Developing an in-depth understanding of the prevalence, risk factors and treatment recommendations for phantom limb pain, and patient-generated care priorities for people who have undergone lower limb amputations.

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Declaration

I, Katleho Limakatso, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and have used the Vancouver system of referencing. I declare that neither the whole work nor part of it has been, is being, or is it to be submitted for another degree at the University of Cape Town or any other university. I empower the University of Cape Town to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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2. Limakatso, K. and Parker, R., 2021. Treatment recommendations for phantom limb pain in people with amputations: an expert Delphi study. *Physical Medicine and Rehabilitation.* *https://doi.org/10.1002/pmrj.12556*

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Signed by candidate

_____

Signature

Date: 25/11/2021

Acknowledgements

First and foremost, I thank God for life, intelligence, wisdom, supervisors, and family which without, I would not have been able to complete this degree.

A special thank you to:

My supervisor Prof. Romy Parker for her commendable leadership and support. I thank you for providing me with opportunities that have helped me grow in my career. I am eternally grateful for your invaluable contribution in all the important areas of my life. May the Lord bless you and keep you. May he make his face to shine upon you and be gracious to you. May he lift up his countenance upon you and give you peace always.

Dr. Victoria J. Madden for challenging me to think intelligently and creatively. Your support, and insightful input towards my career development is highly appreciated.

My beautiful wife Mamello Tholoana Limakatso for her unwavering support and encouragement. Thank you for celebrating every victory with me. I also thank you for allowing me to lean on you during difficult and challenging times. Without you, I would have crumbled. Kea u rata Mokuena e motle! Morena a mpolokele uena.

My lovely and cheerful daughter Busizwe Abigail Limakatso. Thank you for keeping me company when I wrote the final chapter of this thesis. Daddy loves you unconditionally!

My father – my biggest fan and cheerleader. I dedicate this work to you. It is through your earnest prayers, support and encouragement that I have achieved this milestone. “Katleho eaka ke Katleho ea hau”.

Groote Schuur Hospital for making this research possible.

The participants who took part in this research with so much enthusiasm.

Ms. Bonolo Mafojane for assisting with patient recruitment and data collection. Sadly, Ms Mafojane passed away recently, and she will be truly missed.

Abstract

Introduction:

Phantom limb pain is a common complication in people who have undergone limb amputation, with prevalence estimates ranging between 29% and 85.6%. Current systematic-review evidence suggests that recommended treatments are no more effective than placebo for reducing Phantom Limb Pain (PLP). Moreover, there is evidence suggesting that people with amputations may not be getting the treatment they want at different time-points after amputation. In consideration of these points, a research project comprised of a series of interconnected studies aimed to develop an in-depth understanding of the global burden of PLP and patient care priorities after limb amputations, and generate expert recommendations on the best management of PLP in people with amputations.

Methods:

The research project is comprised of a series of four interconnected studies addressing the four primary aims of the project. A systematic review and meta-analysis were conducted to determine the pooled prevalence estimate and risk factors for PLP in people with amputations. A cross-sectional study was conducted to determine the prevalence and risk factors for PLP in people who had undergone lower limb amputations at Groote Schuur Hospital. An expert Delphi study was conducted to reach expert consensus and make recommendations on the effective treatments for PLP in people with limb amputations. Lastly, a patient Delphi study was conducted to generate patient consensus on care priorities for people who have had lower limb amputation for a year or less and for those who have had lower limb amputations for more than a year.

Results:

The systematic review and meta-analysis of 39 studies revealed a pooled PLP prevalence estimate of 64% [95%CI: 60.01 – 68.05], with a significantly higher prevalence estimate in studies conducted in developed countries 66.55% [95% CI: 62.02 –71.64] than those conducted in developing countries 53.98% [95% CI: 44.79–63.05] (U = 57, p = 0.03). Risk factors that were consistently positively associated with PLP included having an amputation of a lower limb, stump pain, non-painful phantom sensations, persistent pre-amputation pain, proximal site of amputation, and diabetic cause of amputation. The cross-sectional study using a sample of African people with amputations showed a PLP prevalence of 50.78% [95% CI: 41.80 – 59.72] during the week preceding data collection. In this group of patients, persistent pre-operative pain was the only risk factor associated with PLP in the multivariate logistic regression analysis [OR 2.25 (1.03 – 5.05); P=0.04]. In the expert Delphi study, consensus was reached on one pharmacological (amitriptyline) and six non-pharmacological (Graded Motor Imagery, mirror therapy, Cognitive Behavioural Therapy, virtual reality training, sensory discrimination training, use of a functional prosthesis) treatments that were considered effective for managing PLP, and on two treatments [citalopram (60%) and Pulsed Radiofrequency Stimulation of the dorsal root ganglion (70%)] that were considered ineffective. In the patient Delphi study, consensus was reached on 24 short-term care priorities and 12 long-term care priorities. The general consensus among the participants was that pre-amputation, they wanted education support to help them manage their expectations and prepare for life after amputation. In the early stage after amputation, they wanted help with dealing with the psychological trauma of having lost a limb. In the long-term, however, the participants prioritised the need for living a functional and normal life, with respect and dignity like everyone else.

Conclusion:

The prevalence of PLP in people with limb amputations is high, and awareness of this condition needs to be raised among healthcare professionals to implement evidence-based strategies for alleviating PLP by targeting the relevant underlying mechanisms and modifiable risk factors. Evidence-based medicine indicates that PLP is best managed using non-pharmacological and non-interventional treatments addressing biopsychosocial contributors for PLP. Finally, preparing people for life after amputation and helping them deal with the psychological trauma of having lost a limb may contribute to improved clinical outcomes that may enable them to live a functional and normal life, with respect and dignity.

Kakaretso: Phetolelo ya Sesotho.

Selelekela:

Bohloko bo utlwahalang dikarolong tsa mmele tse siko ke sewa se tlwaelehileng hara batho ba lahlehetsweng ke matsoho kapa maoto. Dipalo di hakanya hore dipakeng tsa 29% le 85.6% ya batho ba kgaotsweng maoto le matsoho bana le bohloko bona. Dipatlisiso tsa honajwale di bontsha hore meriyana e kgothaletswang ho fedisa bohloko bona ha e sebetse. Ho fetisa moo, hona le bopaki bo bontshang hore batho ba kgaotsweng maoto le matsoho ha ba fumane kalafo le tlhabollo eo bae hlokang. Ka mabaka ana, patlisiso e bopiloeng ke di projeke tse nne tse latelanang ene e ikemiseditse ho fumana kutlwisiso e chorileng ya dipalo tsa batho ba utlwang bohloko dikarolong tsa mmele tse siko, le ho fumana hotswa ho bona hore na baka thabela ho fumana thuso e jwang ka mora hore ba kgaolwe dikarolo tsa mmele, le ho fumana dikgothaletso hotswa ho ditsebi hore batho ba nang le bohloko dikarolong tsa mmele tse siko baka hlabollwa jwang.

Mekgwa:

Patlisiso ena e bopilwe ka diprojeke tse nne tse latelanang, ho hlakisisa maikemisetso a mane a mantlha a projeke ena. Tlhahlobo e hlophisitsweng le tlhahlobo ea *meta* di ile tsa etswa ho fihlela dikgakanyo tsa ho ata ha kopanelo le mabaka a kotsi sebakeng sa bohloko bo utlwahalang dikarolong tsa mmele tse siko, ho batho ba kgaotsweng dikarolo tsa mmele. Boithuto ba dikarolo tse fapaneng bo ile ba etswa ho fumana ho ata le mabaka a kotsi sebakeng sa bohloko bona ho batho ba kgaotsweng maoto sepetleleng sa Groote Schuur. Boithuto ba ditsebi ba *Delphi* bo ile ba etsoa ho fihlela tumellano ya Ditsebi leho fana ka dikhothaletso ka diphekolo tse sebetsang hantle sebakeng sa bohloko bo utlwahalang dikarolong tsa mmele tse siko ho bakudi ba khaotsweng maoto. Qetellong boithuto ba bakudi ba Delphi bo ile ba etswa, ho hlahisa tumellano ea bakudi hodima dintho tse tlang pele maphelong a batho ba kgaotsweng maoto nako ea selemo kapa ka tlase, le ho ba kgaotsweng maoto nako e fetang selemo.

Diphetho:

Tlhahlobo e hlophisitsweng le tlhahlobo ya *meta* ya dithuto tse 39 e bontshitse hore kakaretso ya ho ata ha bohloko bo utlwahalang dikarolong tsa mmele tse sieo e hakanyetswa ho 64% [95%CI: 60.01 – 68.05]. Ho ata ha bohloko bona hone ho phahame haholo dithutong tse entsweng dinaheng tse tswetseng pele [66.55% (95% CI: 62.02 –71.64)] ho feta ho tse entsweng dinaheng tse ntseng li tswela pele [53.98% (95% CI: 44.79–63.05)] (U = 57, p = 0.03). Mabaka a kotsi, a amanang le bohloko bo utlwahalang dikarolong tsa mmele tse siko a kenyelelitse ho khaolwa maoto, bohloko ba kutu ya leoto, maikutlo a senang bohloko karolong e kgaotsweng, bohloko ba sebaka se haufi le setho se khaotsoeng, le ho khaoloa setho sa mmele ka lebaka la lefu la tswekere. Boithuto ba likarolo tse fapaneng bo sebedisitseng mohlala wa batho ba Afrika ba khaotsweng dikarolo tsa mmele bo bontshitse ho ata ha bohloko bo utlwahalang dikarolong tsa mmele tse siko hwa 50.78% [95% CI: 41.80 – 59.72] nakong ea beke pele ho pokello ea dintlha. Sehlopheng sena sa bakudi, bohloko bo phehellang pele ho opereishene ene ele bona fela lebaka la kotsi le amanang le bohloko bo utloahalang likarolong tsa 'mele tse sieo, tlhahlobong wa ho fokotseha ha lintho tse ngata [OR 2.25 (1.03 – 5.05); P=0.04]. Boithutong ba litsebi ba *Delphi*, tumellano e ile ea fihleloa ka moriena o le mong (amitriptyline) le liphekolo tse tsheletseng tseo eseng meriana (Graded Motor Imagery, mirror therapy, Cognitive Behavioural Therapy, virtual reality training, sensory discrimination training, use of a functional prosthesis) tse nkoang li sebetsang hantle ho laola bohloko bo utloahalang dikarolong tsa mmele tse sieo. Diphekolo tse peli [citalopram (60%) le Pulsed Radiofrequency Stimulation of the dorsal root ganglion (70%)] di fumanoe di sena matla a ho laola bohloko bo utloahalang dikarolong tsa 'mele tse sieo. Boithutong ba bakudi ba Delphi, ho ile hoa fihlellwa tumellano ea dinthla tsa tlhokomelo tse 24 tsa nako e khutshwanyane le tse 12 tsa nako e telele. Tumellano e akaratsang e ileng ea fihlelwa ke bankakarolo, ke hore pele ba khaoloa likarolo tsa mmele ba batla tsehetso ea dithuto hoba thusa ho laola ditebello tsa bona le ho itukisetsa ho phela ba sena dikarolo tse ling tsa 'mele. Mekhahlelong ea pele ka mora ho khaolwa dikarolo tsa mmele, bakudi bare ba hloka thuso ea ho sebetsana le ho sithabela maikutlo ka mora ho lahleheloa ke karolo ea mmele.

Leha ho le joalo, nakong e telele bakuli ba behile ka pele tlhokahalo ea ho phela bophelo bo tloaelehileng ba tlhompho le seriti joalo ka motho emong le emong.

Qetello:

Ho ata ha bohloko bo utlwahalang dikarolong tsa mmele tse siko bathong ba khaotsoeng dikarolo tsa mmele ho phahame, mme tlhokomediso ea bohloko bona e hloka ho phahamiswa hara ditsebi tsa bophelo bo botle ele ho kenya tshebetsong maano a thehilweng bopaking. Sena setla fokotsa bohloko bo utloahalang dikarolong tsa mmele tse siko, kaho tsepamisa maikutlo mekgweng ya motheo e amehang le maemong a kotsi a fetohang. Dipatlisiso tsa hona joale di bontsha hore bohloko bo utlwahalang dikarolong tsa mmele tse siko boka laolwa hantle ka ho fetisisa haho sebeliswa lipheko tseo eseng tsa meriana le maano a dipheko a shebaneng le dikarolo tsohle tsa bophelo ba motho mabapi le bohloko bona. Hodima tsena tsohle, ho lokisetsa batho bophelo kamora ho kgaolwa dikarolo tsa mmele le ho ba thusa ho sebetsana le ho sethabela maikutlo ka mora ho lahleheloa ke karolo engwe ya mmele, hoka kenya letsoho ho ntlafatsa diphetho tsa bophelo ditleleniking leho nolofaletsa bakudi bo phela bophelo bo tlwaelehileng bo nang le tlhompho le seriti.

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List of abbreviations

ADL	Activities of Daily Living
BPI	Brief Pain Inventory
CBT	Cognitive Behavioural Therapy
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
fMRI	Functional Magnetic Resonance Imaging
GMI	Graded Motor Imagery
GRADE	Grading and Recommendations Assessment, Development, and Evaluation
GSH	Groote Schuur Hospital
HREC	Human Research Ethics Committee
ICD	International Classification of Disease
IDF	International Diabetes Federation
IQR	Inter-Quartile Range
LLAs	Lower Limb Amputations
MeSH	Medical Subject Headings
NICE	National Institute of Health and Care Excellence
NMDA	N-Methyl D-Aspartate
OR	Odds Ratio
PLP	Phantom Limb Pain
PRFS	Pulsed Radiofrequency Stimulation
PRISMA	Preferred Reporting Items of Systematic Reviews and Meta-Analysis
P-value	Probability value
UCT	University of Cape Town
UK	United Kingdom

USA	United States of America
VAS	Visual Analogue Scale
WESP	World Economic Situation and Prospect

Chapter 1: Introduction

Limb amputation is the most common consequence of complications arising from diabetes and peripheral vascular diseases (1). Up to 90% of surgical amputations performed worldwide are linked to diabetes (2, 3), which is over a million amputations per year (4). Following limb amputation, up to 85% of patients report PLP which is defined as pain felt in the missing portion of the amputated limb (5-7). Phantom limb pain is a debilitating condition characterised by a variety of painful sensations such as sharp, shooting, burning and piercing pain (8). In addition to the psychological trauma linked to the loss of a limb, PLP contributes further to problems with mobility and prosthesis use, anxiety, depression and poor health-related quality of life (9, 10).

