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REVIEW ARTICLE

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More than half of persons with lower limb amputation suffer from chronic back pain or residual limb pain: a systematic review with meta-analysis

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ABSTRACT

Purpose: The aim of this study is to systematically review and critically assess the methodological quality of literature regarding prevalence, characteristics and factors influencing pain, other than phantom limb pain (PLP) in persons with lower limb amputation (LLA).

Materials and methods: A systematic review was performed (PROSPERO CRD42019138018). Literature was searched using PubMed, EMBASE, PsycINFO, and PEDro. Studies were included if describing pain other than PLP at least three months after amputation. For residual limb pain (RLP) and back pain, a meta-regression was performed.

Results: Fifty-one studies were included in which predominantly young males with a unilateral traumatic amputation using a prosthesis were investigated. Pooled prevalence of RLP was 0.51 (95% CI 0.40–0.62) with a positive association with presence of back pain ($p = 0.044$) in the univariate meta-regression. Pooled prevalence of back pain was 0.55 (95% CI 0.45–0.64), with a positive association of time since amputation ($p < 0.001$) and co-occurrence of RLP ($p = 0.050$).

Conclusions: Back pain and RLP are common after LLA. The prevalence of back pain was positively associated with the presence of RLP, and vice versa. Future studies should give more attention to other chronic pain types, to persons with a diabetic or vascular cause of amputation, and to pain-related interference.

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KEYWORDS
Pain; amputation; meta-analysis; review; back pain; residual limb pain

➤ IMPLICATIONS FOR REHABILITATION

- Both back pain and residual limb pain occur in more than 50% of persons with lower limb amputation (LLA), and both pain types are positively associated.
- Clinicians should be aware that chronic pain is common after LLA and can have a significant impact on the functioning of persons with LLA.
- Future research on this topic should give more attention to other chronic pain types, to persons with a diabetic or vascular cause of amputation, and to pain-related interference.

Introduction

Chronic pain, specific and non-specific, is common after lower limb amputation (LLA) [1]. Chronic pain is defined as recurrent or persistent pain which persists past the normal time of healing. Three months is the most common applied division between acute and chronic pain [2]. Most of the post-amputation pain literature has focused on phantom limb pain (PLP), and to a lesser extent on residual limb pain (RLP). Phantom limb pain is defined as painful sensations in the missing part of the limb [2]. Residual limb pain is pain in the part of the amputated limb that is still present [2]. Residual limb pain can be prosthesis-related, neurogenic, arthrogenic, vascular, osteogenic including heterotopic ossification, dermatogenic, sympathogenic, referred, and can be related to wound problems [3]. In literature, these types of pain are seldom distinguished [4,5]. In addition to RLP and PLP, recently more and more attention has been given to other types of pain occurring after LLA. Back pain seems to be occurring more frequently in persons with LLA compared to the general population [6]. The exact cause is unknown, but biomechanical factors like leg length discrepancy, spinal movement during prosthetic gait, prosthesis type, skeletal muscle atrophy, and strength loss may play a role [7–10]. Other, again less investigated pain types are knee pain and hip pain, in both the prosthetic leg and the contralateral leg. All mentioned pain types seem to occur frequently and can have a significant impact on the functioning of persons with LLA [5,6,11]. Pain-related interference seems to vary depending on the type of pain and the number of pain sites [12,13]. Pain can significantly impact the health-related quality of life of persons with LLA [14]. Additionally, experiencing multiple pain conditions can negatively influence the psychosocial adjustment to LLA [15].

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Supplemental data for this article can be accessed here.

To the best of our knowledge, no overview of the literature of pain types other than PLP exists, therefore, the extent of the problem is currently unknown. Such an overview could inform the clinician working with persons with LLA concerning the prevalence and characteristics of the different kind of pain types, and possible influencing factors for these pain types. Furthermore, this overview could reveal possible gaps in knowledge concerning pain in persons with LLA, which in return provides directions for future research.

Therefore, the aim of this study was to systematically review and to critically assess the methodological quality of the literature regarding the prevalence, characteristics and factors influencing pain, other than PLP in persons with LLA, and to perform a meta-regression if sufficient data were present.

Materials and methods

Study identification and selection

This systematic review and meta-analysis was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplemental file 1) [16]. A systematic literature search was performed in PubMed, EMBASE, PsycINFO, and PEDro from inception to April 2020. The search was performed using database specific keywords and free text words associated with amputation, lower extremity, including all amputation levels, and pain (Supplemental file 2). In PEDro, no database specific keywords were available. Therefore, 12 different combinations of free text words were used (Supplemental file 2). An information specialist has assisted with the preparations of the search. No restrictions to publication year were made. The protocol for this systematic review was registered on PROSPERO (Central Registration Depository: CRD42019138018).

Studies were selected in two rounds. In the first round, titles and abstracts were assessed. In the second round, full-texts were assessed. Two observers (MO, JHBG) assessed independently all studies at each stage of the review according to our predefined inclusion and exclusion criteria. Only studies that were excluded by both observers were removed. If opinions differed, agreement through discussion was reached. When disagreement remained, a third observer (PUD) provided a binding verdict. The reason of exclusion was recorded for the full-text selection. As measure of agreement, Cohen's kappa was calculated between the two observers for both stages of the selection process.

The adjusted cross-sectional/prevalence checklist of the Agency for Healthcare Research and Quality (AHRQ), was used by two authors independently to assess risk of bias assessment of the included studies (Supplemental file 3) [17,18]. We decided to use this checklist due to its focus on quality assessment of cross-sectional studies.

Inclusion and exclusion criteria

Observational studies were included if the sample size was at least 10 persons with LLA (Syme amputation or more proximal up to hemipelvectomy), and if describing any type of pain (RLP and/or back pain, and/or any other type of pain) present at least three months after amputation, with type and location of pain being specified. The number of 10 persons per study was chosen because studies of this small size would have a great uncertainty in estimated pain prevalence (wide 95% confidence intervals) and would not be of added value to our review. Excluded were experimental or laboratory studies, expert opinions, case reports, case series, letters to the editor, reviews, and studies written in a language other than English, Dutch, or German. Studies were also excluded if containing only data about PLP, and if pain was studied related to the effectiveness of an intervention. Furthermore, studies solely describing amputation due to complex regional pain syndrome (CRPS) were excluded, because these data have been described in a recent systematic review [19].

Summary data extraction

Studies were assessed for design, subject characteristics, and level of functioning. Pain prevalence, pain frequency, pain intensity, and pain impact were grouped according to RLP, back pain, and other types of pain. If data were not presented in the studies, authors were requested by e-mail to provide additional information.

Pain prevalence was grouped by reason for amputation and level of amputation; unilateral above knee amputation including knee-disarticulation and more proximal amputation levels up to hemipelvectomy, unilateral below knee amputation including transtibial amputation and Syme amputation, and bilateral amputation including any bilateral amputation between Syme amputation and hemipelvectomy level.

Descriptive statistics were calculated in IBM SPSS Statistics 23 (Armonk, NY). A meta-analysis, random effects model, was performed with prevalence as outcome variables for RLP and back pain, using Comprehensive Meta-Analysis version 3. We used a random effects model because of clinical and methodological heterogeneity between studies. Studies were included in the meta-analysis when presenting outcome and potential predictors for RLP and/or back pain. Potential predictors of back pain and RLP were explored for the association with the reported prevalence of back pain and RLP univariately. The following potential predictors were explored: mean age of the study population, time since amputation, proportion traumatic amputations, proportion vascular amputations, proportion males, proportion of persons using a prosthesis, proportion below knee amputations, proportion above knee amputations, proportion bilateral amputations, proportion RLP/back pain and publication year. Studies did not need to report all these data to be included in the analyses. Due to lack of data we could not take other potential predictors into account. No within-study data were available for all studies, therefore only between-study data were taken into account. Logit event rates (natural logarithm of (prevalence/1 – prevalence) were used to prevent the disproportionately weighing of proportions at the lower and higher range. Funnel plots were not made because of a clinical and methodological heterogeneity between included studies. Outliers, however, were explored for their impact on reported prevalence using Comprehensive Meta-Analysis version 3. All p values were two-sided, with $p \leq 0.05$ considered statistically significant.

Results

Study characteristics

In total, 5539 studies were identified after excluding duplicates and triplicates (Figure 1). After screening by title and abstract, 5393 studies were excluded (Kappa 0.451, absolute agreement 0.973). After full-text screening, another 101 studies were excluded (Kappa 0.674, absolute agreement 0.844). Five studies were included after a reference check of the included studies. One study was found by coincidence, not stating any keywords in title or abstract. In total, 51 studies were included in this review. Three times two studies used the same dataset. Data per pair

