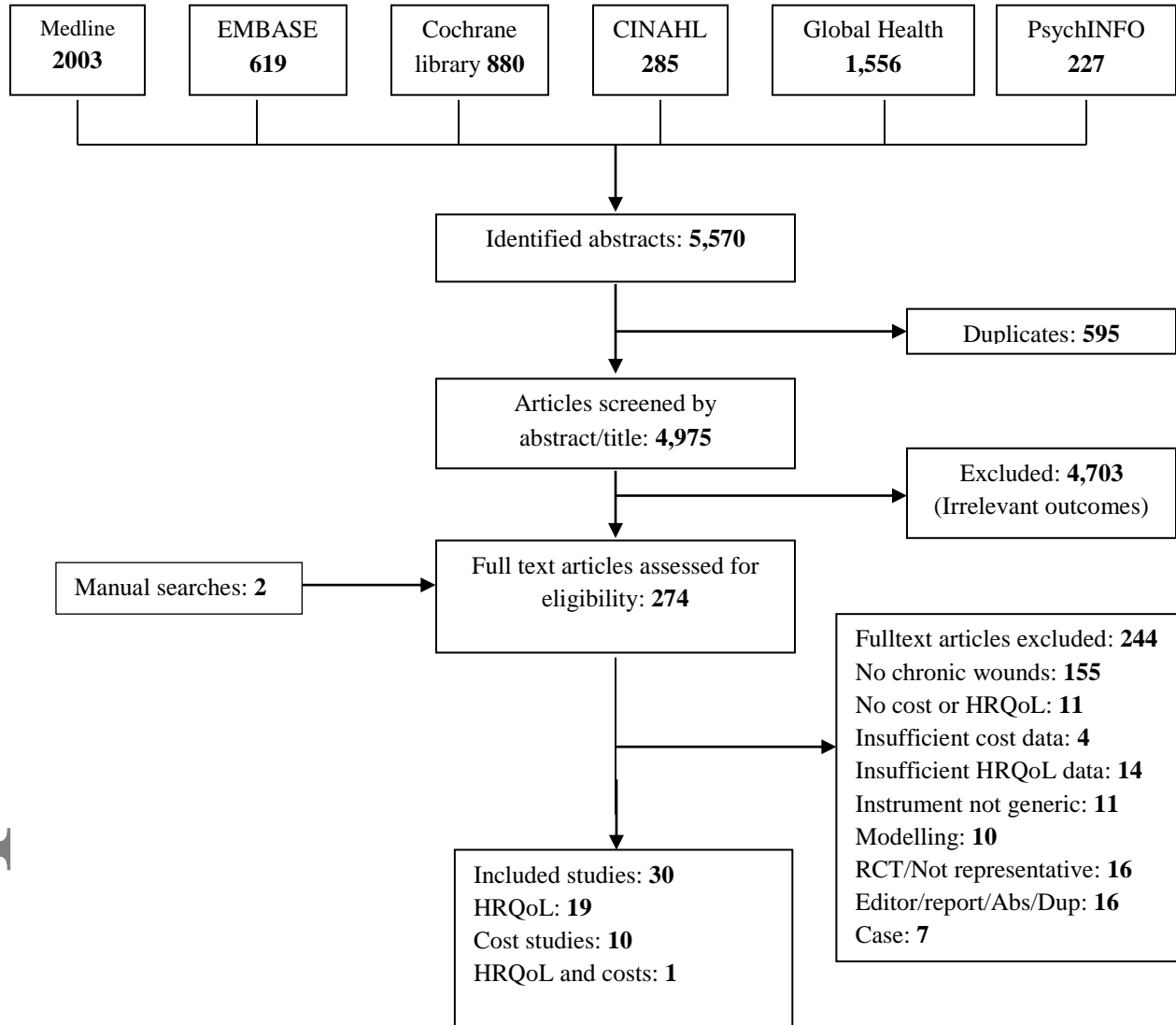
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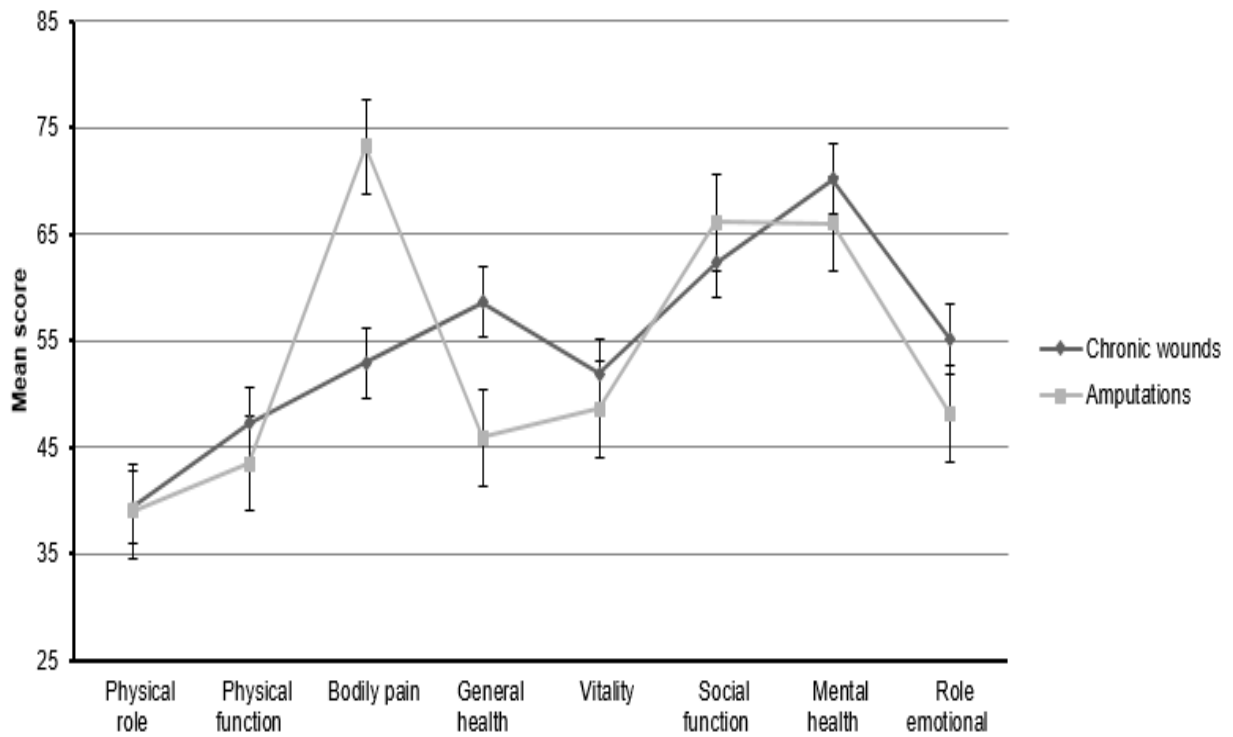
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**Figure 1.** Flow chart of study selection