There are varying reports on the prevalence of phantom limb pain in people who have undergone amputations. While some studies report a high point prevalence of 85% (11, 12), the majority of the studies report a point prevalence of between 33% and 72% (13-15). The conflicting reports in the literature regarding the prevalence of PLP indicate a need for pooling of the evidence through a systematic review and meta-analysis to establish a reliable prevalence estimate of PLP in people who have undergone limb amputations. Currently, no studies could be found that were conducted to determine the prevalence of PLP in amputees living in South Africa, and research in this area remains a priority. Identifying the prevalence of PLP in amputees living in South Africa will enable relevant stakeholders to motivate for allocation of adequate resources that may enable clinicians to reduce suffering, disability, and the negative consequences of pain on the patient's health.

Several studies have identified risk factors for PLP including persistent pre-amputation pain, pre-amputation depression, and a lack of pre-amputation education and planning of support (7, 16-18). Although causal mechanisms between these risk factors and PLP have not be studied, the evidence suggests they play an important role in initiating and maintaining PLP.

The important role of these risk factors could also be explained to some degree, by the effectiveness of psychological interventions targeting them in reducing PLP (19).

Risk factors are commonly known as factors occurring prior to the onset of disease. In light of this, mainly the pre-amputation risk factors for PLP have been studies. However, considering that the onset varies widely after amputation, it is also worth exploring perioperative and post-amputation risk factors for PLP. The knowledge of associations is useful for identifying causality between variables or predicting an outcome (20). In this study, a risk factor is defined as a predictor for an outcome (PLP).

Despite strategic efforts aimed at improving peri-operative pain management, PLP continues to be a challenge to treat (21). A recent review of clinical guidelines on PLP management recommends tricyclic antidepressants (e.g amitriptyline), anticonvulsants (e.g pregabalin) and N-methyl D-aspartate (NMDA) receptor antagonists (e.g Memantine) (22). However, there is systematic-review evidence suggesting that these treatments are marginally effective at best, and no more effective than placebo (23). Although the results of a recent systematic review by our team suggest that non-pharmacological interventions such as Graded Motor Imagery (GMI) and mirror therapy may be effective for reducing PLP, currently the best practice for PLP management in people with amputations is unclear. Therefore, development of a guideline for PLP management is indicated as such a guideline may contribute to effective care and improved patient outcomes (24).

In recent years, strategies have been implemented to promote patient involvement in healthcare with the overall aim of improving patient outcomes. Nevertheless, it has been proposed that some patients do not receive the treatment they want or need as a result of not being involved in clinical decision making (25). This idea is supported by the results of several studies suggesting that some patients may have different outcome priorities for treatment compared to those of treating clinicians (24, 26, 27). Thus far, there is no published literature aimed at identifying the healthcare priorities of patients who are suffering from PLP after limb amputations. Research aimed at

identifying care priorities in this population may improve patient clinical outcomes, adherence to treatment, accountability and efficient health-service delivery (28).

1.1 Research rationale

As presented above, it is apparent that there are several gaps in the literature relating to the worldwide prevalence estimate of PLP, as well as the prevalence of PLP in South Africa. In addition, the best practise for PLP management and patient outcome priorities following amputations have yet to be established. The research presented in this thesis addresses these gaps and builds on the existing literature using various research designs: systematic review and meta-analysis; cross-sectional; and 3-step Delphi designs. The results of the proposed research are written into four manuscripts that have been published in, or have been prepared for submission to, internationally accredited journals.

1.2 Research questions

- What is the global prevalence of PLP in people with limb amputations?
- What is the prevalence and associated risk factors for PLP in African people with amputations, who live in Cape Town, South Africa?
- What are the treatment recommendations for the best management of PLP in people with limb amputations?
- What are self-reported patient care priorities after lower limb amputations in the South African population?

1.3 Research aim

The broad aim of this research is to develop an in-depth understanding of the prevalence, risk factors, and treatment recommendations for PLP, and patient-generated care priorities for people who have undergone lower limb amputations.

1.4 Objectives

- To determine the pooled prevalence estimate of PLP in people with limb amputations (*Systematic review and meta-analysis*).
- To determine pre-operative, peri-operative, and post-operative risk factors for PLP in people with limb amputations (*Systematic review and meta-analysis*).
- To evaluate whether there is a significant difference in the prevalence of PLP between studies conducted in developing and developed countries (*Systematic review and meta-analysis*).
- To determine the prevalence of PLP in a sample of African people with limb amputations (*Cross-sectional study*).
- To determine pre-operative, peri-operative, and post-operative risk factors for PLP in a sample of African people with limb amputations (*Cross-sectional study*).

- To reach expert consensus and make recommendations on the effective treatments for PLP in people with amputations (*Expert Delphi study*).
- To reach patient consensus and make recommendations on care priorities after lower limb amputations (*Patient Delphi study*).

The objectives of this research project will be investigated using four distinct but interconnected studies using different designs. Altogether, these studies will contribute to an in-depth understanding of the global burden of phantom limb pain and patient care priorities after limb amputations, and the best management of PLP in people with amputations.

1.5 Ethical approval to conduct research

Ethical approval for conducting this research project was sought from and granted by the University of Cape Town, Faculty of Health Sciences, Human Research Ethics Committee (HREC) for the following studies:

- Limakatso, K., Rayamajhi, S., Kloppers, C., Østlie, k. and Parker, R., 2021. Phantom Limb Pain: a cross-sectional survey of the prevalence and risk factors in amputees living in Cape Town, South Africa. The European Journal of Pain (*In preparation*). HREC Ref: 066/2020 (Appendix 1).
- Limakatso, K. and Parker, R., 2021. Treatment recommendations for phantom limb pain in people with amputations: an expert Delphi study. *Physical Medicine and Rehabilitation.* *https://doi.org/10.1002/pmrj.12556*. HREC Ref: 355/2019 (Appendix 2).
- Limakatso, K. and Parker, R., 2021. Care priorities for patients with lower limb amputations: a patient Delphi study. (*In preparation*). HREC Ref: 771/2020 (Appendix 3).

The results of the studies making up this research project will be disseminated by publication in high-impact international journals, poster and oral presentations at national and international scientific meetings, and teaching at undergraduate and postgraduate levels at the University of Cape Town and affiliated institutions.

1.6 Reporting structure

The four interrelated studies investigating the seven objectives of this research project are presented in Chapters 2 – 5. Each chapter is comprised of declarations from the author and co-authors, a study background and motivation for conducting the study, aims and objectives, a summary of main findings, a copy of the peer-reviewed published article or submission ready article, and supplementary material. Chapter 6 integrates the results of all the studies and draws conclusions and recommendations for research and clinical practice.

Chapter 2: The prevalence and risk factors for phantom limb pain in people with amputations: A systematic review and meta-analysis.

2.1 Publication reference:

Limakatso, K., Bedwell, G.J., Madden, V.J. and Parker, R., 2020. The prevalence and risk factors for phantom limb pain in people with amputations: A systematic review and meta-analysis. *PloS one*, *15*(10), p.e0240431. https://doi.org/10.1371/journal.pone.0240431

2.2 Declarations from authors and co-authors.

2.2.1 Declaration from author

The following co-authors contributed to the published study: Gillian J. Bedwell, Victoria J. Madden, and Romy Parker. The contribution of the authors for this publication is as follows: Katleho Limakatso conceptualised the study with the input from Victoria J. Madden and Romy Parker. Katleho Limakatso designed the customised search strategy with the assistance of Mary Shelton - the Faculty of Health Sciences reference librarian at the University of Cape Town. Katleho Limakatso and Gillian J. Bedwell collected and curated data. Katleho Limakatso conducted the formal analysis of the data with input from Victoria J. Madden, and Romy Parker. Katleho Limakatso wrote the original draft of the manuscript. All the authors reviewed and edited the manuscript and approved the publication of the final version of the manuscript.

Extent of contribution:

- Katleho Limakatso: 75%
- Gillian Bedwell: 10%
- Prof Romy Parker: 7.5%
- Dr Victoria J. Madden: 7.5%

_____

Signed by Katleho Limakatso Date: 25/11/2021

2.2.2 Declaration of co-authors

undersigned hereby certifies that:

1. The above declaration correctly reflects the nature and extent of the candidate's contribution to this work and the nature of the contribution of each of the co-authors.
2. They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise.
3. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication.
4. There is no other author of the publication according to these criteria.
5. Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit.
6. The original data are stored at the following location and will be held for 10 years from the date of the study's completion.

Location of stored data: Data were stored on a password-protected computer. Back-up data were stored on an external hard drive and shared on a secure online data repository (https://Zenodo.org/DOI:10.5281/zenodo.6355501). Data will be securely kept for 10 years after the completion of the study. Deidentified data will be made public in perpetuity according to Open Science principles (29). The peer-reviewed manuscript developed from this study was shared on OpenUCT (www.open.uct.ac.za/katleho_limakatso) according to the Open Access Policy at UCT.

Romy Parker Date: 25/11/21

Victoria J. Madden Date: 25/11/21

Gillian Bedwell Date: 25/11/21

2.3 Background and motivation

Numerous studies have consistently shown that PLP is common in people with limb amputations, and a significant proportion of people report this as debilitating pain that interferes with cognition, function, and Activities of Daily Living (ADL) (9, 30). Despite the compelling evidence showing high PLP prevalence, the literature has revealed substantial disparities in the prevalence reports. While one study showed a prevalence of 29% [95%CI: 25.9 – 34.0], another study showed a markedly high prevalence of 86% [95%CI: 80.0 – 93.54]. The conflicting prevalence reports suggest that a firm conclusion on the prevalence of PLP cannot be drawn at this stage. Prevalence studies are key for informing policy-makers' decisions on the allocation of sufficient resources towards the treatment of a disease. In addition, they enable healthcare professionals to develop strategies for prevention, and identifying plausible targets for treatment. The wide variation in PLP prevalence reports raises a need to systematically review and pool the literature on PLP prevalence to generate a robust prevalence estimate for PLP.

Pain is a biopsychosocial construct influenced by recognisable psychological, social and economic factors. Recent evidence shows that biopsychosocial and economic factors associated with pain vary significantly between people living in developed and developing countries (31-33). For example, key factors such as low levels of pain education (34, 35), a lack of healthcare facilities providing acceptable pain management (36), and a lack of financial resources necessary for accessing high-quality healthcare (37), are relatively common in developing countries. In consideration of these disparities, it is plausible to hypothesise that prevalence estimates of PLP may vary between people living in developed countries versus those living in developing countries. To date, no subgroup analyses has been conducted comparing the prevalence estimates in developed and developing countries. Therefore, research on this subject is indicated to inform us about the prevalence estimates and additional factors influencing PLP in people living in developed and developing countries.

There is increasing evidence supporting the role of various mechanisms underlying PLP: spontaneous nociceptive firing at a neuroma, cortical sensory-motor mismatch, maladaptive cortical reorganisation, and stochastic entanglement of the pain neurosignature with impaired sensory motor circuitry (38-40). However, there is a lack of research aimed at systematically reviewing the literature on the role of pre-operative, perioperative and post-operative risk factors for PLP. The exposure to risk factors has been shown to increase the risk of developing and maintaining PLP in people with phenotypes susceptible to pain (41). Pain phenotype is defined as the observable or self-reported proxy measure that reflects the processing of pain in the central nervous system (42). Pain phenotypes are highly variable across the global population, and this variability predisposes some patients to a higher risk of developing chronic pain that others (43). The knowledge of modifiable risk factors that are consistently positively associated with PLP may enable healthcare professionals to identify treatment targets in the hopes of preventing and managing PLP.

2.4 Aims and objectives

2.4.1 Aim

The aim of the systematic-review and meta-analysis is to pool and critically synthesise relevant literature to determine the pooled prevalence estimate of PLP in people with limb amputations.

2.4.2 Objectives

- To evaluate whether there is a significant difference in the prevalence of PLP between studies conducted in developing and developed countries.
- To conduct an exploratory analysis of pre-operative, peri-operative, and post-operative risk factors associated with PLP in people with limb amputations.

2.5 Summary of main findings

- The comprehensive search of the literature identified 37 studies that were eligible for inclusion in the systematic review. Because two studies reported two studies each, a total of 39 data sets totalling 12738 participants were included in the analysis.
- Thirty-two of the 39 studies had been conducted in developed countries. Of these, the majority were conducted in Europe (N=19) and North America (N=9). Only seven studies were conducted in developing countries. Surprisingly, no relevant study conducted in Africa could be found.
- Phantom limb pain prevalence estimates ranged between 29% [95%CI: 25.9 – 34.0], and 86% [95%CI: 80.0 – 93.5], with 31 out of 39 studies reporting prevalence estimates between 50% and 86%. The pooling of all studies using the random-effects model revealed a prevalence estimate of 64% [95%CI: 60.0 – 68.0].
- The subgroup analyses stratified by the development status of the countries in which the studies were conducted showed an estimated pooled prevalence of 67% [95% CI: 62.0 –71.6] in developed countries and 54% [95% CI: 44.8–63.0] in developing countries. The Mann-Whitney U test showed a statistically significant difference between the prevalence estimates of these two meta-analyses [U = 57, p = 0.03].
- Twenty-five potential risk factors were identified from 15 eligible studies representing 4102 participants. Risk factors that were consistently positively associated with PLP include having an amputation of a lower limb, stump pain, non-painful phantom sensations, persistent pre-amputation pain, a proximal site of amputation, and a diabetic cause of amputation.