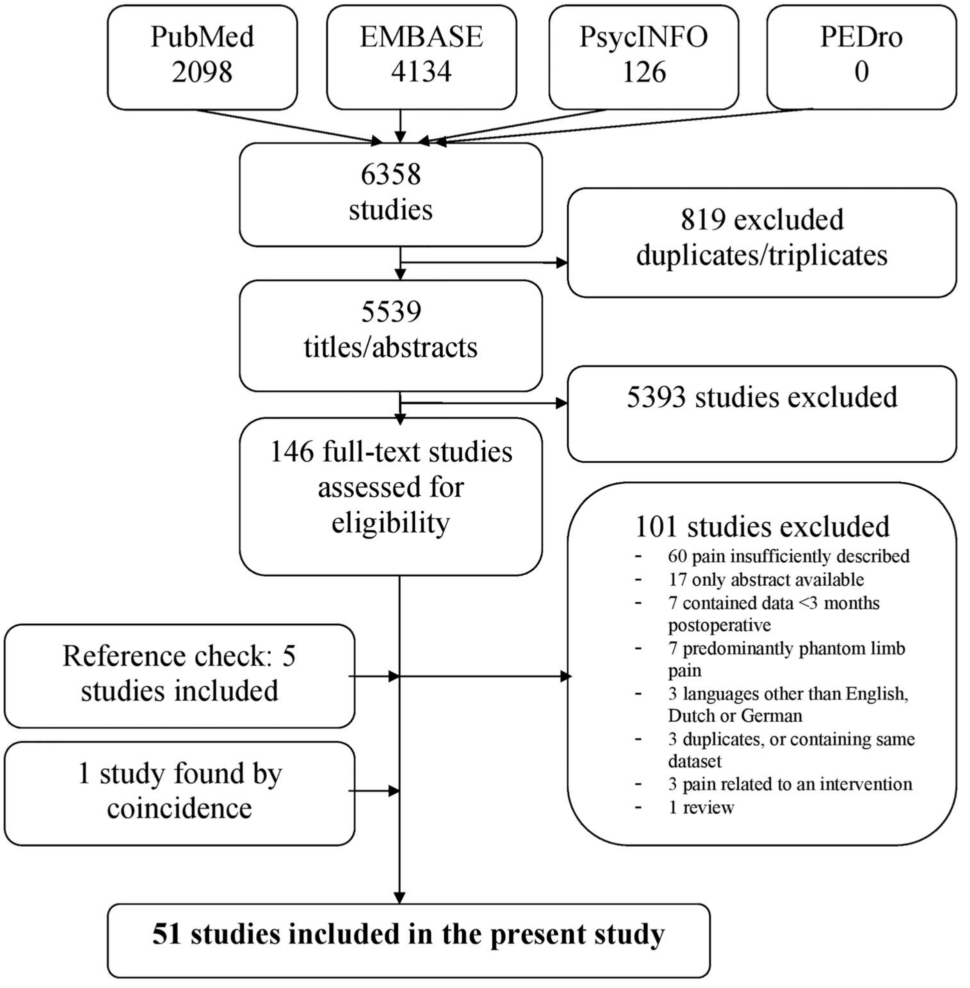

Figure 1. Flowchart showing the inclusion process.

were combined in the table and meta-regression [5,6,20–23]. Nine authors were requested to provide additional data [4,5,24–30]. Three authors responded to our request and their data were processed in the analyses [5,26,27]. Five studies used a retrospective cohort design [11,31–34], three studies a prospective cohort design [25,35,36], one study was a secondary analysis of a randomized clinical trial (Table 1) [25]. All other studies were cross-sectional in design. Persons were most often identified in hospital and rehabilitation center registries, in some studies specific national databases were used. In most studies, questionnaires were sent to participants to gather the necessary data. Two studies used International Classification of Diseases Ninth or Tenth Revision codes (ICD-9 or ICD-10) [33,34].

Patient characteristics

Regarding RLP and back pain, number of persons ranged from 19 to 1569 per study, in total 10 201 persons. The weighted mean ± SD (standard deviation) age of study persons was 51 ± 10 years, ranging from 23 to 73 years. The weighted mean ± SD time since amputation was 15 ± 7 years, ranging from 0.4 to 32 years. The median proportion prosthesis use was 0.98 (IQR 0.80–1.00), the median proportion male gender 0.82 (IQR 0.70–0.99). Most persons had undergone a traumatic amputation with a weighted mean proportion of 0.68, followed by the proportion vascular cause of 0.20, and a proportion diabetic cause of 0.08. A mean weighted proportion of 0.51 had undergone an above knee amputation, a mean proportion of 0.40 a below knee amputation, and a mean proportion of 0.08 a bilateral amputation.

Risk of bias assessment

Inter observer agreement of the risk of bias assessment expressed as kappa was 0.897 (absolute agreement 0.946). The mean score of the quality assessment was 6.8, ranging from 3 to 11 points out of 12 possible points (Supplemental file 3). In 22 out of the 51 studies, time frame of inclusion was reported. Exclusion criteria were reported in 26 out of 51 studies. Subjects were recruited consecutively or population based in 20 studies. Confounding was assessed and controlled for in 32 out of 51 studies, 12 studies reported missing data.

Residual limb pain

Thirty-three studies reported on RLP in persons with LLA ($n = 7062$). The reported RLP prevalence in the individual studies ranged from 6% to 92% (Table 2). Eighteen studies reported RLP within a certain timeframe, ranging from only actual pain to pain during the last three months (Table 2). Residual limb pain was mostly reported as being intermittent in 61–87% of persons and as constant in the remaining persons [5,42,43,49,53]. Residual limb pain episodes occurred four times per week or less in most of the persons; however, a frequency of more than four per week was reported in 30–42% of persons [5,15,49]. If being reported, the

Table 1. Study and patient characteristics.

Author, publication year	Study design	Patient recruitment	Source of pain data	Reason for amputation (%) Trauma	Vascular	Diabetes	Infection	Tumor	Congenital	Other/ unknown	♂/♀	Age Mean (range)	Years (range) since amputation	Amputation level	Level of functioning
Burke et al., 1978 [37]	CS	PO	Q,PE,RA	81			12	7			38/4	48.4	24.6	1 HD 19 AK 22 BK	100% prosthesis use
Kramer et al., 1979 [38]	CS	H	FI,PE,RA	100							111/–	56.4	31.5 (27–36)	111 TF	98% prosthesis use
Hoaglund et al., 1983 (trauma) [39][a]	CS	PO,H	Q,TI,PE	74	23			2			132/–	47	20.7 (1–39)	38 AK 74 BK 1 KD 2 Syme 17 BL	Prosthesis use: 86% all day, 11% 5–8 h Walking distance: 3% none, 5% only in home, 45% 1–6 blocks, 23% >6 blocks, 24% unlimited Devices: 61% none, 28% one cane, 5% two canes, 5% wheelchair. 12% assistance in ADL 72% employed. 11% unemployed due to amputation
Hoaglund et al., 1983 (vascular) [39][a]											42/–	60	2.3 (1–21)	1 HD 8 AK 21 BK 1 Syme 11 BL	Prosthesis use: 51% all day, 24% 5–8 h Walking distance: 10% none, 21% only in home, 55% 1–6 blocks, 10% >6 blocks, 5% unlimited Devices: 25% none, 39% cane, 19% 2 canes, 17% wheelchair. 38% assistance in ADL 26% employed. 21% unemployed due to amputation
Friberg, 1984 [8]	CS	RC	Q,PE,RA	100							113/–	65.1 (54–80)		29 AK 84 BK	100% prosthesis use TF 41% highly physical active TT 51% highly physical active
Jensen et al., 1984 [40]	P,CO	H	FI,PE		88		2	9			29/29	69.8 (24–91)		23 AK 1 KD 32 BK 2 UPL	71% prosthesis use at latest examination
Pohjolainen, 1991 [31]	R,CO	PO	FI,PE	9.7	81		0.6	6.5		1.9	124	62.8 (14–87)[b]		46 AK 78 BK	100% prosthesis use
McCartney et al., 1999 [32]	R,CO	DB	Q							100	24/16			12 AK 28 BK	93% prosthesis use 40% received home help services, 23% additional nursing support, 13% both
Smith et al., 1999 [41]	CS	H	Q	66.6	40.7[c]	40.7[c]	40.7[c]	1.1	33.3		79/13	(22–81)	18.0, SD 17.2 (1–53)	23 TF 3 KD 58 TT 8 Syme	100% prosthesis use 37% employed
Ehde et al., 2000 [5,6][d,e]	R,CS	H	Q	57.2	17.4	8.5	20.9	6.0	2.0	37.3	165/36	56.0, SD 14.0	15.4, SD 16.0	65 TF 12 KD 115 TT 3 Syme 6 HD	83% prosthesis use: average 13.2 h/day, SD 4.1 31% employed. 29% unemployed due to disability, 3% due to pain

(*continued*)

Table 1. Continued.

Author, publication year	Study design	Patient recruitment	Source of pain data	Reason for amputation (%): Trauma	Vascular	Diabetes	Infection	Tumor	Congenital	Other/ unknown	♂/♀	Age Mean (range)	Years (range) since amputation	Amputation level	Level of functioning
Dillingham et al., 2001 [42]	CS	H	TI	100							68/10	32.9, SD 10.6	7.5, SD 2.8	16 TF 13 KD 40 TT 2 F 7 BL	95% prosthesis use. Average prosthesis use 80.5 h/week, SD 32.9 19% used a cane; 13% crutches; 12% wheelchair all or mostly
Gallagher et al., 2001 [43]	CS	PO	Q	49				23.1	6.7	19.3	78/26	45.3, SD 18.9	8.3, SD 9.9	44 AK 54 BK 6 BL	Average prosthesis use 12.9 h/day, SD 3.88
Hagberg and Branemark, 2001 [44]	CS	PF,RC	Q	55				35		10	60/37	48 (20–69)	22 (2–52)	97 TF	95% prosthesis use: 67% >13 h/day, 22% 7–12 h/day, 11% not daily Walking aids outdoor: 60% none, 27% 1 crutch/stick, 10% 2 crutches/sticks Walking habits outdoor last 3 months > several days/week: 85% 50 m, 63% 200 m, 35% 500 m, 14% 2 km 63% employed. 22% full sickness benefit
Stam et al., 2004 [45]	CS	PF	Q	55	15.8			16.2			161/79		–[f]	240 TF	100% prosthesis use Activity level males: 13% low, 67% moderate, 19% high. Activity level females: 15% low, 60% moderate, 25% high
Ephraim et al., 2005 [4]	CS	DB,PF	TI	39.1	37.2[g]	37.2[g]		23.7			552/362	50.3, SD 13.3.	Median 4 (0–66)	352 AK 372 BK 88 BL	Prosthesis use: 20% none, 18% 1–8 h/day, 63% 9 h+/day
Friel et al., 2005 [46]	CS	PF,AD,PO	Q,PE	42						58	16/3	56.5, SD 14.3	11.8, SD 9.3	8 TF 11 TT	100% prosthesis use 5% limited mobility; 53% unrestricted community ambulation; 37% high mobility OSW mean 13.03, range 0–36
Kulkarni et al., 2005 [47]	CS	RC	Q,PE,RA	100							17 4/28	48 (20–62)	19 (2–40)	77 TF 115 TT 10 BL	
Norvell et al., 2005 [11]	R,CO	H	TI	100							62/0	63.9, SD 11.9		18 TF 44 TT	100% prosthesis use
Kusljugic et al., 2006 [48]	CS	–	Q	70.2						29.8	37	46.2, SD 10.9		5 AK 27 BK 5 F	30% employed
Richardson et al., 2006 [35]	P,CO	H	FI		100						37/22	63.8, SD 10.4	0.5	29 AK 27 BK 1 BL AK 2 BL BK	
Ebrahimzadeh and Rajabi, 2007 [24]	CS	DB	Q,FI,PE	100							27/–	At injury: 21.3 (16–54)	17.4 (15–22)	20 Syme 7 F	48% employed

(*continued*)

Table 1. Continued.