**Figure 2.** Average scores with 95% confidence intervals for the eight domains of SF-36**Table 1.** Characteristics of the included HRQoL studies presented by wound type (n=20)

Reference	Country	Type of wound	Setting	No. of patient	Age (mean)	HRQoL instrument

				s	n)	
Blome et al. 2014 <sup>27</sup>	German y	Leg ulcer	Wound care clinic, hospital vascular unit	154	65	EQ-5D, EQ-5D VAS, NRS
Renner et al. 2014 <sup>24</sup>	German y	Leg ulcer	Outpatient wound clinic	103	68	EQ-5D
Faria et al. 2011 <sup>35</sup>	Brazil	Leg ulcer	Hospital, outpatient clinics, family health clinic	80	64	SF-36
Moffatt et al. 2009 <sup>26</sup>	United Kingdo m	Leg ulcer	Acute and community leg ulcer service	95	59 % ≥7 5	NHP
Park et al. 2008 <sup>30</sup>	Brazil	Leg ulcer	Outpatient clinic	40	68	WHOQL- bref + PI- NRS
Guarnera et al. 2007 <sup>31</sup>	Italy	Leg ulcer	Outpatient vascular surgery and angiology unit	381	*	SF-12 + VAS
Yamada et al. 2005 <sup>28</sup>	Brazil	Leg ulcer	Vascular surgery outpatient clinics	89	53	Ferran's and Power's QLI
Jull et al. 2004 <sup>36</sup>	New Zealand	Leg ulcer	Population based	230	75	SF-36
Franks et al. 2003 <sup>40</sup>	United Kingdo m	Leg ulcer	Community (general practice, community nurses and hospital services in and out-patient)	118	78	SF-36