"The content of the published manuscript from which these summarised results were extracted is presented below"

2.6 Manuscript published in PLOS ONE

Title: The prevalence and risk factors for phantom limb pain in people with amputations: a systematic review and meta-analysis.

Short title: Prevalence of phantom limb pain in amputees.

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2.6.1 Abstract

Background

Phantom limb pain (PLP)—pain felt in the amputated limb–is often accompanied by significant suffering. Estimates of the burden of PLP have provided conflicting data. To obtain a robust estimate of the burden of PLP, we gathered and critically appraised the literature on the prevalence and risk factors associated with PLP in people with limb amputations.

Methods

Articles published between 1980 and July 2019 were identified through a systematic search of the following electronic databases: MEDLINE/PubMed, PsycINFO, PsycArticles, Cumulative Index to Nursing and Allied Health Literature, Africa-Wide Information, Health Source: Nursing/Academic Edition, SCOPUS, Web of Science and Academic Search Premier.

PLP was previously stigmatised as a psychopathological disorder (44). Therefore, studies conducted before this period were at risk of performance bias and reporting imprecise prevalence estimates due to patients' fear of being stigmatised as having a mental condition. Due to this, we decided to exclude the early studies as they had a risk of affecting the validity and robustness of the conclusions drawn from our meta-analysis. Grey literature was searched on databases for preprints. Two reviewers independently conducted the screening of articles, data extraction and risk of bias assessment. The meta-analyses were conducted using the random effects model. A statistically significant level for the analyses was set at $p<0.05$.

Results

The pooling of all studies demonstrated a prevalence estimate of 64% [95% CI: 60.0 – 68.0] with high heterogeneity [I2 = 95.95% (95% CI: 95.1–96.6)]. The prevalence of PLP was significantly lower in developing countries compared to developed countries [54% vs 66.6%; p = 0.03]. Persistent pre-operative pain, proximal site of amputation, stump pain, lower limb amputation and phantom sensations were identified as risk factors for PLP.

Conclusion

This systematic review and meta-analysis estimates that six of every 10 people with an amputation report PLP–a high and important prevalence of PLP. Healthcare professionals ought to be aware of the high rates of PLP and implement strategies to reduce PLP by addressing known risk factors, specifically those identified by the current study.

1. Introduction

Phantom limb pain (PLP) - pain felt in the amputated limb – is often accompanied by significant suffering (8). The condition is difficult to manage and can lead to disability and reduced health-related quality of life (45). Several risk factors, including stump pain, diabetic cause of amputation and depression, have been found to be associated with the onset and continuation of PLP (7, 14, 46). While there are reports of PLP in people with congenital amputations (47), PLP appears to be more prevalent in people with traumatic or surgical limb amputations (6).

There are conflicting reports on the prevalence of PLP in people with limb amputations. Whereas one study reported a high prevalence of 86% (48), another reported a substantially lower prevalence of 29% (49). The inconsistent reports on the prevalence of PLP are perplexing, but may be due to differences in the study samples (upper- vs lower-limb amputees or mixed populations), countries in which the research was undertaken, and methodologies between studies (50).

Higher prevalence rates of PLP have been reported in people with lower limb amputations than in those with upper limb amputations (14, 51). Lower limb(s) amputations are performed chiefly to treat complications of diabetes, and may be associated with risk factors for PLP such as pre-amputation pain and depression (52). The high PLP prevalence could be explained by these risk factors, which are typically absent in people with upper limb amputations, who are typically healthy and undergo amputation due to trauma (53). Studies that report PLP prevalence in people receiving continuing medical care have a selection bias (7, 14, 54), in that they fail to account for patients not receiving continuing medical care, who may have different prevalence rates (55). In addition, previous studies suggest that PLP prevalence rates may be lower in developing countries (56). However, no clear hypothesis for these lower prevalence rates has been proposed. Further, it is not clear if the prevalence rates in developing countries are significantly lower to those seen in developed countries.

Epidemiological studies are essential to inform health care professionals and health system planners about the burden of diseases in a population (57). Estimates of the burden of PLP have provided conflicting data. To our knowledge, no systematic review has been conducted on the prevalence and risk factors for PLP. Therefore, to obtain an accurate estimate of the burden of PLP, we gathered and critically appraised the literature on the prevalence and risk factors associated with PLP in people with limb amputations.

The primary aim of this systematic review was to estimate the prevalence of PLP in people with limb amputations. The secondary aim was to determine whether there is a difference in the prevalence of PLP in developed and developing countries, as per the World Economic Situation and Prospects classification system (58). The exploratory aim was to identify risk factors associated with PLP in people with limb amputations.

2. Materials and methods

This systematic review was designed according to the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) guidelines (59). The review protocol was registered on PROSPERO [ID: CRD42018094821], and published in Systematic Reviews (Appendix 4) (55). The PRISMA criteria fulfilled by this systematic review are presented in Supplementary file 2.1.

2.1 Data sources and search procedure

The lead investigator (KL) and a senior librarian (MS) developed a comprehensive search strategy (Supplementary file 2.2) using five Medical Subject Headings (MeSH): prevalence, risk factors, amputation, phantom limb and epidemiology. Articles published between 1980 and July 2019 were identified through a systematic search of the following electronic databases: MEDLINE/PubMed (via EBSCOhost), PsycINFO (via EBSCOhost), PsycArticles, Cumulative Index to Nursing and Allied Health Literature (CINAHL) (via EBSCOhost), Africa-Wide Information (via EBSCOhost), Health Source: Nursing/Academic Edition (via EBSCOhost), SCOPUS, Web of Science and Academic Search Premier.

We deviated from protocol and searched for grey literature on bioRxiv (www.biorxiv.org), Preprints (www.preprints.org), Open Science Framework (www.osf.io) and medRxiv (www.medrxiv.org). The reference lists of eligible studies were searched manually to identify more studies that may have been eligible for inclusion in this review. Studies identified from the literature search were saved using the citation manager software programme (EndNote x8, Clarivate Analytics), which was also used to remove duplicates (60, 61).

2.2 Study selection

We included cross-sectional and cohort studies that investigated the prevalence of PLP in adults (18 years or older) with surgical and traumatic upper or lower limb amputations. Only studies written in English, with full text published between 1980 and 2019, were eligible for inclusion in this review. The risk factors for PLP were identified from the included studies. We excluded literature reviews and experimental studies. Two reviewers (KL and GJB) independently screened study titles and abstracts for eligibility. Studies identified in the initial screening as potentially eligible were assessed for eligibility in full-text form by the same reviewers, using the inclusion/exclusion criteria. The study selection procedure was performed using a Microsoft Excel spreadsheet (2016) on which the studies were listed and marked as either eligible or ineligible. In this, we deviated from the registered protocol, which specified the use of Covidence, because Covidence has limited usability offline. A PRISMA flow diagram (Figure 2.1) represents the entire screening process detailing the numbers of included and excluded studies, with reasons for exclusion. After each stage, results were compared, and disagreements resolved through discussion.

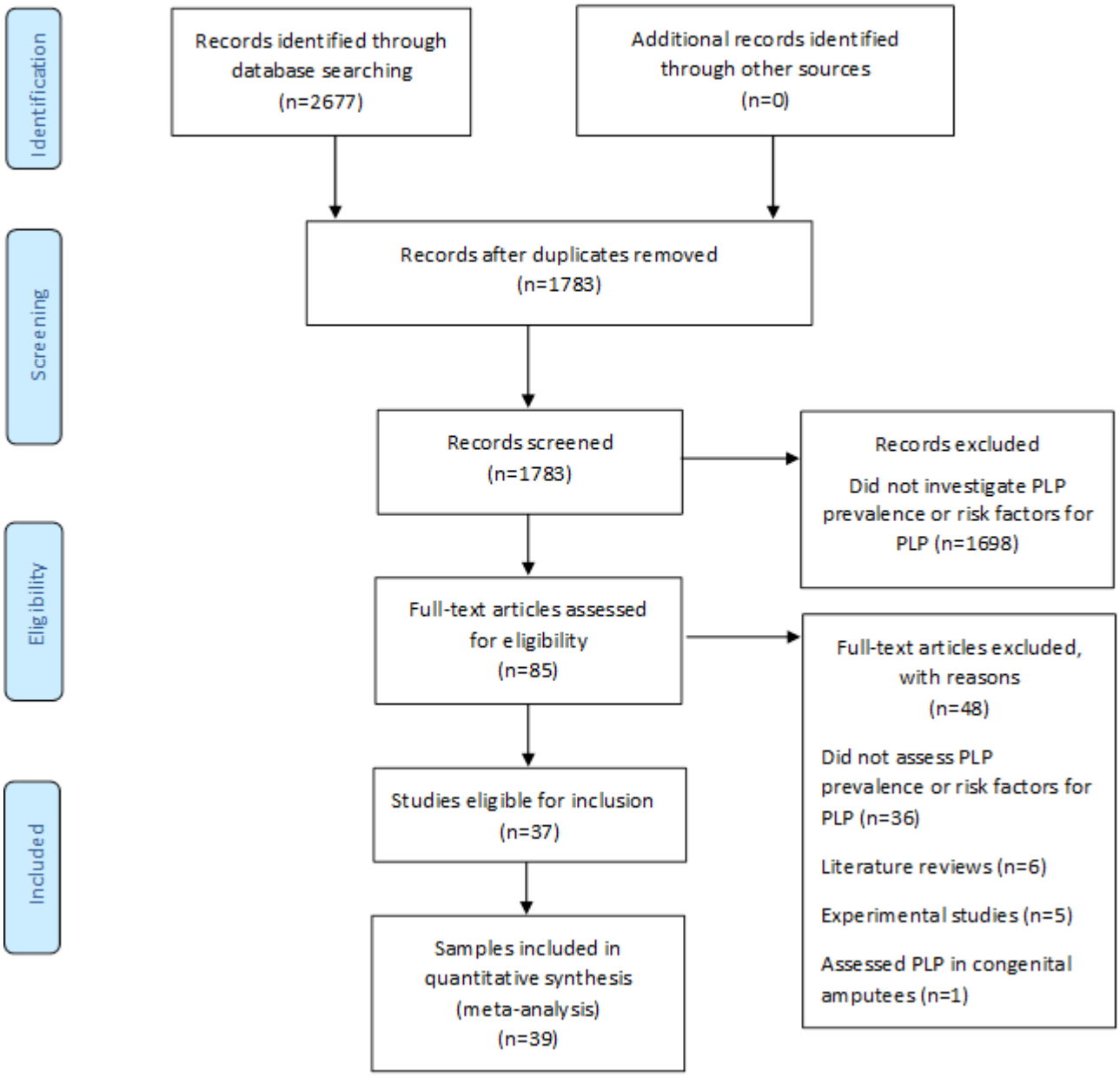


Figure 2.1: The PRISMA flow diagram illustrating the screening process.

2.3 Risk of bias assessment

Two reviewers (KL and GJB) independently assessed the included articles for risk of bias using a risk of bias assessment tool for prevalence studies that had been developed by Hoy et al (Supplementary file 2.3) (62). This tool assesses the risk of bias based on 10 categories which evaluate the study's external and internal validity. Each category of the risk of bias tool was set as "high risk" if the study scored "high risk" for any single item within that category, and "low risk" if it scored "low risk" for all items in that category. Categories with "low risk" and "high risk" were given a rating of zero and one respectively. The summary risk of bias rating for each study was presented as "low risk" (score: 0-3), "moderate risk" (score: 4-6), or "high risk" (score: 7-10).

2.4 Data extraction

Two reviewers (KL and GJB) used a pre-piloted customised data extraction sheet to independently extract relevant data from included studies. Data extracted included: the names of authors, year of study publication, study design and setting, country of study, sample size, participants' age and sex, site of amputation, method of data collection, PLP prevalence (%), as well as risk factors and their measures of association with PLP. The developmental status of each country was identified using the World Economic Situation and Prospects classification system (58).

3. Data analysis

Data extracted from individual studies were entered into an Excel spreadsheet for analysis. All meta-analyses were conducted using Open Meta Analyst software available on (http://www.cebm.brown.edu/openmeta). In this, we deviated from the registered protocol, which specified the use of Review Manager 5, because Review Manager 5 is not suitable for conducting meta-analyses of single arm studies. Cohen's Kappa was used to report inter-rater agreement during screening, data extraction and risk of bias assessment, and can be interpreted as minimal (0 – 0.39), weak (0.40 – 0.59), moderate (0.60 – 0.79) or strong (0.80 – 0.90) (63).

Clinical heterogeneity was evaluated qualitatively, based on similarities or differences in participant and outcome characteristics, recruitment and assessment procedures, and study setting (64). Statistical heterogeneity was assessed using the I^2 statistic, and the results were presented as low (<25%), moderate (25-50%) and high (>50%) (65). Subject to consideration of heterogeneity and risk of bias, studies were pooled for meta-analysis using a random effects model to determine a sample-weighted summary estimate of PLP prevalence. A funnel plot was generated to assess for possible publication bias. Furthermore, the Egger's test was conducted to assess the funnel plot for asymmetry (66). To address high statistical heterogeneity, we deviated from protocol to sub-group studies into those with low risk of bias and those with moderate and high risk of bias, and conducted separate meta-analyses, and compared the two pooled estimates using a two-tailed Mann-Whitney U test. We also sub-grouped studies by the developmental status of the country in which each study had been conducted (58), as planned in the protocol and, again, compared the estimates using a two-tailed Mann-Whitney U test. Potential risk factors for PLP were identified from the included studies and analysed descriptively. When an association was confirmed, the strength of association between PLP and each risk factor was classified as either "weak", "moderate", "strong" or "very strong", according to the guidelines for interpreting the strength of association in epidemiology studies (67-70). We calculated Phi (Ø) to determine the strength of association in studies that used the chi-square test as a measure of association. This sample-size-adjusted chi-square statistic has been shown to provide a more accurate reflection of the strength of association between two variables than the interpretation of chi-square and probability (P) values, where high chi-square and p values are thought to represent a strong association between variables (71). Alpha was set at 0.05 for all analyses.