Author, publication year	Study design	Patient recruitment	Source of pain data	Reason for amputation (%) Trauma	Vascular	Diabetes	Infection	Tumor	Congenital	Other/ unknown	♂/♀	Age Mean (range)	Years (range) since amputation	Amputation level	Level of functioning
Hanley et al., 2007 [25]	RCT	H	FI,TI	70	4	16	5			5	39/18	44.2, SD 12.6 (17–68)	2	8 TF 2 KD 42 TT 3 F 2 O	
Smith et al., 2007 [49]	CS	PO,RC	Q, RA	42	21	13					88/19	51.1, SD 14.3 (16–83)	17, SD 14.6	2 HD 32 TF 4 KD 57 TT 2 Syme 10 BL	100% prosthesis use 42% employed; 31% unemployed, mostly due to disability
Raichle et al., 2008 [26][,e]	CS	H, RC,AD	Q	58.6	20.4	11.5	22.8	5.2	2.7	31.5	431/161	54.7, SD 14.7	14.9, SD 15.7	3 HEP 17 HD 193 TF 28 KD 343 TT 8 Syme	84% prosthesis use 30% employed; 39% unemployed due to pain or disability
Desmond et al., 2008 [15]	CS	RC,PO	Q	35.2	18.0	15.7		3.4		27.3	62/27			30 AK 4 KD 55 BK	
Behr et al., 2009 [13]	CS,CC	H,PO,AD	Q	74	41		12				35/7	55.1, SD 11.0	12.4, SD 14.9	14 TF 14 KD 14 TT	TF prosthesis use 87%: 8.9, SD 6.4 h/day KD prosthesis use 79%: 7.6, SD 6.2 h/day TT prosthesis use 100%: 13.0 SD 4.5 h/day 36% employed, 45% unemployed due to pain or disability
Ebrahimzadeh et al., 2009 [22,23][h]	CS	DB	Q,FI,PE	100							200/–[i]	40.5	17.4	31 TF 96 TT	TF prosthesis use 83%: average 11.5 h/day. 61% employed TT prosthesis use 100%: average 11.5 h/day. 65% employed
Taghipour et al., 2009 [50]	CS	PO	FI	100							141/–	45.2, SD 6.5 (36–63)	21.6, SD 4 (20–27)	43 TF 38 KD 60 TT	100% prosthesis use 60% employed
Berke et al., 2010 [29][,j]	CS	DB	Q,TI	100							473/8[k]	45.4, SD 4.4[l]		110 TF 203 TT 7 F	89% prosthesis use 1% not walking; 7% household walker; 16% community walker; 29% varying speed walker; 21% low impact activities; 15% high impact activities 67% employed
Hammarlund et al., 2011 [51]	CS	PO	Q	72				28			34/12	48 (19–79)	23 (3–58)	19 TF 9 KD 18 TT	100% prosthesis use TF prosthesis use: 100% everyday, 47% >15 h/day, 47% no walking aids KD prosthesis use: 89% everyday, 33% >15 h/day, 98% no walking aids TT prosthesis use: 94% everyday,

(*continued*)

Table 1. Continued.

Author, publication year	Study design	Patient recruitment	Source of pain data	Reason for amputation (%) Trauma	Vascular	Diabetes	Infection	Tumor	Congenital	Other/ unknown	♂/♀	Age Mean (range)	Years (range) since amputation	Amputation level	Level of functioning
															33% >15 h/day, 72% no walking aids
Sinha et al., 2011 [30]	CS	RC,PO	FI	63	22[m]	22[m]				15	530/75	43.7, SD15.0	9.9, SD 10.3	151 AK/KD 410 BK 14 O (HD/HEP/ F/A) 29 BL	AK/KD: 60% prosthesis use. Use of cane/crutches 41% Walking distance <500 m 33%. In total 48% employed BK: 68% prosthesis use. Use of cane/crutches 46% Walking distance <500 m 31%. In total 48% employed Other: 67% prosthesis use. Use of cane/crutches 60% Walking distance <500 m 13%. In total 48% employed BL: 69% prosthesis use. Use of cane/crutches 24% Walking distance <500 m 41%. In total 48% employed
Ashraf et al., 2012 [20,21][n]	CS	DB	Q	100							327/8	42		75 TF BL 126 TT BL 83 TF + TT 51 ≥ 1 from the knee BL	71.9% prosthesis use 28% dependent with transfers, 23% with bathing, 13% with toileting 30% employed, 70% unemployed or student
Devan et al., 2012 [52][o]	CS	DB	Q	100							120/25	56.8, SD 14.6	27.1, SD 16.1	145 TF	96% prosthesis use
Sprunger et al., 2012 [53]	CS	AD	Q	88.2						11.8	58/0	48.3 SD 14.3 (23–67)		22 TF + KD UL 26 TT UL and below 10 above TF + BL	100% prosthesis use. 14% prosthesis wear <4 h/day, 19% 4–6 h/day, 77% >6 h/day. 58% wheeled mobility devices usage besides prosthetic device, of those 62% daily TF + KD 14% walker, 18% crutches, 18% single cane, 5% canes TT 4% walker, 15% crutches, 23% single cane BL 20% walker, 10% crutches, 20% single cane
Akarsu et al., 2013 (UL) [54][p]	CS	RC	Q, PE	100							15/–	27.3 SD 6.6	9.06, SD 5.6	2 AK 13 BK	100% prosthesis use: 100% everyday, 87% all day, 13% 6–10 h/day 6MWT 524m
Akarsu et al., 2013 (BL) [54][p]	CS	RC	Q, PE	100							15/–	31.9 SD 8.4	7.3 SD 5.0	6 AK BL 4 BK BL 5 AK + BK	100% prosthesis use: 73% everyday, 7% often, 20% occasionally. 73% all day, 13% 6–10 h/day, 13% <1 h/day 6MWT 350m

(*continued*)

Table 1. Continued.

Author, publication year	Study design	Patient recruitment	Source of pain data	Reason for amputation (%) Trauma	Vascular	Diabetes	Infection	Tumor	Congenital	Other/ unknown	♂/♀	Age Mean (range)	Years (range) since amputation	Amputation level	Level of functioning
Akyol et al., 2013 [28]	CS	RC	Q	100							30/–	31.3 SD 6.02	6.6 SD 0.5	1 HD 12 TF 6 KD 18 TT 2 F-A	LCI 34.6 SD 1.2
Ebrahimzadeh et al., 2013 [55]	CS	DB	Q,FI,PE	100							76/–	44.1, SD 7.0	26.6, SD 3.7	7 HEP 69 HD[q]	68%[r] prosthesis use 4% normal walking without aid, 11% abnormal walking without aid, 16% single crutch, 59% double crutch, 1% walker, 9% wheelchair. 54% active in sports
Richardson et al., 2015 [56],[s]	CS	H	Q		100						19/5	63.7, SD 9.3	0.4, SD 0.5	17 BK 6 AK 2 BL	
Buchheit et al., 2016 [57],[t]	CS	RC	Q,PE	100							122/2	26.9, SD 6.8	0.7, SD 0.4	113 LOL 11 UPL	100% prosthesis use
George et al., 2016 [58]	R, CS	H	Q				1000				24/29	65.2, SD 10.7		53 AK UL	67% prosthesis use At last available follow up 47% non-ambulators, 28% household ambulators, 26% community ambulators
Morgan et al., 2016 [12]	CS	AD,PO,RC	Q	46.6	42.3					11.1	908/385	54.4, SD 13.7	12.2, SD 14.1	386 TF 704 TT 71 TF BL[u] 135 TT BL[u]	100% prosthesis use: mean 12.3 h/day, SD 4.1 33.1% on disability, 66.7% not on disability
Kelle et al., 2017 [59],[v]	R, CS	H	FI	45	17	21	5	9		3	52/14	57.58, SD 15.9	0.5	2 HD 15 TF 8 KD 39 TT 2 Syme	
Yasar et al., 2017 [60],[w]	R	RC		100							398/1	23.4, SD 6.0	10.0, SD 5.7	1 HP 4 HD 49 TF 16 KD 223 TT 17 Syme	51.1% employed
Devan et al., 2017 [27],[o]	CS	DB	Q								154/54	52, SD 9	21, SD 13	78 TF 130 TT	100% prosthesis use 64% employed
Esfandiari et al., 2018 [61]	CS	DB	Q,PE	100							587/0	43, SD 6.5	22, SD 4.0	29 HD 458 TF 94 KD 6 BL	76% prosthesis use 27% employed 51% active in sports
Larbig et al., 2019 [36],[x]	P, CO	H	FI, Q		50	35	6	10			41/11	63.0			
Luetmer et al., 2019 [33]	R, CO	DB	ICD	13	88			13			50/46	72.9		96 TF	25% prosthesis use
Welke et al., 2019 [34]	R, CO	DB	ICD									62.6		1569 TF	100% prosthesis use

(*continued*)

Table 1. Continued.

Author, publication year	Study design	Patient recruitment	Source of pain data	Reason for amputation (%)							♂/♀	Age Mean (range)	Years (range) since amputation	Amputation level	Level of functioning
				Trauma	Vascular	Diabetes	Infection	Tumor	Congenital	Other/ unknown					
Allami et al., 2019 [62]	CS	DB	FI, Q	100							245/2	52.4, SD 7.3	29.8, SD 6.2	247 BK	98% prosthesis use 44% use of walking aids 34% employed

A: ankle; AD: advertisement; AK: above knee; BK: below knee; BL: bilateral amputation; CC: case-by-case matching; CO: cohort study; CS: cross-sectional study; DB: database; F: foot; FI: face-to-face interview; H: hospital; HD: hip disarticulation; HEP: hemipelvectomy; ICD: International Classification of Diseases code; KD: knee disarticulation; LCI: locomotor capability index; LOL: lower limb; Mo: month(s); O: other; P: prospective; PE: physical examination; PF: patient(amputee) foundation; PO: prosthetic and orthotic clinic; Q: questionnaire; R: retrospective; RA: radiological assessment; RC: rehabilitation center; RCT: randomized clinical trial; T: toes; TF: transfemoral; TI: telephone interview; TT: transtibial; UL: unilateral; UPL: upper limb; 6MWT: 6-min walk test.