Chase et al. 2000 <sup>34</sup>	United States	Leg ulcer	Outpatient clinics	21	72	SF-36
McDonald et al. 2014 <sup>42</sup>	Australia	Diabetes amputation	Diabetes and amputee member's association in Sydney	50	63	WHOQOL-bref
Happich et al. 2008 <sup>38</sup>	Germany	Diabetes amputation	Multicentre	71	67/ 68	SF-12
Ribu et al. 2007 <sup>43</sup>	Norway	Diabetes amputation	Outpatient clinics	26	60	SF-36
Willrich et al. 2005 <sup>23</sup>	USA	Diabetes amputation	Hospital rehabilitation centre	20	*	SF-36
Boutolle et al. 2008 <sup>33</sup>	France	Diabetes amputation  Diabetic foot ulcer	Patients living at home one year after amputation  Outpatients receiving regular care for diabetic foot ulcers	25  9	68  70	SF-36  SF-36
Alzahrani 2013 <sup>39</sup>	Saudi Arabia	Diabetic foot ulcer	Outpatient diabetic foot clinic	60	57	SF-36
Garcia-Morales et al. 2011 <sup>25</sup>	Spain	Diabetic foot ulcer	Diabetic foot ulcer unit	163	62	SF-36
Goodridge et al. 2006 <sup>37</sup>	Canada	Diabetic foot ulcer	Hospital/diabetic foot ulcer clinic	57	64 <sup>a</sup>	SF-12

de Souza et al. 2013 <sup>41</sup>	Brazil	Ulcers of mixed aetiologies	Hospital and outpatient clinic	75	62	SF-36
Oien et al. 2013 <sup>29</sup>	Sweden	Ulcers of mixed aetiologies	Primary care wound clinic	50	79 <sup>b</sup>	EQ-5D, EQ-5D VAS

\* Age was not reported or reported in an incomprehensive manner

<sup>a</sup> Mean age for the whole sample also consisting of healed wounds

<sup>b</sup> Presented as median

EQ-5D	EuroQol-5D
EQ-5D	VAS EuroQol-5D Visual Analogue Scale
VAS	Visual Analogue Scale
NRS	Numerical Rating Scale
NHP	Nottingham Health Profile
SF-36	MOS 36-item Short-Form Health Survey
SF-12	<u>MOS 12-Item Short Form Survey Instrument</u>
Ferran's and Power's QLI	Ferrans and Powers Quality of Life Index
WHOQOL-bref	WHO Quality of Life-BREF

**Table 2.** Details of extracted SF-36 domain scores (n=8)

Reference	Group	N	SF-36 domain scores, mean (SD)							
			Physical role	Physical function	Bodily pain	General health	Vitality	Social function	Mental health	Role emotional
Alzahra ni 2013	Chronic wounds	60	32,13 (5,4)	38,97 (5,6)	31,53 (7,1)	30,95 (4,3)	33,72 (5,6)	43,59 (11,6)	69,21 (5,7)	57,11 (61)
	Control DM	60	71,73 (1,8)	75,10 (2,1)	68,25 (11,1)	67,63 (3,6)	68,61 (3,2)	75,12 (12,07)	77,60 (7,8)	78,87 (8,9)
	Control healthy	60	81,25 (2,7)	84,75 (4,4)	85,03 (3,6)	76,02 (1,8)	75,67 (2,6)	83,68 (3,6)	84,43 (3,2)	85,65 (4,06)
Boutoille 2008	Chronic wounds	9	25 (28)	62 (18)	33 (17)	35 (18)	59 (14)	53 (19)	62 (9)	63 (42)

(Median )	Minor amputations	19	58 (39)	55 (29)	75 (26)	39 (18)	46 (20)	69 (26)	61 (19)	61 (46)
	Major amputations	6	33 (34)	35 (39)	84 (20)	54 (20)	55 (22)	62 (25)	65 (21)	33 (42)
Chase 2000	Chronic wounds	21	67,9	56,2	75,5	72,7	50	83,9	80	81
Faria 2011	Chronic wounds	80	22,5	48,68	57,81	66,18	59,37	56,25	64,9	41,61
	Control	80	75,31	80,06	72,29	73,13	70,75	81,6	71,94	80,34
Franks 2003	Chronic wounds	118	41,5	29,6	53,3	54,9	46,3	56,5	69,1	57,1
	Control	118	63,0	50,7	65,5	58,2	48,7	78,6	73,2	84,9
Jull 2004	Chronic wounds	230	43,2	49,5	55,3	59,2	53,2	69,9	76,2	68,9