4. Results

The initial literature search returned 2677 records, of which 1783 remained after the removal of duplicates. Initial screening of titles and abstracts identified 85 studies that were eligible for full-text review. Full-text review identified 37 studies that were eligible for inclusion in this systematic review. Two of these studies reported two studies each (72, 73). Therefore, a total of 39 studies were included in our analysis. The entire screening process reflected moderate agreement (Kappa=0.70) between reviewers.

3.1 Study characteristics

The study characteristics are summarised in Table 2.1. The included studies had used cross-sectional (n=35) and cohort (n=4) study designs. Thirty-two of 39 studies had been conducted in developed countries (58). Of these, the majority were conducted in North America [USA (n=7); Canada (n=2)] and Europe [United Kingdom (n=8); Germany (n=5); Netherlands (n=3); Ireland (n=2); Poland (n=1)] (Figure 2.2). Only seven studies were conducted in developing countries [Iran (n=2); Iraq (n=1); India (n=1); Brazil (n=1); Pakistan (n=1); Cambodia (n=1)]. Table 2.1 reflects the wide range of data collection approaches used in the studies. The included studies were published between 1986 and 2019. The data extraction process had moderate agreement (Kappa=0.71) between reviewers prior to discussion. The included studies provided data from a total of 12738 participants (9814 male; 2183 female) who had undergone upper limb (n=2757) and lower limb (n=10539) amputations. Participant characteristics are provided in Table 2.1.

Table 2.1: Summary of study and participant characteristics by study.

Authors	Study type	Country of study	Development status	Method of data collection	Sample size (person years)	Age Mean (SD)	Sex M/F	Level of amputation (UL/LL)	PLP prevalence (%)
Ahmed et al., 2017	Cross-sectional	India	Developing	Self-reported questionnaire	139	38.23 (1.54)	102/37	36/103	41
Aldington et al., 2014	Cross-sectional	UK	Developed	Self-reported questionnaire	48	28.8 (6.7)	-	11/54	49
Bekrater et al., 2015	Cross-sectional	Germany	Developed	Postal and telephone questionnaire	3234	64.37 (15.89)	2637/597	824/2410	62.55
Bin Ayaz et al., 2015	Cross-sectional	Pakistan	Developing	Face-to-face interview	268	28 (6)	266/2	35/233	42.5
Bosmans et al., 2007	Cross-sectional	Netherlands	Developed	Face-to-face interview	16	66.5 (39-86)*	11/5	0/16	81.25
Buchanan et al., 1986	Cross-sectional	Canada	Developed	Face-to-face interview	716	-	616/100	43/647	62.4
Byrne et al., 2011[a]	Cross-sectional	New Zealand	Developed	Face-to-face interview	29	41.7 (4.8)	25/4	7/24	69
Byrne et al., 2011[b]	Cross-sectional	Cambodia	Developing	Face-to-face interview	29	40.3 (10.5)	25/4	1/28	51.7

Clark et al., 2013	Cross-sectional	UK	Developed	Postal and telephone questionnaire	102	70.9 (1.27)	-	0/97	85.6
Datta et al., 2004	Cohort	UK	Developed	Postal questionnaire	60 (10)	58.1 (-)	48/12	60/0	60
Desmond et al., 2010	Cross-sectional	Ireland	Developed	Self-reported questionnaire	141	74.8 (-)	138/3	141/0	42.6
Dijkstra et al., 2002	Cross-sectional	Netherlands	Developed	Postal questionnaire	536	-	367/150	99/433	72
Ehde et al., 2000	Cross-sectional	USA	Developed	Postal questionnaire	255	55.1 (14.3)	207/48	0/255	72
Ephraim et al., 2005	Cross-sectional	USA	Developed	telephone interview	914	50.3 (13.3)	552/362	100/812	79.9
Gallagher et al., 2001	Cross-sectional	Ireland	Developed	Postal questionnaire	104	45.3 (18.9)	78/26	0/104	69.2
Hanley et al., 2006	Cross-sectional	USA	Developed	Postal and telephone questionnaire	255	55 (14.3)	207/48	0/255	72
Hanley et al., 2009	Cross-sectional	USA	Developed	Postal questionnaire	104	46.9 (14.1)	75/29	104/0	79
Hnoosh et al., 2014	Cross-sectional	Iraq	Developing	Self-reported questionnaire	118	32 (12.9)	97/21	0/181	61

Houghton et al., 1994	Cross-sectional	UK	Developed	Postal questionnaire	176	71 (-)	-	0/176	78
Kern et al., 2012	Cross-sectional	Germany	Developed	Postal questionnaire	537	59 (-)	382/155	24/513	74.5
Ketz et al., 2008	Cross-sectional	Germany	Developed	Self-reported questionnaire	30	-	30/0	7/27	77
Kooijman et al., 2000	Cross-sectional	Netherlands	Developed	Unclear	72	44.2 (35-65)*	57/15	72/0	51
Larbig et al., 2019	Cohort	Germany	Developed	Face-to-face interview and self-reported questionnaire	52 (24)	-	41/11	2/50	75
Morgan et al., 2017	Cross-sectional	USA	Developed	Self-reported and internet questionnaire	1296	54.4 (13.7)	909/387	0/1296	48.1
Noguchi et al., 2019	Cross-sectional	Japan	Developed	Medical records	44	-	33/11	22/22	50
Penna et al., 2018	Cohort	Australia	Developed	Medical records	96 (96)	-	74/22	0/96	52.2
Probstner et al., 2010	Cross-sectional	Brazil	Developing	Self-reported questionnaire	75	54.4 (18.5)	50/25	6/69	46.7

Rafferty et al., 2015	Cross-sectional	UK	Developed	Self-reported questionnaire	75	26.3 (18-42)*	74/1	0/84	85
Rahimi et al., 2012	Cross-sectional	Iran	Developing	Face-to-face interview	335	42.1 (6.32)	324/11	0/670	66.7
Rayegani et al., 2010	Cross-sectional	Iran	Developing	Face-to-face interview and self-reported questionnaire	335	-	327/8	0/670	64
Razmus et al., 2017	Cross-sectional	Poland	Developed	Face-to-face interview and self-reported questionnaire	22	61 (11.3)	15/7	3/22	59
Reiber et al., 2010[a]	Cross-sectional	USA	Developed	Postal, internet and telephone questionnaire	298	60.7 (3.0)	298/0	78/300	72.2
Reiber et al., 2010[b]	Cross-sectional	USA	Developed	Postal, internet and telephone questionnaire	283	29.3 (5.8)	274/9	78/273	76
Resnik et al., 2019	Cross-sectional	Canada	Developed	Telephone interview	808	63.2 (14.2)	787/21	840/0	76.1
Richardson et al., 2007	Cohort	UK	Developed	Face-to-Face interview	59 (29.5)	63.8 (10.4)	37/22	0/59	78.8

Richardson et al., 2015	Cross-sectional	UK	Developed	Face-to-face interview	89	65.5 (11.4)	64/25	0/89	63
Schley et al., 2008	Cross-sectional	Germany	Developed	Postal and telephone questionnaire	65	45 (18-80)*	60/5	65/0	44.6
Wartan et al., 1997	Cross-sectional	UK	Developed	Unclear	526	73 (-)*	526/0	99/471	62
Yin et al., 2017	Cross-sectional	China	Developed	Telephone interview	391	-	-	-	29

* Indicates the median age and range

The number of amputations and males versus females do not add up to the total sample size because some participants had more than one amputation and these data were not provided.

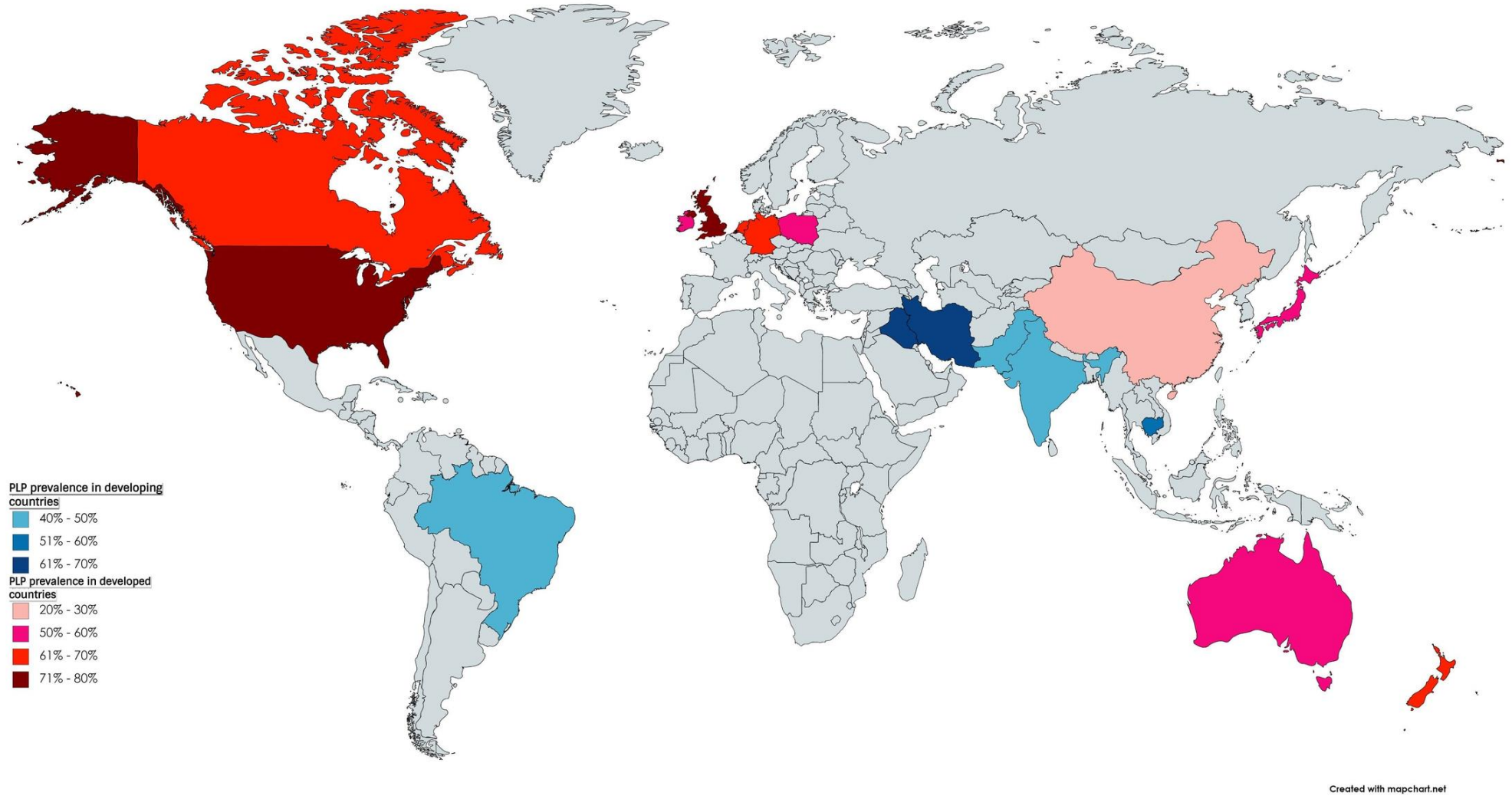


Figure 2.2: World map showing the countries in which the studies were conducted.

3.2 Risk of bias assessment

The risk of bias assessment revealed moderate agreement (Kappa=0.69) between reviewers prior to discussion. The results of the risk of bias assessment are reported in Supplementary file 2.4. Four studies had an overall rating of "low risk" (74-77). Six studies scored "low risk" for selection bias, for using a sample that was a close representation of the national population (45, 75, 76, 78-80). Eight studies scored "low risk" for study participation bias, because their response rates for participation were ≥75% (45, 53, 75, 77, 81-84). Twelve studies scored "low risk" for measurement bias, for using a clear definition of PLP (8, 14, 46, 52, 56, 74, 76-79, 85, 86). Other studies scored "high risk" for measurement bias, for not providing a clear definition of PLP (e.g. pain felt in the limb after amputation). All the studies scored "high risk" for measurement bias, for using an instrument that has not been shown to be valid and reliable for measuring the outcome of interest. However, all studies scored "low risk" for reporting bias, for appropriately reporting the numerators and denominators for the outcome of interest.

3.3 Prevalence of phantom limb pain

The estimates of PLP prevalence in people with limb amputations ranged between 27% and 86% (48, 53), with most studies (31 out of 39) reporting a prevalence between 50% and 86% (48, 72). The pooling of all studies using a random effects model yielded an estimated prevalence of 64% [95% CI: 60.0 – 68.0], but with high statistical heterogeneity [I^2=95.95% (95% CI: 95.1 – 96.6)] (Figure 2.3). The Egger's regression analysis of all the included studies revealed no publication bias [-0.80 (95%CI: -4.32 – 2.01); p=0.60].