[a] Data were divided between a traumatic and vascular cause of LLA.

[b] Mean age of the original cohort. Out of the complete sample of 155 persons, 16 (10%) died during the first postoperative year.

[c] Chronic diseases, including diabetes, ulcers, infections, and vascular disease, accounted for 40.7% of the amputations in this sample in total.

[d] Data from the following studies were combined, due to use of the same dataset: Ehde et al. [5,6].

[e] Additional data were provided by the author excluding foot, toes, and bilateral amputations.

[f] Time since amputation: 0–10 years in 38% males and 29% females; 11–20 years in 19% males and 19% females; 21–30 years in 15% males and 23% females; >31 years in 25% males and 27% females.

[g] Diabetes and vascular disease accounted for 37.2% of the amputations in this sample in total.

[h] Data from the following studies were combined: Ebrahimzadeh et al. [22] and Ebrahimzadeh MH et al. Long-term outcomes of wartime transtibial amputations. Pain Pract. 2009;9:60.

[i] The total number also including other amputation levels at the lower limb, and persons with an upper limb amputation.

[j] Additional data were substracted from the following study: Reiber GE et al. Service-members and veterans with major traumatic limb loss from Vietnam war and OIF/OEF conflicts: survey methods, participants, and summary findings. J Rehabil Res Dev. 2010;47(4):275–298.

[k] Original number also including 70 persons with a unilateral upper limb amputation and 104 persons with multiple limb amputations.

[l] Recalculated to fit the table: data from persons from the Vietnam and OIF/OEF war were combined.

[m] Diabetes and vascular disease accounted for 22% of the amputations in this sample in total.

[n] Data from the following studies were combined, due to use of the same dataset: Ashraf et al. [21] and Rahimi et al. [20].

[o] A proportion of the included persons might be represented in both included studies of Devan et al., published 2012 and 2017, respectively.

[p] Data from this single study were divided in persons with a unilateral and bilateral amputation.

[q] Fifty-one persons had had hip disarticulation, and 18 persons had had amputation through the intertrochanteric region (which was considered to be hip disarticulation). .

[r] Sixty-eight percent routinely wear prostheses. Eleven percent never used any prostheses. Twenty-one percent abandoned prostheses.

[s] Only data from the outpatient group were used in this study. In total, 92% unilateral persons with LLA; the percentage unilateral AK/BK was not specified, and therefore calculated using the available data.

[t] Characteristics of the subjects having significant RLP only.

[u] Highest level of amputation in either limb.

[v] Data concerning patient groups 1 and 2 were combined and included, data concerning group 3 were excluded. Furthermore, only the RLP data 6 months post-amputation were included.

[w] Only 366 amputation levels were reported. In total, 86.7% unilateral amputations, 13.0% bilateral amputations, and 0.3% three sided amputations were reported. Data concerning amputation levels were not specified according to unilateral or bilateral level. Percentages concerning amputation levels were used to estimate the proportion unilateral below knee versus above knee level of amputation. Furthermore, the data also included 50 Chopart amputations, 4 toe amputations, and 2 Pirogoff amputations.

[x] Type of lower limb amputations not specified. Furthermore including 2 upper limb amputations. Finally, only the RLP data 12 months post-amp were included.

Table 2. Residual limb pain: prevalence, pain characteristics, and causes.

Author, publication year	RLP prevalence by amputation level					Timeframe reported RLP	Pain frequency/intensity/impact/cause in total group
	All levels	AK	KD	BK	BL		
Hoaglund et al., 1983 (trauma)[b]		42%[c]		43%[c]	53%[c]		Frequency 100% frequent/always present[a] Intensity AK: 37% moderate; 18% severe. BK: 34% moderate; 18% severe. BL: 29% moderate; 29% severe
Hoaglund et al., 1983 (vascular)[b]		67%[c]		55%[c]	45%[c]		Frequency 100% frequent/always present[a] Intensity AK: 22% moderate; 22% severe. BK: 55% moderate; 5% severe. BL: 27% moderate; 27% severe
Jensen et al., 1984	21–22%[d]					0	Cause 3% neuroma
Pohjolainen, 1991		2%		8%		0	Intensity 1 year post-amp: 43% moderate[a]
McCartney et al., 1999	68%[e]						Duration 23% at least daily RLP, 40% variable 45% low disability – low intensity, 24% low disability – high intensity, 7% high disability – moderately/ severely limiting[a,f]
Smith et al., 1999	76%					4 weeks	Frequency 40% more than half of the time in the preceding 4 weeks Intensity 25% moderate, 38% severe[a]
Ehde et al., 2000[g]	76%					3 months	Frequency past 4 weeks: 72% intermittent; 41% $\leq$1/week, 30% $>$4–6 times. Duration $>$ several hours in 34%, few minutes in 32%[a] Intensity mean pain scale 5.4, SD 2.7[a,h] Average bothersomeness (0–10) 5.2, SD 2.9: 27% moderately, 33% severely[a]
Dillingham et al., 2001	36%[i]					4 weeks	Frequency 39% constant, 61% occasional[a] Intensity 100% extremely/very bothersome[a]
Gallagher et al., 2001	48%					1 weeks	Frequency 48% pain last week: 13% 1–2 times, 41% 2–5, 13% continuous[a] Duration 27% seconds, 25% minutes, 9% 30 minutes, 18% hours[a] Intensity 48% discomforting, 26% distressing, 9% horrible, 4% excruciating[a] Interference caused: 17% moderate, 13% quite a bit, 9% a lot[a]
Hagberg and Branemark, 2001		TF 36–51%[j]				4 weeks	Intensity when not wearing prosthesis: 36% moderate or worse, 15% considerable or worse severity/reduction QoL While standing/walking 51% moderate or worse, 20% considerable or worse severity/reduction QoL 11% $\geq$1 day no prosthesis use due to RLP
Ephraim et al., 2005	66%					4 weeks	Intensity 30% severe[a,k] Mean pain scale 5.1, SD 2.4[a,h] Bothersomeness 60% somewhat, 27% extremely bothersome[a,k]
Kulkarni et al., 2005	57%						Frequency 27% occasionally, 17% often, 13% constant Intensity 32% moderate, 13% severe, 12% extreme
Richardson et al., 2006	52%					0	
Ebrahimzadeh et al., 2007				44%[l]			
Hanley et al., 2007	57–66%[m]					1 week	Intensity 6 months post-amp 31% pain scale $>$3, mean 2.5 (SD 2.6)[h] 12 months post-amp 31% pain scale $>$3, mean 2.5 (SD2.9)[h] 24 months post-amp 27% pain scale $>$3, mean 2.1 (SD 2.4)[h]
Smith et al., 2007	56%					3 months	Frequency 83% intermittent, 15% constant. Frequency weekly: 33% $<$1, 35% 2–3, 13% 4–6, 18% $>$6[a] Duration: 39% minutes, 30% up to 1 h, 11% $>$1 h, 21% $>$1 day[a]

(continued)

Table 2. Continued.

Author, publication year	RLP prevalence by amputation level: All levels	AK	KD	BK	BL	Timeframe reported RLP	Pain frequency/intensity/impact/cause in total group
							Intensity mean pain scale 5.7, SD 2.3[a,h] Interference (0–10) with ADL 2.9, SD 3.2[a] Interference (0–10) with social life 2.8, SD 3.1[a] Interference (0–10) with ability to work 3.9, SD 6.9[a] Cause 52% a prosthetic problem
Raichle et al., 2008[g]	77%					3 months	Intensity mean pain scale past 3 months 4.7, SD 2.7[a,h] Cause 42% a prosthetic problem
Desmond et al., 2008	56%					–/1 weeks[n]	Frequency past week: 33% 1–2 episodes, 24% 3–4, 11% 5–6, 31% ≥7[a]. Duration: 73% 1–2 h, 9% 3–4 h, 2% 5–6 h, 13% ≥7 h[a] Average pain intensity past week: 16% mild, 49% discomforting, 11% distressing, 18% horrible, 4% excruciating[a] Interference with normal lifestyle during past week: 27% not at all, 33% a little bit, 20% moderate, 11% quite a bit, 7% a lot[a]
Behr et al., 2009		TF 86%	71%	TT 86%		0/3 months[o]	Intensity TF mean pain scale 2.0, SD 2.5[a,h]. KD mean pain scale 1.7, SD 1.6[a,h]. TT mean pain scale 3.0, SD 2.8[a,h] Interference with daily activities past 3 months (0–10): TF 3.0, SD 3.4[a]; KD 2.4, SD 2.2[a]; TT 4.7, SD 3.5[a]
Ebrahimzadeh et al., 2009		TF 65%		TT 42%			Cause TT 30% neuroma, 20% bone overgrowth, 20% ulcers and/or scar hypersensitivity, 2.5% foreign bodies, 27.5 % unknown/idiopathic Cause TF 50% neuroma, 20% bone overgrowth, 10% ulcers and/or scar hypersensitivity, 25% unknown/idiopathic
Taghipour et al., 2009	92%						
Berke et al., 2010[p]	57%[p]						
Sinha et al., 2011	28%[q]	26%[r]	26%[r]	29%	21%		Intensity SF-36 bodily pain 85.6 SD 27.2
Sprunger, et al., 2012	59%						Frequency 19% RLP 7 days/week. Duration: 54% ≤2 h Intensity 41% discomforting, 30% distressing, 5% horrible, 5% excruciating[a] Interference with normal daily activities: 76% some interference[a]
Akarsu et al., 2013 (UL)[s]	33%						Intensity SF-36 bodily pain: 51.6, SD 29.3–62.7
Akarsu et al., 2013 (BL)[s]					20%		Intensity SF-36 bodily pain: 42.2, SD 29.3–62.7
Akyol et al., 2013	87%[t]						Intensity Mean pain scale 4.1, SD 2.9[h]. NHP subgroup pain: 34.8 SD3.5
Richardson, et al., 2015[u]	48%						
Buchheit et al., 2016[v]	61%[v]					1 week	Intensity 100% significant pain, NRS ≥ 3[a] Cause 49% sensitized neuroma, 20% CRPS, 41% somatic pain, 11% either neuroma or CRPS
Morgan et al., 2016	35%	33%		37%	33%	1 week	Intensity 100% somewhat," "quite a bit," or "very much" a problem[a]
Kelle, et al., 2017[w]	29%	52%		15%			Intensity AK: mean VAS 3.46, SD 1.4. BK: mean VAS 4.20, SD 1.3
Yasar et al., 2017[x]	38%						
Esfandiari et al., 2018	49%						

(*continued*)

Table 2. Continued.