**Table 3.** Characteristics of the included cost studies presented by wound type (n= 11)

Reference	Country	Type of wound	Economic perspective	Annual cost per patient adjusted	Cost components	
					Direct costs	Indirect costs

				ust ed for yea r 201 5 (co st yea r)		
Augustin et al. 2014 <sup>46</sup>	Ger man y	Leg ulce r	Soci etal  Stat utor y Heal th Insu ranc e	US \$ 13, 334 (20 06)  US \$ 11, 303 (20 06)	Community cost for drugs, dressing material, physician fees and inpatient cost	Prod uctiv ity losse s for patie nts and fami ly mem bers
Tennvall et al. 2006 <sup>50</sup>	Swe den	Leg ulce r	Heal th care prov ider	US \$ 449 ulc ers  <1 0c	Primary- and community care cost, cost for nurses working time, travel cost, dressing material and inpatient costs	N/A

				m <sup>2</sup> (20 05) a  US \$ 1,1 81 ulc ers ≥1 0c m <sup>2</sup> (20 05) a		
Muller- Buhl et al. 2013 <sup>31</sup>	Ger man y	Leg ulce r	Heal th care prov ider	US \$ 2,3 07 (20 08)	Primary care cost, cost for prescriptions, drugs and dressing materials	N/A
Purwins et al. 2010 <sup>44</sup>	Ger man y	Leg ulce r	Soci etal  Stat utor y	US \$ 13, 761 (20 07)	Wound care centre cost, cost for drugs, dressing materials, therapeutics, physician/nurse fees, inpatient cost, transport and laboratory cost, co-payments and out-of-pocket expenses	Prod uctiv ity losse s, retra ining

			Heal th Insu ranc e  Patie nt cost	US \$ 10, 974 (20 07)  US \$ 1,4 78 (20 07)		, early retir eme nt and days lost to sick leav e.
Assadian et al. 2011 <sup>52</sup>	Ger man y	Leg ulce r Pres sure ulce r	Heal th care prov ider	US \$ 8,6 64 (20 00) a  US \$ 6,3 91 (20 00) a	Hospital cost, wound treatment costs including staff cost, surgical procedures and dressing material	N/A
Kumar et	USA	Ulc	Med	US	Hospital cost, physician fees and cost for prescription	N/A

al. 2004 <sup>35</sup>		ers of mix ed aeti olog ies	icaid fee- for- servi ce	\$ 597 ,62 3 <sup>b</sup> (20 00)		
Alzahrani 2013 <sup>47</sup>	Saudi Arabia	Dia bete s amp utati on Min or resp . maj or	Heal th care prov ider	US \$ 13, 950 res p- 16, 267 (20 08) c	Hospital cost	N/A
Davis et al. 2006 <sup>49</sup>	Australia	Dia bete s amp utati on Min or resp . maj or	Heal th care prov ider	US \$ 12, 851 (20 00) d	Hospital cost	N/A

Happich et al. 2008 <sup>38</sup>	German y	Diabetes amputation	Societal	US \$ 19,635 <year Stat 200 2 (20 02) Health Insurance \$ 33,499 in year 200 2 (20 02)  US \$ 13,906 <year 200 2	Hospital - and outpatient care costs, patient charges, rehabilitation, physician fees, diagnostic, laboratory, drugs, help services, transportation and other health care provider costs	Productivity losses for temporary working disability, early retirement and early retirement pensions.
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				(2002) US \$ 28,511 in year 2002 (2002)		
Hoffman et al. 2013 <sup>48</sup>	Germany	Diabetes	Insurance claims data	US \$ 77,790 (2009)  US \$ 71,035 (2009)	Hospital- and outpatient care costs, cost for rehabilitation, , outpatient drug prescription, non-physician services, durable medical equipment, long-term care (up to one year after amputation )	N/A
		Non-diabetes	amputation			

Tennvall et al. 2000 <sup>45</sup>	Swe den	Dia bete s r/t amp utati on Min or resp . maj or	Heal th care prov ider	US \$ 35, 393 res p. US \$ 31, 922 (19 97) e	Hospital- and outpatient care costs, surgery, diagnostic investigations, antibacterial, visits to foot-care team, orthopaedic appliances, dressing materials, nurse staff cost	N/A
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<sup>a</sup> Original cost converted to annual to enable comparisons

<sup>b</sup> Total mean cost over 5 years

<sup>c</sup> Total median cost

<sup>d</sup> Median cost per hospital admission

<sup>e</sup> Average cost per patient until healing