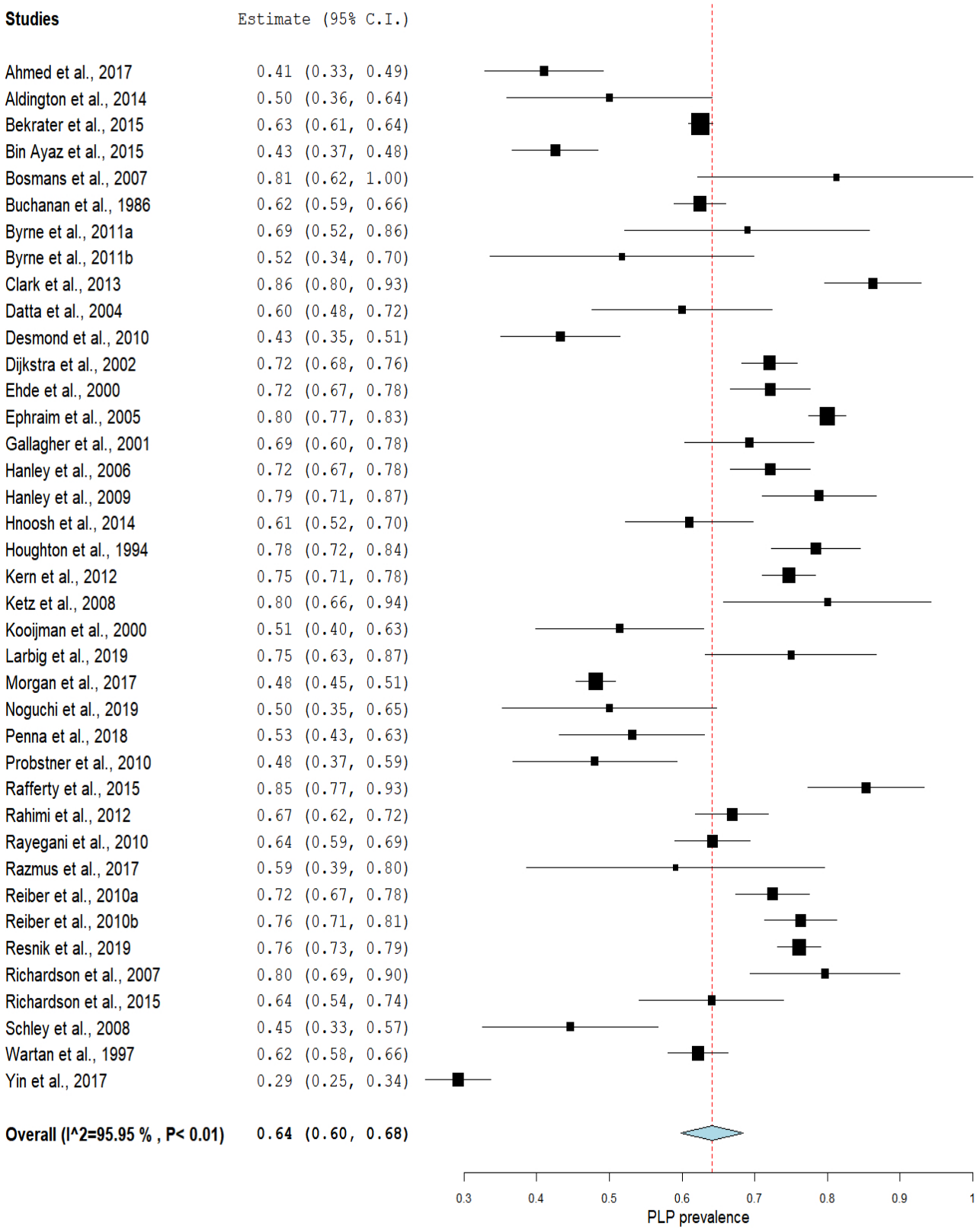


Figure 2.3: A forest plot showing the overall pooled estimated prevalence of PLP in people with amputations.

3.4 Exploratory subgrouping

We were concerned by the high statistical heterogeneity in the primary meta-analysis, so we opted to deviate from protocol to conduct two exploratory meta-analyses with studies sub-grouped according to risk of bias score. The first exploratory subgroup analysis, including only the studies that scored low risk of bias overall, estimated prevalence at 63% [95% CI: 58.3 – 67.9] with moderate statistical heterogeneity [I^2=44.91 (95% CI: 43.9 – 45.2)] (Figure 2.4).

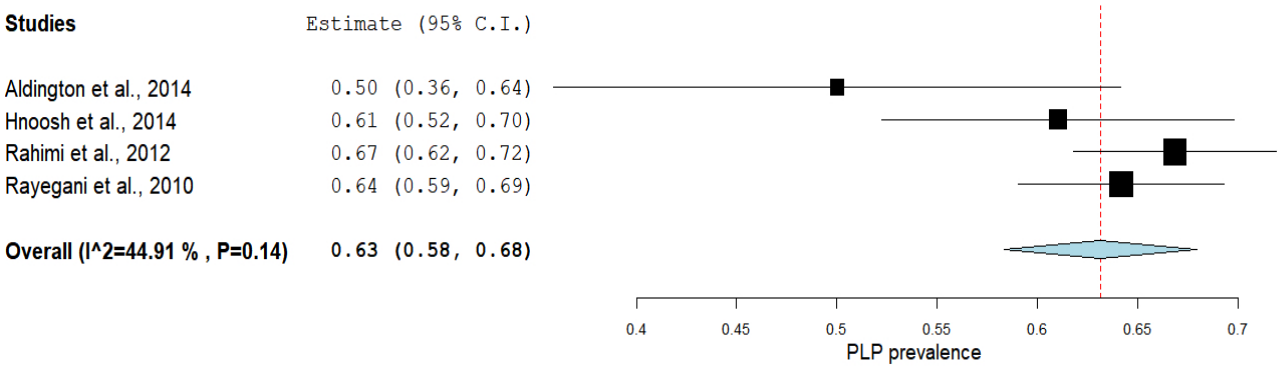


Figure 2.4: A subgroup analysis showing the pooled estimated prevalence of PLP in studies with low risk of bias.

The second exploratory subgroup analysis, including only the studies with moderate-high risk of bias, estimated prevalence at 64% [95% CI: 60.2 – 69.4)], but with high statistical heterogeneity [I^2=96.35% (95% CI: 96.1 – 98.4)] (Figure 2.5). The Mann-Whitney U test that served as the sensitivity analysis for the effect of moderate-high risk of bias showed no difference between the estimated prevalence from these two meta-analyses [U=63.5, p=0.3; Z= -1.18] (Supplementary File 2.5)

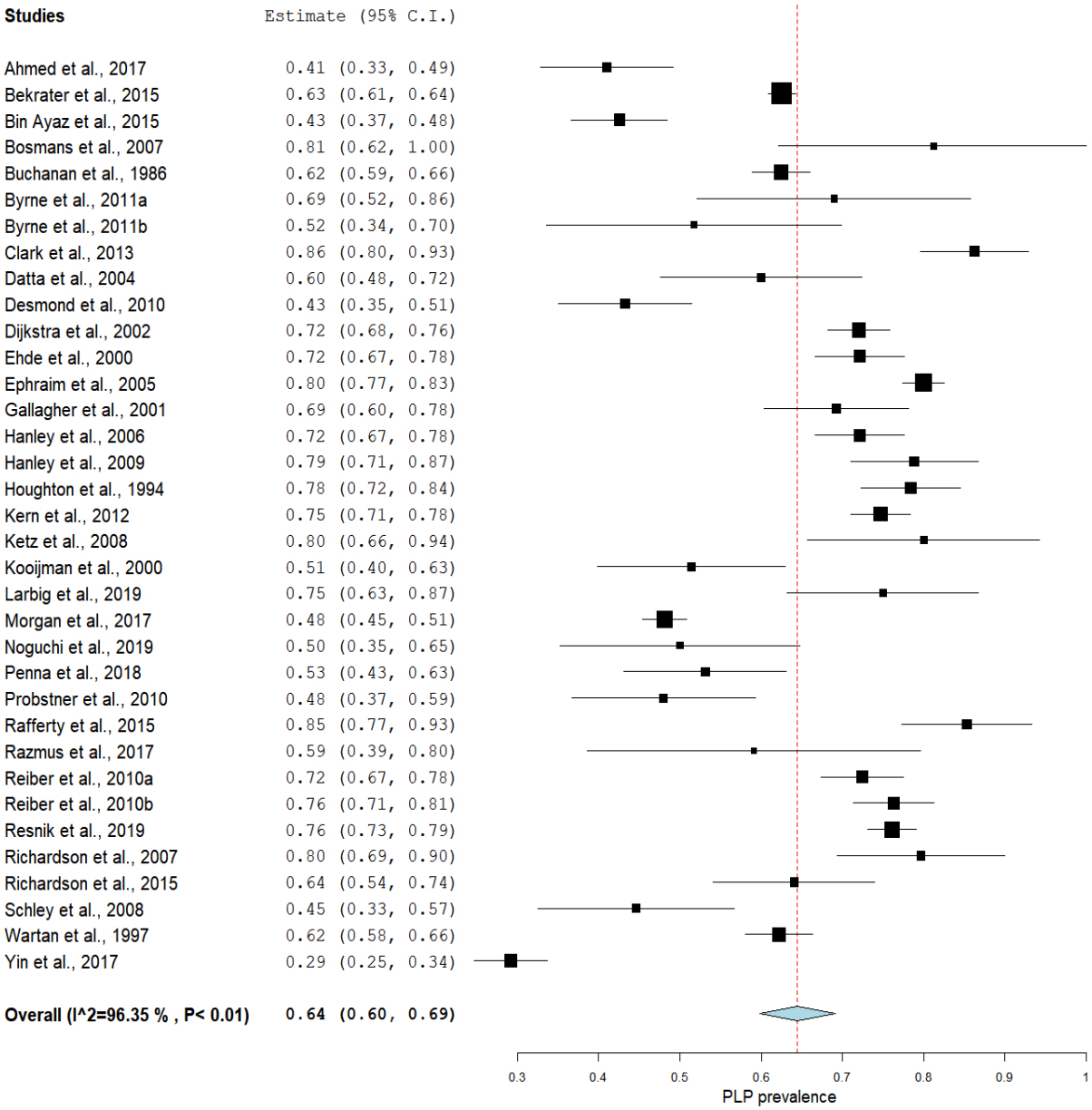


Figure 2.5: A subgroup analysis showing the pooled estimated prevalence of PLP in studies with moderate to high risk of bias.

The subgroup analyses stratified by the developmental status of the countries in which the studies were conducted showed an estimated pooled prevalence of 67% [95% CI: 62.0 – 71.6] in developed countries and 54% [95% CI: 44.8 – 63.0] in developing countries (Figures 2.6 & 2.7). The Mann-Whitney U test showed a statistically significant difference between the prevalence estimates of these two meta-analyses [U=57, p=0.03].

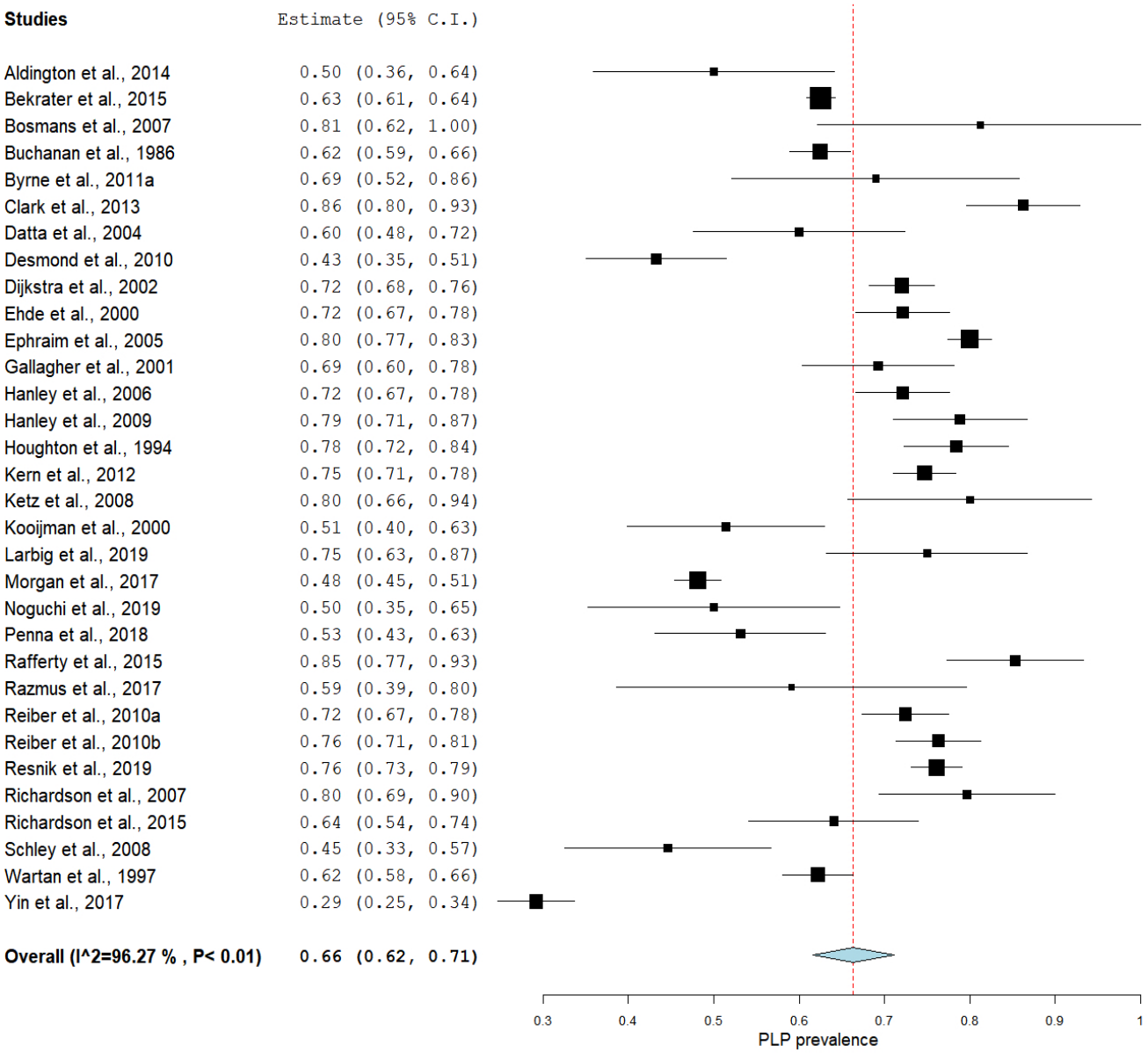


Figure 2.6: A subgroup analysis showing the pooled estimated prevalence of PLP in developed countries.