Author, publication year	RLP prevalence by amputation level All levels	AK	KD	BK	BL	Timeframe reported RLP	Pain frequency/intensity/impact/cause in total group
Larbig et al., 2019[y]	39%					0	
Allami et al., 2019				73%		0	Intensity at present mean NRS 3.2, SD 3.4; at worst mean NRS 7.9, SD 2.4

ADL: activity of daily living; AK: above knee; BK: below knee; BL: bilateral; CRPS: complex regional pain syndrome; KD: knee disarticulation; NHP: Nottingham Health Profile; NRS: numeric rating scale; post-amp: postamputation; QoL: quality of life; RLP: residual limb pain; TF: transfemoral; TT: transtibial; UL: unilateral; VAS: visual analogue scale.

[a]Containing data only from persons with pain, instead of the total patient group.

[b]Data from this study were divided between persons with traumatic and vascular cause of LLA.

[c]Data containing RLP frequent-always: data containing RLP seldom-never were left out.

[d]Including data from 2 persons with upper limb amputation; RLP 22% 6 months post-amp, 21% 2 year post-amp. In the meta-analysis, the RLP percentage 2 year post-amp was included.

[e]67.5% RLP at some time following amputation (26% immediate onset, 30% within week-month, 44% after a month), 53% current RLP.

[f]Including data from persons with phantom limb pain, and combined phantom limb pain and RLP.

[g]Additional data were provided by the author excluding foot, toes, and bilateral amputations.

[h]NRS or VAS used.

[i]Recalculated to fit the table: data containing constant and occasional RLP were combined. Including data from 2 persons with a foot amputation.

[j]Thirty-six percent moderate or worse RLP when not wearing prosthesis, 51% moderate or worse RLP while standing/walking.

[k]Including data from 100 persons with an upper limb amputation.

[l]Persons with a Syme amputation, also including data from 7 persons with a foot amputation.

[m]RLP 6 months post-amp 66%, 12 months post-amp 65%, and 24 months post-amp 57%. In the meta-analysis, the RLP percentage 24 months post-amp was included. Including data from 3 persons with a midfoot amputation and 2 persons with "other" amputation.

[n]No initial timeframe was given; when RLP was reported, pain frequency, intensity, and pain related interference during the last week were assessed.

[o]Current pain was assessed; pain interference with daily activity was assessed over the past 3 months.

[p]Recalculated to fit the table: data from the Vietnam and OIF/OEF war were combined.

[q]Twenty percent RLP in 14 persons in "other" group(hip disarticulation, hemipelvectomy, foot amputation, or ankle amputation).

[r]Data from AK and KD levels were presented as a single group in this study.

[s]Data from this study were divided in persons with a unilateral and bilateral amputation.

[t]Including data from 2 persons with a foot-ankle amputation.

[u]Only data from the outpatient group were included in the study. In total, 92% persons with a unilateral amputation; percentage unilateral and bilateral AK/BK level was not specified.

[v]Including data from 11 persons with an upper limb amputation. Concerning the cause of amputation: a selection of persons with significant RLP subtypes was made. Furthermore, somatic pain was not further specified in the study.

[w]Data concerning groups 1 and 2 were combined and included, data concerning group 3 were excluded. Furthermore, only the RLP data 6 months post-amp were included.

[x]Only 366 amputation levels were reported. In total, 86.7% unilateral amputations, 13.0% bilateral, and 0.3% three sided. Data concerning amputation levels were not specified according to unilateral or bilateral level. Percentages concerning amputation levels were used to estimate the proportion unilateral below knee versus above knee level of amputation. Pain data also including 50 Chopart amputations, 4 toe amputations, and 2 Pirogoff amputations.

[y]Type of lower limb amputations not specified. Furthermore including 2 upper limb amputations. Finally, only the RLP data 12 months post-amp were included.

episodes of pain lasted mostly less than one to two hours [5,15,43,49,53]. However, several studies reported a considerable amount of persons with longer lasting RLP, varying from a duration of several hours in 18% of persons, more than several hours in 34% of persons, and more than one day in 21% of persons in different studies [5,43,49].

The mean RLP intensity scores ranged from 1.7 to 5.7 on a 10-point NRS between the studies, with the majority of studies reporting intensity scores of 5 or higher [4,5,13,25,26,28,49,59,62]. Severe pain intensity was reported in 30–38% of persons [4,5,41], with 27–33% of persons reporting a severe or extreme bothersome RLP [4,5,15]. One study found a small decrease of intensity in RLP over time, with a mean intensity of 2.5 at six months, 2.5 at 12 months, and 2.1 at 24 months after amputation [25]. Residual limb pain intensity declined by 30% or more for 56% of persons, and increased by 30% or more for 22% of persons during the course of two years. Another study found a greater RLP intensity in the dysvascular group of persons with LLA compared to the traumatic and diabetic groups, and suggested a more proximal arterial disease resulting in ischemic pain as the reason for this difference [49].

Few studies reported about the impact of RLP on the functioning of persons with LLA. Pain-related interference assessed on a 10-point scale was 2.9 for ADL, 2.8 for social life, and 3.9 for ability to work in one study [49]. Comparable results were reported in other studies [5,32,43,53]. Pain-related interference in persons with a knee disarticulation compared to persons with a transfemoral or transtibial amputation did not differ significantly, but groups were small [13].

Few studies evaluated the cause of RLP (Table 2). If reported, a neuroma was found in 3–50% of persons [22,23,40,57], a prosthetic problem in 42–52% of persons [26,49], bone overgrowth in 20% of persons [22,23], ulcers and/or scar hypersensitivity in 10–20% of persons [22,23], and foreign bodies in 2.5% of persons [23]. Although several other studies did mention the presence of prosthetic and skin problems, no association with RLP was reported. None of the studies specifically reported ischemic pain as cause of RLP.

Back pain

Twenty-nine studies reported on back pain in persons with LLA ($n = 7887$). The prevalence of back pain ranged from 34% to 95% (Table 3). Twelve studies reported back pain within a certain timeframe, ranging from only actual pain to pain during the last six months (Table 3). Some studies reported on back pain in different

Table 3. Back pain: prevalence, pain characteristics, and causes.

	Back pain prevalence by amputation level						
Author, publication year	All levels	AK	KD	BK	BL	Timeframe reported back pain	Pain frequency/intensity/impact/cause in total group
Burke et al., 1978	48%						Intensity 40% moderate or severe[a]
Kramer et al., 1979		TF 70%					Impact 65% in medical treatment, 20% (partly) disabled
Hoaglund et al., 1983 (trauma)[b]		58%		66%	54%		
Hoaglund et al., 1983 (vascular)[b]		25%		35%	11%		
Friberg, 1984	95%						Frequency 23% occasional and mild; 30% frequent/constant and severe. 20% chronic unilateral sciatica Cause: leg length discrepancy >10 mm in 66%, >20 mm in 34% of persons, adequate length (<10 mm) in 12% TT, in 24% TF. When low back pain significantly greater leg length discrepancies than without pain
Smith et al., 1999	71%[c]					4 weeks	Frequency 33% more than half of the time in the preceding 4 weeks. 9% pain free last 4 weeks Intensity 25% moderate, 39% severe[a] Cause: 24% osteoarthritis after radiological investigation, 53% postural and gait abnormalities
Ehde et al., 2000[d,e]	50%					3 months	Frequency 72% intermittent (47% ≤1/week, 58% ≥several hours), 26% constant[a] Mean 49, SD 36.43 days BP in last 3 months[a] Intensity mean pain scale 5.2, SD 2.3[f]: 25% moderate, 31% severe[a] Average bothersomeness (0–10): 4.9, SD 3.4: 21% moderate, 31% severe[a] Interference in ADL: mean (0–10) 3.9, SD 2.9: 20% moderate, 22% severe[a] Interference in social activities: mean (0–10) 3.8, SD 3.1: 16% moderate, 23% severe[a] Interference in work/housework: mean (0–10) 4.0, SD 3.4: 15% moderate, 28% severe[a]
Hagberg and Branemark, 2001		TF 47%				4 weeks	Intensity 47% moderate or worse severity/ reduction in QoL, 24% considerable or worse
Stam et al., 2004		TF 76%[g]					Frequency 50% occasional, 18% frequent, 9% permanent[g]
Ephraim et al., 2005	64%					4 weeks	Bothersomeness: 69% somewhat, 24% extremely[a,h]
Friel et al., 2005	79%					1 week/1 months[i]	Intensity mean pain scale 3.04, range 0.63–6.90[f]: 5% moderate and 15% severe levels of pain
Kulkarni et al., 2005	63%	TF 81%		TT 62%			Frequency 26% occasional, 27% often, 9% constant Intensity in total group: 23% moderate, 27% severe, 11% extreme BP interfered significantly with lifestyle in 38% of persons Cause: no differences in lumbar range of motion, leg length, BMI and MRI-findings, comparing back pain and pain free persons
Kusljugic et al., 2006	89%[j]						
Ebrahimzadeh et al., 2007				44%[k]			
Smith et al., 2007	48%					3 months	Frequency 84% intermittent, 16% constant. Frequency weekly: 33% <1, 33% 2–3 times, 15% 4–6 times, 17% >6 times[a] Duration: 29% minutes, 31% up to 1 h, 26% >1 h, 14% >1 day[a] Mean duration: 7.7 years (SD 6.7)[a] Intensity mean pain scale 5.3(SD 2.1)[a,f] Interference (0–10) with ADL 3.5, SD 3.2[a]; with social life 3, SD 3.4[a]; with ability to work 3.4, SD 3.1[a]
Behr et al., 2009		TF 50%	50%	TT 29%		0/3 months[l]	Intensity TF mean pain scale 3.3, SD 3.7[a,f]. KD mean pain scale 2.9, SD 3.1[a,f]. TT mean pain scale 3.0, SD 2.2[a,f] Interference with ADL past 3 months (0–10) TF 4.3, SD 3.0[a]; KD 2.9, SD 3.4[a]; TT 4.3, SD 3.1[a]
Ebrahimzadeh et al., 2009		TF 61%		TT 44%			
Taghipour et al., 2009	77%						
Berke et al., 2010[m]	47%[m]						

(*continued*)

Table 3. Continued.