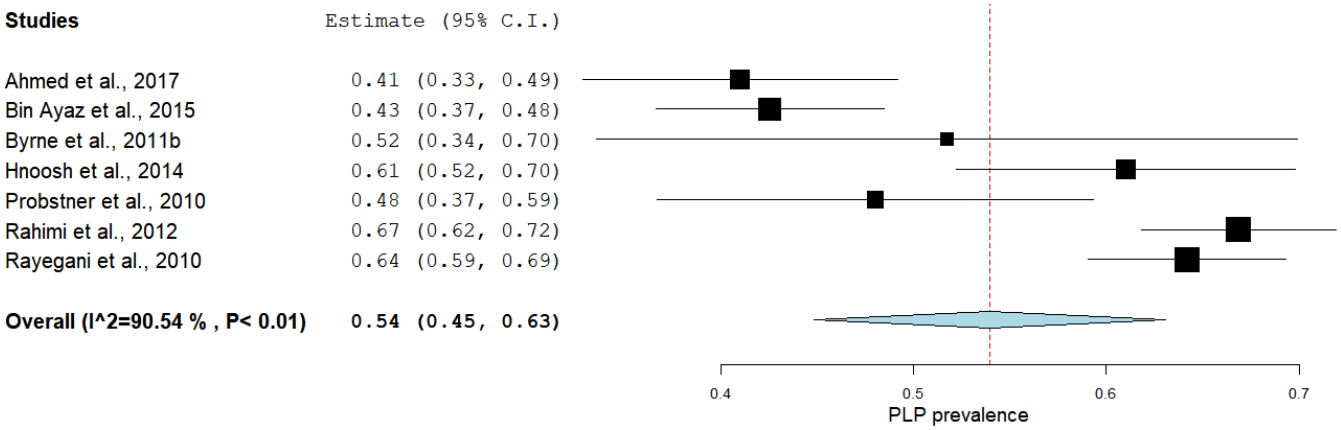


Figure 2.7: A subgroup analysis showing the pooled estimated prevalence of PLP in developing countries.

3.5 Risk factors for phantom limb pain

Twenty-five potential risk factors had been studied in 15 studies representing 4102 participants. Of these, 10 pre-amputation, three peri-operative and eight post-amputation risk factors had data to support their positive association with PLP, and six pre-amputation, four peri-operative and three post-amputation risk factors had not been found to be positively associated with PLP. The risk factors found to be positively associated with PLP and their measures of association are summarised in Table 2.2. Lower limb amputation was positively associated with PLP (moderate to strong association) in two studies representing a total of 1450 participants (52, 79). Stump pain was consistently positively associated with PLP (weak to very strong association) in seven studies representing a total of 1254 participants (7, 14, 17, 18, 52, 53, 82). Phantom sensations were consistently positively associated with PLP (strong to very strong association) in four studies representing a total of 1156 participants (52, 53, 83, 87). Proximal site of amputation was positively associated with PLP (very strong association) in two studies representing a total of 604 participants (52, 88).

Diabetic cause of amputation was positively associated with PLP (moderate to strong association) in two studies representing a total of 580 participants (46, 52). Persistent pre-amputation pain was positively associated with PLP in five studies representing a total of 881 participants (weak to very strong association) (7, 17, 46, 49, 89) but was not associated with PLP in two studies representing a total of 625 participants.

The risk factors which were not found to be positively associated with PLP are summarised in Table 2.3. Sex, age and traumatic cause of amputation were the most commonly assessed of these proposed risk factors. Sex was consistently not associated with PLP in six studies representing a total of 1836 participants (7, 46, 53, 79, 90, 91). Age was not associated with PLP in three studies representing a total of 1062 adult participants (46, 79, 91) but higher age was positively associated with PLP (weak association) in one study representing a total of 716 adult participants (13). A traumatic cause of amputation was not associated with PLP in two studies representing a total of 958 participants (46, 79) but was positively associated with PLP (very strong association) in one study representing a total of 104 participants (16). The meta-analysis of risk factors for PLP could not be conducted because of variations in methods of data collection and analysis across the included studies.

Table 2.2: The summary of the risk factors for PLP and their measures of association with PLP.

Author	Population	Outcome	Risk factor(s)	Measures of association	Strength of association
Ahmed et al., 2017	Cancer patients who had undergone limb amputations	PLP	Post-amputation depression Pre-amputation pain Stump pain Use of prosthesis Sleep disturbance	3.86 (1.75-8.53)‡ 2.83 (1.38-5.76)‡ 31.2 (8.97-108.50)‡ 2.83 (1.19-4.76)‡ 21.43 (8.28-55.43)‡	Strong Moderate Very strong Moderate Very strong
Buchanan et al., 1986	Amputees who were receiving routine prosthetic services	PLP	Age	0.12 ($p<0.01$)¥	Weak
Desmond et al., 2010	Members of the British Limbless Ex-Service Men's Association	PLP	Stump pain	11.17 ($p<0.01$)‡	Very strong
Dijkstra et al., 2002	Amputees who were receiving routine prosthetic services	PLP	Diabetic cause of amputation Proximal site of amputation Lower limb amputation Bilateral amputations Stump pain Phantom sensations	4 ($p<0.001$)‡ 1.60 (0.038)‡ 5.60 ($p<0.001$)‡ 8.20 ($p=0.01$)‡ 3.90 ($p<0.001$)‡ 19.50 ($p<0.001$)‡	Strong Moderate Strong Strong Strong Very strong

Ephraim et al., 2005	Amputees who had contacted the Amputee Coalition of America (ACA) between 1998 and 2000	PLP	Post-amputation depression Lower limb amputation 2 or more comorbidities Widow	2 (1.3-3.1)‡ 2.50 (1.3-4.7)‡ 2.70 (1.3-5.8)‡ 2.70 (1.1-6.5)‡	Moderate Moderate Moderate Moderate
Gallagher et al., 2001	Amputees who were attending the Limb Fitting Clinic.	PLP	Proximal site of amputation Traumatic cause of amputation Sex (male) Other medical problems Lack of pre-amputation counselling	15.65 (p<0.001)‡ 14.60 (p<0.002)‡ 3.76 (p<0.05)‡ 5.93 (p<0.02)‡ 4.74 (p<0.03)‡	Very strong Very strong Strong Strong Strong
Hanley et al., 2009	Patients who had undergone upper-limb amputation 6 months or more before recruitment	PLP	Use of prosthesis	4.23 (p<0.05)¶	Moderate
Hanley et al., 2006	Patients who had undergone lower limb amputation	PLP	Pre-amputation pain Stump pain	0.48 (p<0.01)§ 0.53 (p<0.0001)§	Weak Weak
Kooijman et al., 2000	Amputees using upper limb prosthesis	PLP	Phantom sensations Stump pain	11.30 (p=0.001)† 1.90 (p=0.015)†	Very strong Weak

Larbig et al., 2019	Patients who had undergone upper or lower limb amputations	PLP	Pre-amputation depression Pre-amputation pain Stump pain	2.05 ($p<0.05$)[§] 4.22 ($p<0.01$)[§] 3.90 ($p<0.01$)[§]	Moderate Moderate Moderate
Noguchi et al., 2019	Patients who had undergone upper or lower limb amputations	PLP	Diabetic cause of amputation Pre-amputation pain	2.24 ($p=0.032$)[‡] 6.36 ($p=0.024$)[‡]	Moderate Strong
Razmus et al., 2017	Occupants of the nursing home, and clients of the Public Institute of Orthopaedic Equipment	PLP	Phantom sensations	4.94 ($P<0.05$)[§]	Strong
Richardson et al., 2007	Patients who had undergone amputation of the lower limb due to peripheral vascular disease.	PLP	Stump pain Increased ability to move the phantom limb. Praying/hoping Catastrophizing	7.03 (1.34-36.82)[‡] 8.31 (1.54-44.79)[‡] 2.86 (1.68-13.18)[‡] 3.28 (1.71-14.91)[‡] 4.60 (6.50-25.00)[‡]	Strong Strong Moderate Strong Strong
Wartan et al., 1997	Traumatic amputees	PLP	Phantom sensations	107.30 ($p<0.0001$)[§]	Strong

Yin et al., 2017	Amputees who underwent limb amputations at a tertiary hospital	PLP	Pre-amputation pain Post-amputation epidural analgesia	10.40 (p=0.002)‡ 4.90 (p=0.008)‡	Very strong Strong

¥ Point-biserial correlation analysis; ¶ Pearson's univariate correlation test; § Chi-squared; † Relative risk; ‡ Odds ratio

Table 2.3: The summary of factors not associated with increased risk for PLP and their measures of association with PLP.

Author	Population	Outcome	Risk factor(s)	Measures of association
Ahmed et al., 2017	Cancer patients who had undergone limb amputations	PLP	Sex smoking Regional Anaesthesia Post-amputation analgesia Perioperative gabapentin Radiotherapy	0.65 (0.31-1.40)‡ 1.40 (0.71-2.78)‡ 0.99 (0.68-1.54)‡ 1.41 (0.94-2.10)‡ 0.75 (0.76-1.51)‡ 1.33 (0.66-2.66)‡
Dijkstra et al., 2002	Amputees who were receiving routine prosthetic services	PLP	Sex Prosthesis use (>8 hours per day)	— (p=0.73)‡ — (p<0.13)‡
Ephraim et al., 2005	Amputees who had contacted the Amputee Coalition of America (ACA) between 1998 and 2000	PLP	Sex Age Traumatic cause of amputation Years since amputation	1.4 (0.90-2.20)‡ 1.1 (0.60–1.80)‡ 0.9 (0.50–1.70)‡ 1.0 (0.60–1.90)‡
Gallagher et al., 2001	Amputees who were attending the Limb Fitting Clinic.	PLP	Post-amputation support	— (—)
Hanley et al., 2009	Patients who had undergone upper-limb	PLP	Age Sex	3.78 (p=0.83)¶ 0.78 (p=0.99)¶

	amputation 6 months or more before recruitment			
Kooijman et al., 2000	Amputees using upper limb prosthesis	PLP	Sex Amputation of the dominant limb Pre-amputation pain Upper limb amputation Prosthesis use (>8 hours per day)	— (p=0.21)† — (p=0.59)† — (p=0.59)† — (p=0.08)† — (p=0.06)†
Noguchi et al., 2019	Patients who had undergone upper or lower limb amputations	PLP	Sex Age Traumatic cause of amputation Increased hospital-stay	0.78 (p=0.73)‡ — (p=0.65)‡ 2.941 (p=0.22)‡ — (p=0.26)‡
Wartan et al., 1997	Traumatic amputees	PLP	Pre-amputation pain	10.6 (p<0.30)§

¥ Point-biserial correlation analysis; ¶ Pearson's univariate correlation, χ^2; § Chi-squared; † Relative risk; ‡ Odds ratio; — missing figure

4. Discussion

According to our knowledge, this is the first systematic review to pool the literature on the prevalence and risk factors for PLP in people with limb amputations. The results of this study estimate that PLP affects 64% [95% CI: 60.0 – 68.0] of people with amputations. In addition, the results revealed a significantly higher PLP prevalence of in developed versus developing countries [U=57, p=0.03]. Furthermore, this study identified that lower limb amputation, stump pain, phantom sensations, persistent pre-amputation pain, proximal site of amputation and diabetic cause of amputation are risk factors for PLP.

4.1 Phantom limb pain prevalence

The current meta-analysis estimated that 64% of people with amputations report PLP. This proportion indicates that 8169 of 12765 participants in this study reported PLP. Interestingly, dividing studies by risk of bias revealed no difference in estimated prevalence, despite the 'low risk of bias' subgroup's meta-analysis having lower statistical heterogeneity. In addition, the results of the Egger's regression test indicated that the asymmetry of the funnel plot (Supplementary File 2.6) was not significant (p=0.64), thus failing to suggest the presence of publication bias. Altogether, these findings suggest that the included studies provide a reasonably stable estimate of the prevalence of PLP in the population of people with amputations. The prevalence of PLP appears to be high, supporting that health professionals should be aware of the risk of this complication and that pragmatic interventions for preventing or alleviating PLP are needed.

The meta-analysis which stratified the studies by country developmental status suggested that the prevalence of PLP was significantly lower in developing countries compared to developed countries [54% (95% CI: 44.8 – 63.0) versus 67% (95% CI: 62.0 – 71.6)]; p=0.03]. This discrepancy is surprising and might be an artefact of selection bias linked either to the lower recruitment success rates (57.9% - 68.4%) seen in most of the included studies conducted in developing countries (7, 75).

The strategy of recruiting participants from amongst patients receiving follow-up medical care may have contributed to underestimation of PLP prevalence if amputees with PLP without continuing medical care were excluded from samples (in developing countries), or overestimation if having PLP made amputees more likely to remain in medical care (in developed countries). This lack of clarity regarding recruitment strategies highlights the need to adapt recruitment strategies specifically to people with amputations in developing countries so that they can be accounted for in future studies.

The current literature suggests the standard of surgical care in developed countries differs significantly from that in developing countries. A study investigating the global burden and distribution of surgery revealed that approximately 80% more surgery-related complications and deaths occur in developing than in developed countries, despite accounting for only 26% of surgical procedures conducted globally (92). These data may reflect the disparity in the standard of surgical care between developed and developing countries. Many healthcare facilities in developing countries, particularly in rural areas, have poor infrastructure and lack essential surgical equipment and skilled surgeons (93). Urban areas may have a few skilled surgeons, yet the need for surgical care is typically greater in the rural parts of developing countries. As a result, surgical procedures are often conducted by less trained healthcare professionals under sub-standard conditions. Surgical care in developing countries therefore tends to be substandard than that in developed countries (93).