	Back pain prevalence by amputation level						
Author, publication year	All levels	AK	KD	BK	BL	Timeframe reported back pain	Pain frequency/intensity/impact/cause in total group
Hammarlund et al., 2011	87%	TF 89%	78%	TT 89%			TT frequency: 44% occasional, 22% few times/month, 11% several times/week, 11% daily. KD frequency: 11% occasionally, 11% few times/month, 33% several times/week, 22% daily. TF frequency 37% occasionally, 16% few times/month, 26% several times/week, 11% daily Intensity SF-36 bodily pain TT 51.5 SD 17.3; KD 70.9 SD 27.8; TF 63.3 SD 24.5. RMDQ scores: 7% severe disability, 20% moderate disability, 59% no/some disability
Ashraf et al., 2012[n]					VCP 61%	6 months	Frequency 67% one area, 28% two areas, 5% three areas. VCP locations: 53% lumbosacral, 10% thoracic, 18% neck[a] Intensity all pain bothersome and frequent. 52% bothersome pain >3 times/week. SF-36 bodily pain lumbosacral 45.4, SD 24; thoracic 41.9, SD 19.8; neck 41.2 SD, 22.7
Devan et al., 2012		TF 64%				4 weeks	Frequency 21% every day, 33% on most days, 47% on some days[a] Duration last pain-free month: 28% <3 months, 18% 3–7 months, 11% 7 months to 3 years, 39% >3 years[a] Intensity 27% moderate, 14% severe[a] 39% interference BP with ADL[a]
Ebrahimzadeh et al., 2013		VCP 87%[o]					Frequency 45% cervical spine pain, 32% thoracic, 72% lumbar, 17% sacral
Morgan et al., 2016	39%	40%		39%	35%	1 week	Intensity 100% "somewhat," "quite a bit," or "very much" a problem[a]
Yasar et al., 2017[p]	39%						
Devan et al., 2017[q]	63%					4 weeks	Frequency 46% on some days, 29% on most days, 25% everyday[a] Intensity 35% mild, 35% moderate, 31% severe[a] Bothersomeness 5% not at all, 65% slightly, 29% extremely[a]
Esfandiari et al., 2018	69%						
Luetmer et al., 2019		TF 34%					
Welke et al., 2019		TF 43%					
Allami et al., 2019				78%		3 months	Intensity at present mean NRS 3.4, SD 2.9; at worst mean NRS 7.5, SD 2.5

ADL: activity of daily living; AK: above knee; BK: below knee; BL: bilateral; BP: back pain; KD: knee disarticulation; NRS: numeric rating scale; Post-amp: post-amputation; QoL: quality of life; RMDQ: Roland Morris Disability Questionnaire; TF: transfemoral; TT: transtibial; VAS: visual analogue scale; VCP: vertebral column pain.
[a]Containing data only from persons with pain, instead of the total patient group.
[b]Data from this study were divided between persons with a traumatic and vascular cause of LLA.
[c]Painful sensations in the back, which could include low, mid, and upper back pain.
[d]Data from the following studies were combined, due to use of the same dataset: Ehde et al. [5,6].
[e]Additional data were provided by the author excluding foot, toes and bilateral amputations.
[f]NRS or VAS used.
[g]Recalculated to fit the table: male and female data were combined.
[h]Including data from 100 persons with an upper limb amputation.
[i]Back pain disability was calculated during the month preceding study participation.
[j]Including data from 5 persons with a foot amputation.
[k]Persons with a Syme amputation, also including data from 7 persons with a foot amputation.
[l]Current pain was assessed; pain interference with daily activity was assessed over the past 3 months.
[m]Recalculated to fit the table: data from the Vietnam and OIF/OEF war were combined.
[n]Data from the following studies were combined, due to use of the same dataset: Ashraf et al. [21] and Rahimi et al. [20].
[o]Persons with a hemipelvectomy or hip disarticulation.
[p]Only 366 amputation levels were reported. In total 86.7% unilateral amputations, 13.0% bilateral and 0.3% three sided. Data concerning amputation levels were not specified according to unilateral or bilateral level. Percentages concerning amputation levels were used to estimate the proportion unilateral below knee versus above knee level of amputation. Pain data also including 50 Chopart amputations, 4 toe amputations, and 2 Pirogoff amputations.
[q]Additional data were provided by the author concerning back pain frequency and intensity.

regions. One study found the highest prevalence of lumbar spine pain (72%), followed by cervical spine pain (45%), thoracic spine pain (32%), and sacral pain (17%) [55]. Another study found that 53% of persons reported lumbosacral spine pain, 18% neck spine pain, and 10% thoracic spine pain [21]. Furthermore, 67% of persons experienced pain in one area, 28% in two areas, and 5% in three areas. The other included studies predominantly reported low back pain [4–6,8,12,13,22,24,27,29,33,37–39,41,44–52,60,62]. Several studies reported data about the experienced pain frequency [6,8,27,45,47,49]. Similar to RLP, back pain was reported as intermittent in 70–91% of persons, constant in the remaining persons [6,8,27,45,47,49]. Frequency of back pain episodes was usually low, often not more than three times a week. The duration of back pain episodes ranged from up to one hour in 66% of persons [49], to several hours or more in 58% of persons in another study [6].

The reported mean back pain intensity of the included studies ranged from NRS 3.0 to 5.3 [5,6,13,46,49,62]. Several studies reported moderate back pain in 5–35% of persons, severe back pain in 14–39% of persons, with one study reporting extreme back pain in 11% of persons [6,27,41,46,47,52]. Three studies reported back pain interference on a 0–10 scale, all reporting scores in the mild range: back pain interference with ADL ranged from 2.9 to 3.9, with social activities 3.4 to 3.8, with work 3.4 to 4.0 [6,13,49].

Few studies evaluated possible causes of back pain related to amputation (Table 3). In one study, postural and gait abnormalities were thought to be the possible cause of back pain in 53% of persons [41]. An older study stated that persons with LLA with low back pain had significantly greater leg length discrepancies than those without pain [8]. A more recent study did not find any differences in lumbar range of motion, leg length, body mass index, and magnetic resonance imaging findings, comparing persons with LLA with and without back pain [47]. Some studies did assess the presence of pelvic tilt or a scoliosis, but these findings were not related to the presence of back pain either [37,38].

Other pain

An overview of all the studies reporting other types of chronic pain is presented in Supplemental file 4. Due to the small number of studies, these data were not included in the meta-regression.

Pain in the non-amputated limb

Pain in the non-amputated limb was found in 25–71% of persons [4,5,27,31,39,42,44,50,52,58,61,62]. Seven studies reported contralateral limb pain within a certain timeframe, ranging from only actual pain to pain during the last three months (Supplemental file 4). Two studies reported the presence of vascular and wound problems in the non-amputated limb in some of the persons with LLA, but not specifically related to the presence of pain [31,42]. In general, causes were not specifically stated. Intensity of pain in the non-amputated limb varied from 31% for moderate pain and 19% for severe pain, to 46% moderate or worse severity/reduction in quality of life [4,44].

Hip pain

Hip pain was found in 3–37% of persons [8,22,23,37,55,62]. One study reported hip pain in the last three months (Supplemental file 4). Causes of hip pain were not specifically stated. One study reported hip pain intensity of moderate or more in 30% of persons [37].

Knee pain

Knee pain was found in 9–81% of persons, if stated 9–15% on the ipsilateral side, 19–68% on the contralateral side of the amputation [8,11,12,22–24,37,38,55,62]. Another study found a prevalence of contralateral knee pain in 40% of persons with LLA, compared to 20% knee pain in a control group of persons without an amputation [11]. Three studies reported knee pain within a certain timeframe, ranging from pain during the last week to pain during the last month (Supplemental file 4). The prevalence of symptomatic knee osteoarthritis was 16% in the group of persons with LLA versus 12% in the control group without an amputation. Two studies reported about knee pain intensity, with a moderate knee pain in 32% of persons in the first study, and an average NRS of 4.9 in the second study [11,37].

Meta-analysis

The meta-analysis included 46 studies reporting about back pain or RLP in a total of 10 201 persons with LLA. Not all included studies reported on all predictors explored in meta-regression (Table 1). For RLP (33 studies, $n = 7062$), a pooled mean prevalence of 0.51 (95% CI 0.40–0.62) was found ($I^2 = 97\%$) (Figure 2). In the meta-regression to statistically predict the logit event rate of RLP, only a positive association between the proportion back pain ($p = 0.044$) was found in the univariate regression model (Table 4). Too few studies reported about pain intensity and interference, hence these data could not be included in the meta-regression.

For back pain (29 studies, $n = 7887$), we found a mean pooled prevalence rate of 0.55 (95% CI 0.45–0.64) ($I^2 = 96\%$) (Figure 3). The univariate regression model showed a higher prevalence of back pain with a longer time since amputation ($p < 0.001$), male gender ($p = 0.006$), and a traumatic cause of amputation ($p < 0.001$) (Table 4; Figure 4). Furthermore, we found a borderline significant positive association between the proportion back pain and the co-occurrence of RLP ($p = 0.050$). Only few studies reported about pain intensity and interference, these data could not be included in the meta-analysis.

In a *post hoc* analysis, we calculated Pearson's r between proportion RLP and proportion back pain in the different studies ($r = 0.75$), indicating a strong correlation between the prevalence of RLP and back pain.