Another important consideration is that the prevalence estimates could have been influenced by the under-representation of only seven studies conducted in developing countries compared to 32 studies conducted in developed countries. Limb amputations (by trauma or surgery) are common in some regions in South America, Middle East, and Africa (94-96). However, these regions are underrepresented in the body of studies identified by this review. In fact, we could not find any relevant study conducted in the continent of Africa.

This highlights a concerning dearth of scientific research on PLP in these developing regions. Therefore, we recommend that further studies be focused on the burden of PLP in developing countries, specifically.

The included studies had varying risk of bias. However, the lack of statistically significant difference between the prevalence estimates from pooling of the studies with low risk of bias and pooling of the studies with moderate-high risk of bias suggests that the overall risk of bias in included studies had little impact on the estimated prevalence of PLP. Nonetheless, the high risk of bias attributed to most studies for using an ambiguous definition of PLP (e.g pain felt in the limb after amputation) leaves the possibility that participants might have confused residual limb pain and PLP. We suspect that this might have resulted in an overestimation of the prevalence of PLP.

We found it interesting that the pooled prevalence estimate of PLP in this study was relatively high compared to that reported in the literature on people with congenitally absent limbs. The three studies available on people with congenitally absent limbs (not eligible for this review) reported a markedly low PLP prevalence of 0% (out of 27 participants), 5.7% (out of 88 participants) and 7% (out of 57 participants) (47, 53, 97). Although a robust conclusion cannot be drawn from three small studies, these findings suggest that people with congenitally absent limbs may be less likely to experience PLP than those whose amputations were due to trauma or surgery (16). Perhaps the peripheral nerves severed during amputation play an important role in the initiation of PLP after amputation (98). In addition, the absence of pre-operative and peri-operative risk factors for PLP in this group might contribute to the low prevalence.

4.2 Risk factors for phantom limb pain

Five studies showed that PLP was more likely to occur in people who reported a history of persistent pre-operative pain than in those who did not report having had persistent limb pain prior to their amputation. One physiological mechanism that has been proposed to explain the link between pre-amputation pain and PLP is central sensitisation - where persistent pre-operative pain contributes to the hyperexcitability of the nervous system and functional changes in the cortical areas involved in the generation of pain (99). These changes may continue to upregulate peripheral input after limb amputation, thus promoting PLP that shares the characteristics with pre-amputation pain (100). In fact, over 60% of the patients who experienced persistent pre-amputation pain reported similar characteristics of their PLP (101, 102). This apparent relationship highlights the importance of addressing limb pain very early in patients who are at high risk of having their limbs amputated. The early management of pre-amputation pain using effective treatments such as pre-operative epidural analgesia (e.g. ketamine) and mirror therapy may reduce risk of developing PLP and improve physical and psychological outcomes often related to delayed or ineffective management of PLP (17, 103).

Two studies showed that PLP was more likely to occur after lower limb amputation than after upper limb amputation (79, 90). The authors proposed that the use of a cosmetic prosthetic leg, rather than a prosthesis that provided sensory input was a likely contributor to pain in people with lower limb amputations since 70%-78.8% of cosmetic prosthetic leg users had PLP. Lack of proprioceptive feedback during the use of a prosthetic leg has been linked to poor motor control, possibly leading to stump irritation that may trigger PLP (45, 104). This proposed link is partially supported by seven studies in this review which suggested that PLP was more likely to occur in people with stump pain than in those without stump pain (7, 14, 18, 52, 53, 82, 85). Interestingly, Dietrich and colleagues investigated the effects of a leg prosthesis with somatosensory feedback on pain and lower limb function (105).

In that study, participants used prosthetic legs with pressure sensors that provided comfortable electrical feedback to the patient's thigh whenever the prosthetic foot touched the ground. At the end of two weeks of training, the participants had improved function of the lower limb and reduced severity and frequency of PLP. Further, the patients reported greater satisfaction, longer walking distances, and improved dynamic stability than prior to the training. These results suggest that people with lower limb amputations might benefit more from using a prosthetic leg with somatosensory feedback than from using a cosmetic prosthesis. However, the mechanisms by which prosthetic legs with somatosensory feedback reduce PLP are not clear. Therefore, it would be interesting to investigate the mechanisms by which somatosensory feedback from a prosthetic leg might influence PLP.

Four studies showed that PLP was more likely to occur in amputees with non-painful phantom sensations than in those without non-painful phantom sensations (53, 83, 87). In these studies, 70%-100% of amputees with phantom sensations also had PLP. The co-occurrence of these post-amputation sensations suggest that they may share neural mechanisms with PLP (87). An fMRI study by Andoh et al showed that inducing non-painful phantom sensations in people with amputations activated the somatosensory and premotor cortices contralateral to the amputated limb (106). The activation of similar cortical areas has been recorded in patients with PLP upon induction of their PLP (107-111). The similarities in cortical activation patterns might explain a link between PLP and non-painful phantom sensations.

Two studies showed that PLP was more likely to occur in people with proximal amputations than in those with distal amputations (16, 52). These findings line up with a narrative review that reported an increase in the incidence of PLP with more proximal amputations (112). Proximal amputations are associated with an increased risk of failure of wound healing, which may result in infection or stump pain (113). However, the reasons why proximal amputations should be more likely to lead to PLP than distal amputations are not clear (114).

Another interesting finding was that not having pre-amputation counselling was positively associated with PLP (strong association) in a study representing a total of 104 participants (16). This suggests that patients who receive counselling prior to their amputation maybe less likely to report PLP compared to those who do not receive counselling. We could not find any relevant study to explain this strong association. However, Gallagher et al (16) suggest that pre-amputation counselling may reduce the risk of developing PLP by addressing depression and anxiety prior to limb amputation (115).

Another consideration is that pre-amputation counselling aimed at managing patients' expectations about pain post-operatively (e.g. prognosis) and equipping them with adaptive coping strategies may reduce the risk of PLP by preventing the onset of post-amputation depression that is sometimes triggered by the feeling of helplessness from the overwhelming new reality of life after limb amputation (79). No other study has specifically identified not having pre-operative counselling as a predictor for PLP after limb amputation. Therefore, further studies are required to build on the existing literature.

5. Limitations

The sample in this systematic review was skewed towards males, in that 9814 (77.04%) of the 12738 participants were male. Therefore, the results might not hold for females. The pooling of all the studies revealed high heterogeneity. However, the exclusion of studies with moderate to high risk of bias revealed moderate heterogeneity (116). Nevertheless, these results should be interpreted with care. We could not assess the quality of the evidence of studies reporting on risk factors using the Quality in Prognostic Studies (QUIPS) tool because the evaluation of risk factors for PLP in this study was purely exploratory. In addition, we did not use this tool because its items overlap with those of the tool used for assessing the risk of bias for studies included in this review (117). We could not perform a subgroup analysis by sex because we did not have individual patient data, nor was analysis by sex an objective identified in the protocol.

However, the data on risk factors provide no support for sex influencing the likelihood of PLP after amputation. It was not possible to conduct a meta-analysis on the risk factors for PLP because the included studies used varying methodological approaches and measures of association. None of the included studies used an outcome measure that has been validated for assessing PLP. In fact, we are not aware of any instrument that has been validated for assessing PLP. Such a standardised tool for assessing PLP would be useful to provide us with reliable data. Most studies in this review had moderate-high risk of bias. There is a clear need for high-quality studies to raise the credibility of future meta-analyses. Finally, the search strategy for this study was designed specifically to identify prevalence studies. Therefore, although we did conduct an exploratory search for additional studies of risk factors for PLP, there is a possibility that we could have missed some studies that investigated risk factors for PLP if they did not also estimate PLP prevalence. In consideration of this possibility, the review of risk factors was classified as an exploratory analysis. Thirteen out of 15 included studies determined association between identified risk factors and PLP using a retrospective cross-sectional study design. This study design (compared to a cohort design) is prone to recall bias, resulting from the patient's inability to clearly recall their exposure to a risk factor prior to developing PLP. In fact, a cohort design is the only appropriate research design for informing us about the risk factors for a particular disease (118). Further studies using a cohort design are necessary to provide robust data on risk factors for PLP. It is important to note that studies conducted in developing countries are underrepresented in our meta-analyses. Therefore, the results on PLP prevalence in developing countries should be interpreted with caution. The results of this systematic review were derived from studies conducted mostly in Europe, North America and Asia. To the best of our knowledge, no study has been conducted in Africa, and research in this area is necessary to inform us about the prevalence and risk factors for PLP in the African population.

6. Conclusions

This systematic review and meta-analysis estimates that six of every 10 people with an amputation report PLP – a high and important prevalence of PLP. Health care professionals ought to be aware of the high rates of PLP and implement strategies to reduce PLP by addressing known risk factors, specifically those identified by the current study. Stump pain and post-amputation depression are all known and modifiable risk factors that are consistently positively associated with PLP. Awareness of these risk factors may motivate health care professionals to address them early in treatment to prevent the onset of PLP in people with amputations.

7. Acknowledgements

The authors thank Mrs Mary Shelton (Health Sciences reference librarian, University of Cape Town) for assisting with the development of the search strategy.

8. Supplementary files

Supplementary file 2.1: The PRIMSA reporting checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S2 ; pages 2 and 3.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4 & 5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

Supplementary file 2.2: Customised search strategy

1. Amputation [MeSH] OR Amputation, Traumatic [MeSH] OR Amputation Stumps [MeSH] OR Amputee OR amputees OR amputation OR limb deficiency OR limb loss.
2. Phantom Limb [MeSH] OR Phantom limb OR phantom pain OR phantom sensations OR phantom sensation OR residual limb pain
3. Epidemiology [MeSH] OR Epidemiology [Subheading] OR Prevalence [MeSH] OR Risk Factors [MeSH]
4. associated OR association OR burden OR case-control OR cohort OR correlation OR correlates OR cross-sectional OR determinant OR epidemiology OR epidemiological OR epidemiologic OR frequency OR incidence OR interview OR likelihood ratio OR observational OR occur OR occurrence OR odds ratios OR predict OR predictor OR prediction OR present OR presentation OR prevalence OR prevalent OR probability OR prognosis OR prognostic OR proportion OR prospective OR questionnaire OR questionnaires OR rate OR retrospective OR risk OR risks OR self-report OR statistic OR surveillance OR survey OR surveys
5. 1 AND 2 AND 3 AND 4

Supplementary file 2.3: Risk of bias assessment checklist for prevalence studies (Hoy et al (62))

Name of author(s): **Study title:** **Year of study publication:**		
Risk of bias items	**Risk of bias levels**	**Point scored**
1. Was the study's target population a close representation of the national population in relation to relevant variables (e.g. number of limb amputations, participant's sex and age)?	**Yes (LOW RISK)**: The study's target population was a close representation of the national population in relation to relevant variables OR nationwide survey was conducted	0
	No (HIGH RISK): The study's target population was clearly NOT representative of the national population in relation to relevant variables.	1
2. Was the sampling frame a true or close representation of the target population in relation to relevant variables (e.g. number of limb amputations, participant's sex and age)?	**Yes (LOW RISK)**: The sampling frame was a true or close representation of the target population in relation to relevant variables.	0
	No (HIGH RISK): The sampling frame was NOT a true or close representation of the target population in relation to relevant variables.	1
3. Was some form of random selection used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling), OR, was a census undertaken?	**Yes (LOW RISK)**: A census was undertaken, OR, some form of random selection was used to select the sample.	0
	No (HIGH RISK): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.	1
4. Was the likelihood of non-response bias minimal?	**Yes (LOW RISK)**: The response rate for the study was ≥75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non- responders.	0
	No (HIGH RISK): The response rate was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders	1
5. Were data collected directly from the study participants (as opposed to a proxy)?	**Yes (LOW RISK)**: All data were collected directly from the participants.	0
	No (HIGH RISK): In some instances, data were collected from a proxy, OR, it was	1

	unclear whether data were collected directly from participants.	
6. Was a clear and acceptable case definition used in the study (e.g painful sensation(s) felt in the amputated limb)?	**Yes (LOW RISK)**: An acceptable case definition was used.	0
	No (HIGH RISK): An acceptable case definition was NOT used.	1
7. Was the study instrument that measured the outcome of interest (e.g. prevalence of PLP) shown to have reliability and validity (e.g. test-re-test, piloting, validation in a previous study)?	**Yes (LOW RISK)**: The study instrument had been shown to have reliability and validity.	0
	No (HIGH RISK): The study instrument had NOT been shown to have reliability or validity.	1
8. Was the same mode of data collection used for all participants?	**Yes (LOW RISK)**: The same mode of data collection was used for all participants.	0
	No (HIGH RISK): The same mode of data collection was NOT used for all participants, OR, it was unclear whether the same mode of data collection was used for all participants	1
9. Was the length of the shortest prevalence period for the outcome of interest appropriate	**Yes (LOW RISK)**: The point prevalence for the outcome of interest was reported, OR, the period prevalence on the outcome of interest was reported ≤ 1 year after limb loss.	0
	No (HIGH RISK): The point prevalence for the outcome of interest was NOT reported, AND, the period prevalence on the outcome of interest was reported > 1 year after limb loss.	1
10. Were the numerator(s) and denominator(s) for the outcome of interest (e.g. the prevalence of PLP) appropriate?	**Yes (LOW RISK)**: The paper presented appropriate numerator(s) AND denominator(s) for the outcome of interest.	0
	No (HIGH RISK): The paper did NOT present numerator(s) AND denominator(s) for the outcome of interest, OR, the paper did present numerator(s) AND denominator(s) for the outcome of interest but one or more of these were inappropriate.	1
Summary on the overall risk of study bias	Low risk	0-3
	Moderate risk	4-6
	High risk	7-10

Supplementary file 2.4: Summary of the risk of bias assessment results.