Discussion

The aim of this study was to systematically review and to critically assess the methodological quality of the literature regarding the prevalence, characteristics and factors influencing chronic pain, other than PLP in persons with LLA. We found a pooled prevalence for RLP of 0.51, with a positive association with the presence of back pain in the univariate regression analysis. The cause of RLP was seldom adequately described. For back pain, we found a pooled prevalence of 0.55 with a positive association of the time since amputation, male gender, traumatic cause of amputation and the co-occurrence of RLP in the univariate regression analysis. Only few studies reported about other types of pain, and pain impact in general.

In our RLP meta-regression, we found a significant positive association with the proportion back pain. In the back pain meta-regression, we found a borderline significant positive association with the proportion RLP. We did not find significant outcomes in both directions, possibly explained by the relatively small sample size we had to work with. Our findings however still suggest a

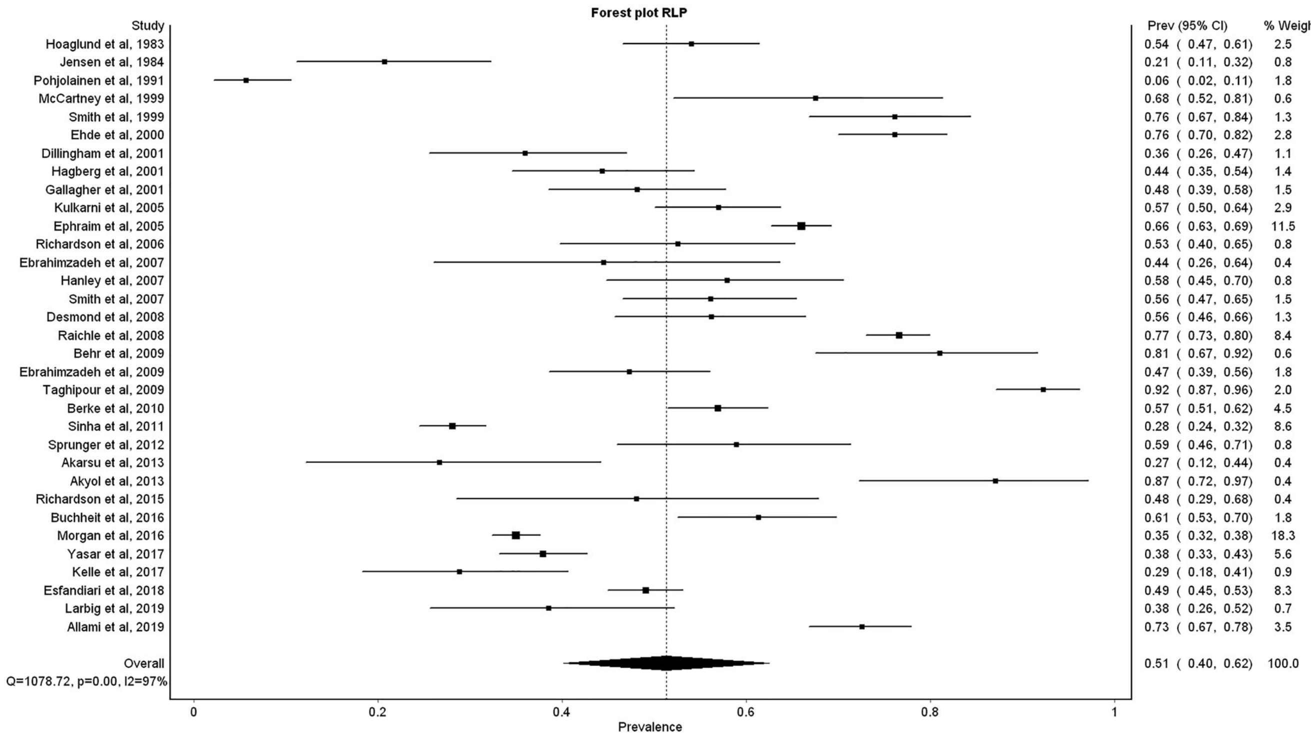

Figure 2. Forest plot residual limb pain.

Table 4. Results of meta-regression to explore which study characteristics are associated with the logit of RLP and logit of back pain: random effects model.

Outcome Predictor	Coefficient (95% CI)	*p* Value
Logit RLP		
BP total	3.43 (0.09–6.77)	**0.0439**
Time since amputation	0.04 (−0.05 to 0.12)	0.4419
Mean age	0.02 (−0.09 to 0.14)	0.6964
Male gender	2.33 (−1.21 to 5.87)	0.1974
Cause trauma	1.37 (−0.83 to 3.56)	0.2225
Prosthesis use	−0.29 (−7.16 to 6.58)	0.9348
Above knee amputation	−0.15 (−1.93 to 1.62)	0.8659
Below knee amputation	0.50 (−1.30 to 2.29)	0.5876
Bilateral amputation	−2.72 (−5.62 to 0.18)	0.0662
Study publication year	0.00 (−0.05 to 0.05)	0.9752
Logit BP		
RLP total	2.06 (−0.00 to 4.12)	**0.0502**
Time since amputation	0.09 (0.05–0.13)	**0.0000**
Mean age	−0.03 (−0.11 to 0.05)	0.4543
Male gender	2.82 (0.82–4.83)	**0.0058**
Cause trauma	1.94 (0.95–2.93)	**0.0001**
Prosthesis use	−0.90 (−6.11 to 4.32)	0.7366
Above knee amputation	−0.01 (−1.45 to 1.44)	0.9934
Below knee amputation	0.15 (−0.61 to 0.91)	0.6978
Bilateral amputation	−4.25 (−9.30 to 0.80)	0.0988
Study publication year	0.02 (−0.03 to 0.07)	0.4152

BP: back pain; CI: confidence interval; Logit: natural logarithm of prevalence/(1 − prevalence); RLP: residual limb pain.
The significant and borderline significant values are highlighted in bold.

strong association between the prevalence of RLP and back pain in LLA, also supported by the strong correlation we demonstrated in our *post hoc* analysis. The underlying mechanism could be related to the measurement instrument used. Another explanation might be a biomechanical explanation for the association between RLP and back pain in persons with LLA. The presence of RLP might influence the gait pattern, perhaps influencing pelvic and spinal movement, which could lead to back pain in the longer term [9,63]. These alterations in movement patterns could also be explained by fear of pain (fear avoidance or pain driving change in gait) due to changes to functional connectivity and sensorimotor integration, as suggested in chronic low back pain in the general population [64].

Further elaborating on this, sensitization might be an explanation for the correlation between RLP and back pain in our study population. Peripheral sensitization represents a reduction in threshold and an amplification in the responsiveness of nociceptors which occurs when the peripheral terminals of these high-threshold primary sensory neurons are exposed to inflammatory mediators and damaged tissue. Peripheral sensitization is restricted to the primary site of tissue injury [65,66]. Central sensitization is defined as an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity and as an increased responsiveness of nociceptive neurons in the central nervous system to their normal afferent input [67,68]. Peripheral and central sensitization nowadays are well-established neurophysiological mechanisms in chronic pain in general [66]. In literature focusing on pain after LLA, central sensitization is only linked to PLP [69].

Considering the positive association of "time since amputation" in our back pain meta-regression, several explanations are present. Biomechanically, it can be hypothesized that prolonged use of a prosthesis might influence the gait pattern which could increase susceptibility for development of back pain. By contrast, the prevalence of back pain might also increase due to the increase of physical inactivity during the process of aging. The process of aging in general might play the same role in aging adults without LLA. A systematic review focusing on the trends of back pain prevalence with age in the general population indeed stated that most included studies considering severe forms of back pain found an increase of prevalence with increasing age [70]. Further elaborating on this, the question remains in which way LLA influences the risk of experiencing back pain. In the recent history, various surveys have been performed to identify the prevalence of low back pain in the general population, showing an estimated prevalence ranging from 22 to 48%, depending on the study population and definitions applied [71–74]. The age distribution of those studies was relatively

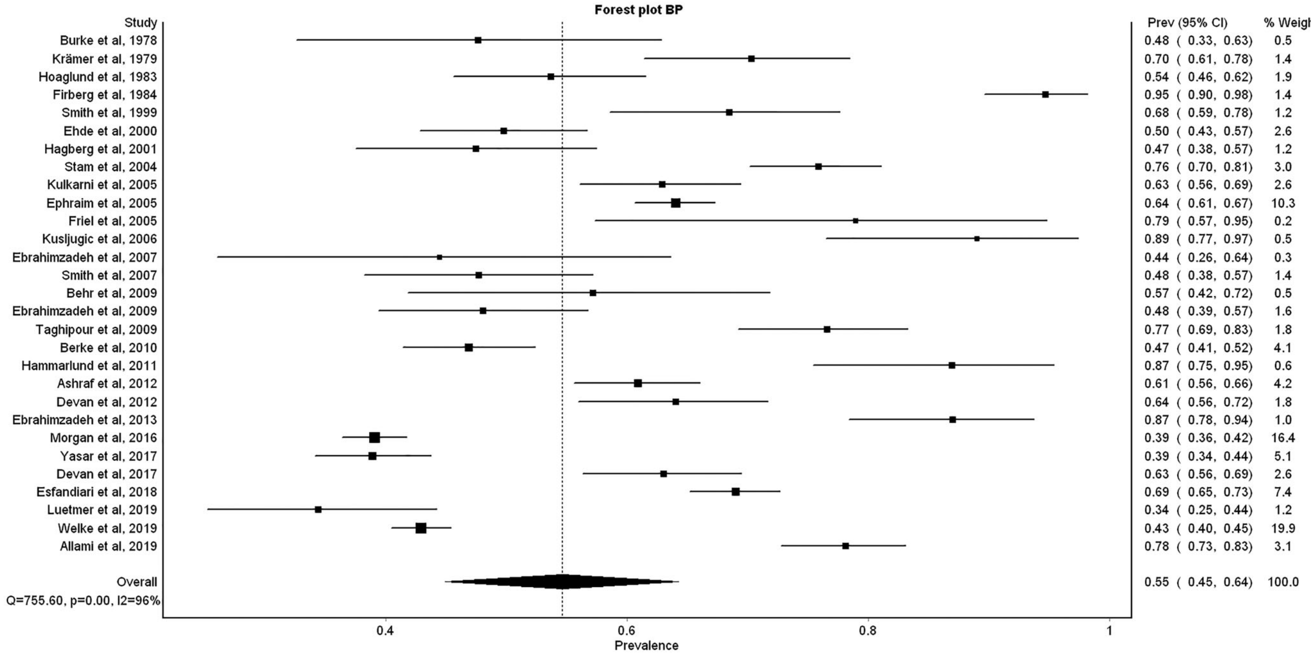

Figure 3. Forest plot back pain.

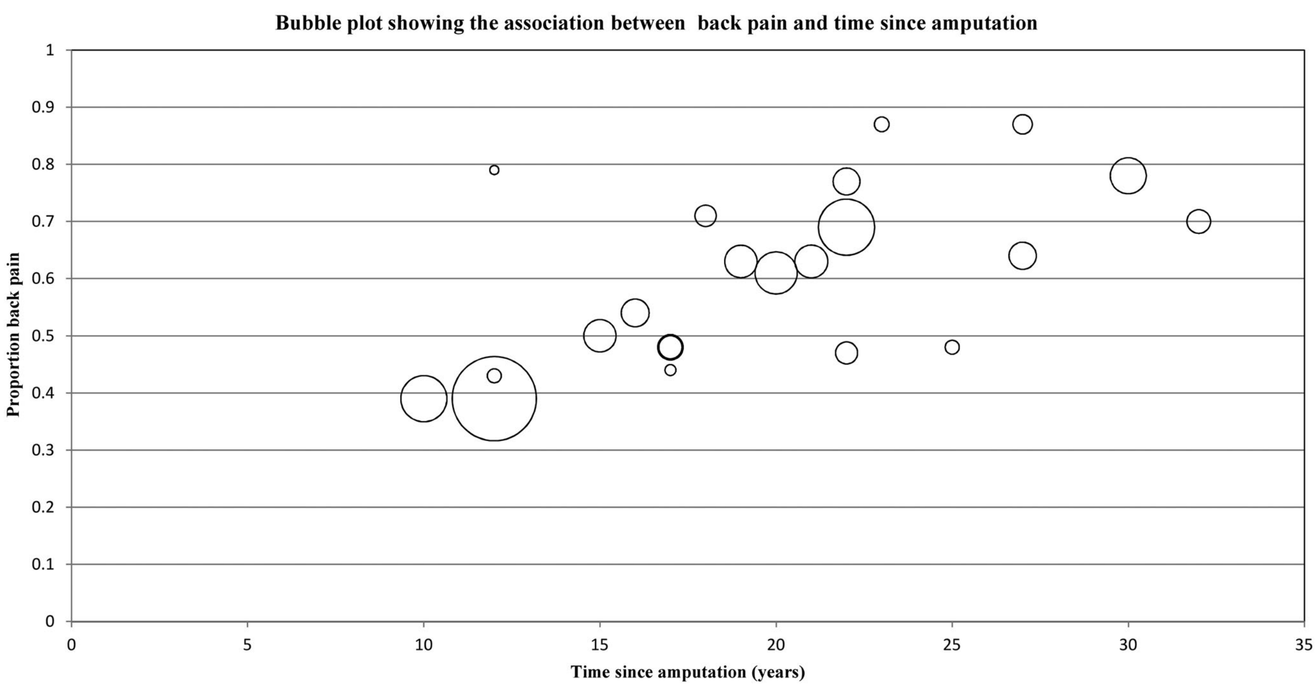

Figure 4. Bubble plot showing the association between back pain and time since amputation.

comparable to our study population, with the proportion male gender however being overrepresented in our study population. This can be explained by the fact that our study population predominantly consisted of war veterans with a traumatic LLA. Taking this into account, the mean pooled prevalence of back pain in our study turned out to be higher in comparison with the previously reported back pain prevalence in the general population. Four of the included studies in our systematic review retrospectively analyzed the back pain prevalence before LLA. Three studies found that only 10–20% of persons with back pain retrospectively recalled experiencing back pain before their amputation, compared to 50–87% after amputation [6,51,62]. One study focusing on persons with transfemoral amputation found a slightly increased frequency of ICD-9 back pain codes postamputation [33]. This study also found a statistically significant increased frequency of back pain events in persons with a dysvascular transfemoral amputation in comparison with a matched control group. For persons with a non-dysvascular cause of amputation, no significant differences were found, the sample size of this group was small however.

In our back pain meta-regression, we found a positive association with male gender and traumatic cause of amputation. As stated earlier, most of our study database consisted of male persons (median proportion 0.82) with LLA due to traumatic reasons (mean proportion 0.68). For this reason, these findings should be interpreted with great caution. No other associations between back pain and cause of LLA were found. Furthermore, no associations between cause of LLA and presence of RLP were found. The proportion of persons with LLA due to vascular reasons in the reviewed studies turned out to be relatively small. RLP could also be a sign of vascular claudication and therefore might be leading to a re-amputation, which happens relatively frequent in persons with LLA due to vascular reasons [75]. This finding might have further influenced the reported prevalence of RLP in the long term.

No association between amputation level and the prevalence of RLP or back pain was found in this review. Thus, we could not confirm the results of the regression analyses performed in other studies on RLP and on back pain, in which such an association was found [4,41].

A recent systematic review focused on summarizing evidence on physical and social determinants for health-related quality of life in veterans with LLA [14]. It found back pain to be one of the determining factors for quality of life, based on two studies also included in our review [20,50]. RLP did not prove to be a determining factor in that review. A meta-analysis could not be performed in that review. Comparing these findings with our data, we did find a higher prevalence of back pain compared to RLP in our pooled data. Our reported RLP and back pain intensity and impact were similar as well. However that systematic review focused solely on veterans with LLA, and we did not specifically take quality of life data into account.

In an expert review, it was stated that back pain is a frequent and bothersome secondary complaint [9]. Our findings underline that statement. We also found a considerable prevalence of contralateral limb pain; knee and hip pain was indeed reported more at the contralateral side. It has been proposed that persons with LLA tend to favor their intact limb which causes more stress on the contralateral side, which makes persons with LLA twice as likely to develop pain in the intact limb [11]. Due to the low amount of studies reporting hip and knee pain, we were not able to confirm this proposed mechanism. As mentioned before, other factors besides the biomechanical aspect as neurophysiological and personal factors could possibly play a role in the experiencing of pain after LLA [64]. Furthermore, our data concerning the cause of the different pain types turned out to be limited and non-conclusive.

The findings presented in this review provide patient and clinician working with persons with LLA with data about pain characteristics of the different chronic pain types other than PLP, and factors related to these pain types. Besides this, this study also provides insight in areas of the field in which the current available knowledge is lacking.

Future studies on this topic should systematically distinguish different pain intensities, preferably using the same cut-off values. We would also like to suggest that future prevalence studies on this topic include pain-related interference as an outcome variable. More information about pain intensity and pain-related interference would provide more insight in the impact of pain on the functioning of persons with LLA [76]. Apart from the possible moderators studied in the present review, factors like health-related quality of life, coping strategy and psychological well-being could also have an important impact on the experienced RLP and back pain in persons with LLA. Next to this, future studies should also give more attention to other chronic pain types than RLP, back pain and PLP, as those pain types could have a significant impact on the functioning of persons with LLA as well. Also, more attention should be given to pain in persons with LLA due to diabetic and vascular reasons, considering the underrepresentation of these categories in the current literature. Finally, more attention should be given to central sensitization in persons with pain after LLA.

Study limitations

The conclusions of this review are limited by the quality and reporting of the source publications, and should therefore be interpreted with caution. The majority of included studies had a poor methodological quality. As mentioned earlier in our risk of bias assessment, aspects like timeframe of inclusion and exclusion criteria were often poorly reported. Subjects were mostly not recruited consecutively, and missing data were mostly not reported. Many studies did not distinguish pain characteristics per amputation level. The timeframe in which pain had to be present varied widely, which may have impacted negatively on pooling of results in our meta-regression. Furthermore, some studies only reported pain if being frequent or always present, or being of high intensity, while other studies reported any intensity and frequency, and some studies used ICD-9 or ICD-10 codes instead of questionnaires or interviews. Most included studies used a cross-sectional design. A large proportion of the study population of the included studies consisted of relatively young male persons with traumatic LLA. As could be a consequence, the proportion prosthesis use in this systematic review was high. A considerable amount of studies in our review excluded persons not using a prosthesis, or only included persons with LLA in prosthetic clinics. Therefore, caution should be taken to generalize the outcomes of this review to the general population of persons with LLA, especially concerning the elderly patient with LLA due to vascular reasons who does not or seldom uses a prosthesis [77].

Furthermore, a considerable amount of studies did not report every predictor of our regression model, which might have contributed to varying and sometimes contradictory outcomes. Interpreting the results of the meta-regression, the reader should be aware that the meta-regression is based on aggregated data and not on individual patient data, thus influence of confounding variables on the associations found cannot be analyzed on a patient level. Thus, regression coefficients are based on between-study variations and weights of the studies included.

During our last search update, we excluded a study reporting on pain and quality of life after amputation in children. While we did not specifically document this in our study protocol, in previous searches we had always focused on adult persons and wanted to prevent additional heterogeneity within our dataset.

Finally, by excluding all studies reporting only PLP during our study selection, some RLP data may have been lost. More importantly, we did not expect to find an association between RLP and back pain with a central sensitization mechanism as a possible explanation. By excluding studies reporting only PLP, we were not able to investigate if the presence of RLP and back pain was associated with the presence of PLP as well.

Conclusions

Chronic back pain and RLP are common after LLA, back pain being more prevalent than RLP. The presence of back pain is positively associated with the presence of RLP, and vice versa. Furthermore, the prevalence of back pain is positively influenced by the time since amputation. Future studies should give more attention to other chronic pain types such as hip pain, knee pain, and pain in the contralateral limb, and to persons with a diabetic or vascular cause of amputation. Finally, more attention should be given to pain-related interference.

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Disclosure statement

The authors report no conflicts of interest.

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Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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