Authors	Was the Study's target population a close representation of the national population?	Was the sampling frame a true or close representation of the target population?	Was some form of random selection used to select the sample, OR, was a census undertaken?	Was the likelihood of non-response bias minimal?	Were data collected directly from the participants?	Was an acceptable case definition used in the study?	Was the study instrument shown to have reliability and validity?	Was the same mode of data collection used for all participants?	Was the length of the shortest prevalence period for the parameter of interest appropriate?	Were the Numerator and denominator for the parameter of interest appropriate?	Overall risk of bias
Ahmed et al., 2017	High	Low	High	High	High	High	High	Low	Low	Low	Moderate
Aldington et al., 2014	High	Low	Low	High	Low	Low	High	Low	Low	Low	Low
Bekrater et al., 2015	Low	Low	High	High	Low	Low	High	High	Low	Low	Moderate
Bin Ayaz et al., 2015	High	High	High	High	High	Low	High	High	High	Low	High
Bosmans et al., 2007	High	Low	Low	High	Low	High	High	Low	Low	Low	Moderate

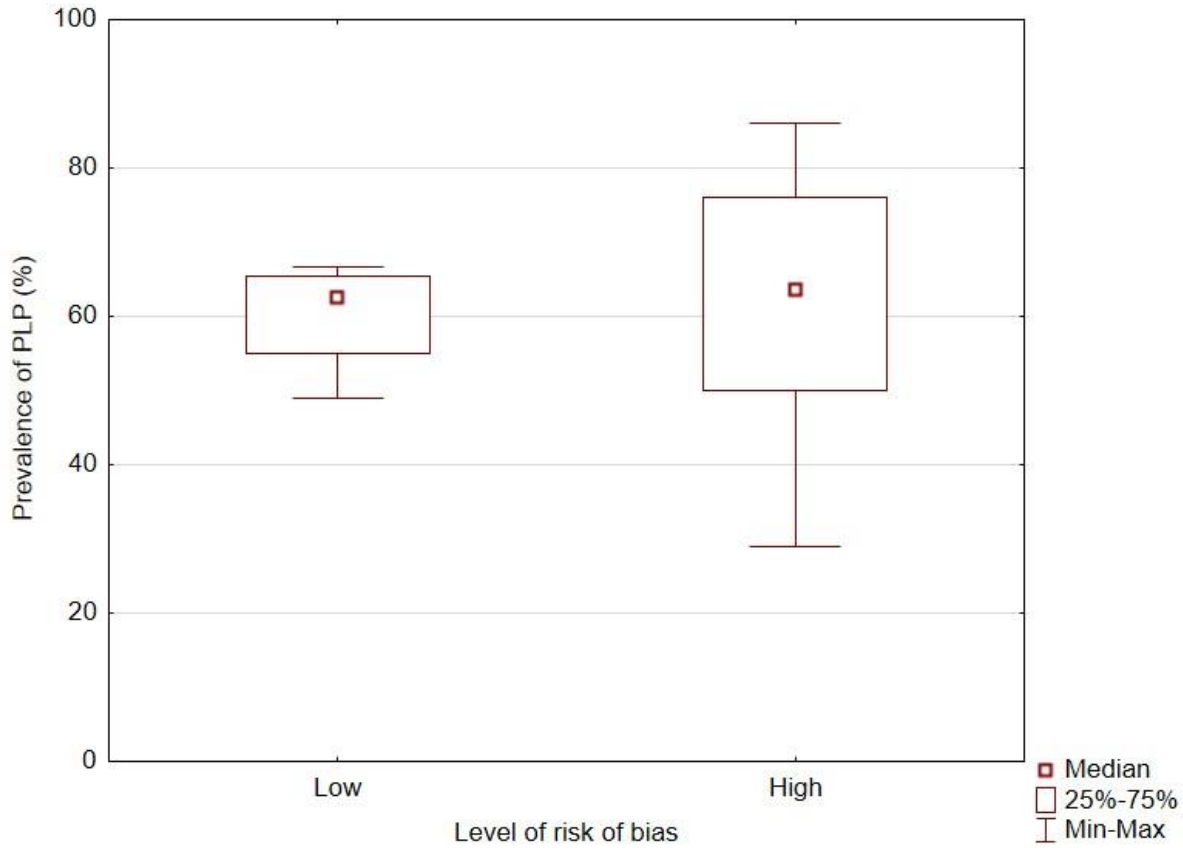
Buchanan et al., 1986	High	High	High	High	Low	High	High	Low	High	Low	High
Byrne et al., 2011[a]	High	High	Low	High	Low	High	High	High	High	Low	High
Byrne et al., 2011[b]	High	High	Low	High	Low	High	High	High	High	Low	High
Clark et al., 2013	High	Low	High	High	High	High	High	High	High	Low	High
Datta et al., 2004	High	Low	High	Low	High	High	High	Low	High	Low	Moderate
Desmond et al., 2010	High	Low	High	High	High	Low	High	Low	Low	Low	Moderate
Dijkstra et al., 2002	High	Low	High	High	High	Low	High	Low	High	Low	Moderate
Ehde et al., 2000	High	Low	Low	High	High	Low	High	Low	High	Low	Moderate
Ephraim et al., 2005	Low	Low	Low	High	High	Low	High	Low	High	Low	Moderate

Gallagher et al., 2001	High	High	High	High	High	High	High	Low	High	Low	High
Hanley et al., 2006	High	Low	Low	High	High	Low	High	High	Low	Low	Moderate
Hanley et al., 2009	High	High	Low	High	High	High	High	Low	High	Low	Moderate
Houghton et al., 1994	High	Low	High	High	High	High	High	Low	High	Low	High
Hnoosh et al., 2014	Low	High	Low	High	Low	Low	High	Low	Low	Low	Low
Kern et al., 2012	Low	Low	Low	High	High	High	High	Low	High	Low	Moderate
Ketz et al., 2008	High	Low	High	High	Low	Low	High	Low	High	Low	Moderate
Kooijman et al., 2000[a]	High	Low	High	Low	High	High	High	Low	High	Low	Moderate

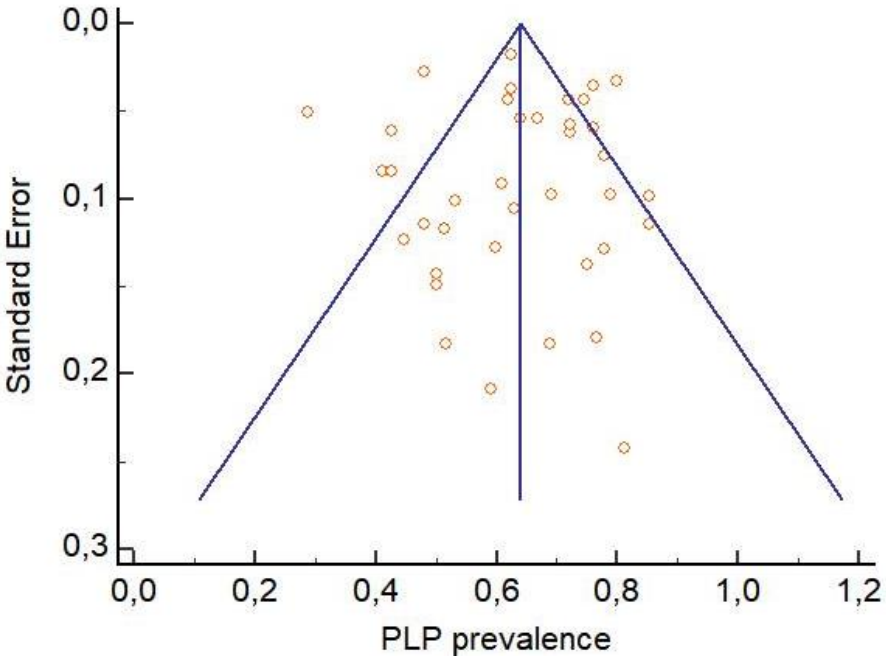
Kooijman et al., 2000[b]	High	Low	High	Low	High	High	High	Low	High	Low	Moderate
Larbig et al., 2019	High	High	High	High	Low	High	High	Low	Low	Low	Moderate
Morgan et al., 2017	Low	Low	High	Low	High	High	High	Low	Low	Low	Moderate
Noguchi et al., 2019	High	High	High	High	Low	Low	High	Low	Low	Low	Moderate
Penna et al., 2019	High	High	Low	High	High	High	High	Low	High	Low	High
Probstner et al., 2010	High	High	High	High	Low	High	High	High	High	Low	High
Rafferty et al., 2015	High	High	High	Low	Low	High	High	Low	Low	Low	Moderate
Rahimi et al., 2012	Low	Low	High	Low	Low	High	High	Low	Low	Low	Low
Rayegani et al., 2010	High	Low	High	Low	Low	Low	High	Low	Low	Low	Low

Razmus et al., 2017	High	High	High	High	Low	High	High	Low	High	Low	High
Reiber et al., 2010[a]	High	Low	High	High	High	High	High	High	High	Low	High
Reiber et al., 2010[b]	High	Low	High	High	High	High	High	High	High	Low	High
Resnik et al., 2019	Low	Low	High	High	Low	High	High	Low	High	Low	Moderate
Richardson et al., 2007	High	Low	High	Low	Low	High	High	Low	High	Low	Moderate
Richardson et al., 2015	High	Low	High	High	Low	High	High	Low	Low	Low	Moderate
Schley et al., 2008	High	Low	High	High	High	High	High	High	High	Low	High
Wartan et al., 1997	High	Low	Low	Low	High	High	High	Low	High	Low	Moderate
Yin et al., 2017	High	Low	Low	High	High	High	High	Low	High	Low	Moderate

Supplementary file 2.5: A plot illustrating the results of a significant difference test between PLP prevalence studies with low risk of bias versus those with moderate-high risk of bias



Supplementary file 2.6: The funnel plot assessing publication bias in a meta-analysis of 39 studies.



Chapter 3: The prevalence of, and risk factors for, phantom limb pain in people who have undergone amputations at Groote Schuur Hospital: a cross-sectional study.

3.1 Declaration from author and co-authors:

3.1.1 Declaration from author

The following co-authors contributed to the manuscript: Shreya Rayamajhi, Christopher Kloppers and Romy Parker. The contribution of the authors for this manuscript is as follow: Katleho Limakatso conceptualised the study with input from Romy Parker. Katleho Limakatso recruited participants with input from Shreya Rayamajhi and Christopher Kloppers. Katleho Limakatso collected and curated data. Katleho Limakatso conducted the formal analysis of the data with input from Romy Parker. Katleho Limakatso wrote the original draft of the manuscript. All the authors reviewed and edited the manuscript and approved it for submission for examination.

Extent of contribution:

- Katleho Limakatso: 75%
- Dr Shreya Rayamajhi: 5%
- Dr Christopher Kloppers: 5%
- Prof Romy Parker: 15%

_____

Signed by Katleho Limakatso Date: 25/11 /2021

3.1.2 Declaration of co-authors

Undersigned hereby certifies that:

1. The above declaration correctly reflects the nature and extent of the candidate's contribution to this work and the nature of the contribution of each of the co-authors.
2. They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise.
3. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication.
4. There is no other author of the publication according to these criteria.
5. Potential conflicts of interest have been disclosed to granting bodies, the editor or publisher of journals or other publications, and the head of the responsible academic unit.
6. The original data are stored at the following location and will be held for 10 years from the date of the study's completion.

Location of stored data: Data were stored on a password-protected computer. Back-up data were stored on an external hard drive and shared on a secure online data repository (https://Zenodo.org/DOI:10.5281/zenodo.6355501). Data will be securely kept for 10 years after the completion of the study. Deidentified data will be made public in perpetuity according to Open Science principles (29). The peer-reviewed manuscript developed from this study was shared on OpenUCT (www.open.uct.ac.za/katleho_limakatso) according to the Open Access Policy at UCT.

Romy Parker Date: 25/11/21

Shreya Rayamajhi Date: 25/11/21

Christopher Kloppers Date: 25/11/21

3.2 Background and motivation

As established in the systematic review and meta-analysis, the global prevalence of PLP is high with 64% [95% CI: 60.0 – 68.1] of people with amputations experiencing this painful phenomenon (119). Our results revealed a significantly lower prevalence of PLP in developing countries relative to developed countries (Chapter 2). However, a lack of representation of studies conducted in developing countries suggests the number of people with PLP in developing countries is under-reported. This is mostly apparent in Africa – where no study investigating the prevalence of PLP could be found during our extensive search of the literature.

The indications for amputations in the African population have evolved in recent years. The primary cause of lower limb amputations in South Africa is vascular diseases secondary to complications of uncontrolled diabetes (120). Historically, trauma (accidents and war-related) and infections were the main predictors for amputations in Africa (121). However, the rapid urbanisation and adoption of western lifestyle and diets has led to a dramatic increase in the number of people with comorbidities including diabetes and hypertension (120, 122). These comorbidities have adverse systemic effects that often result in complications requiring a limb amputation (123). Consequently, the increasing number of limb amputations may contribute to the increasing burden of multiple post-surgical outcomes including the chronic pain condition of phantom limb pain.

The International Diabetes Federation (IDF) estimated that 4.5 million South African adults had diabetes in 2019 (124). Systematic-review data suggest that up to 75% of these people will undergo a limb amputation at some point in their life, particularly after the age of 50 years where a sharp increase in the incidence of amputations is commonly seen (125). Eighty-five percent of diabetic adults in South Africa receive medical care exclusively from public healthcare facilities which are overburdened, poorly resourced, and notoriously inefficient in providing adequate healthcare services (126).

The high proportion of diabetic-related amputations might be an artefact of late screening, poor implementation of preventative strategies and a lack of sustainable management of diabetes and related complications.

Given the high rate of limb amputations and exposure to multiple socioeconomic risk factors for pain that are commonly present in South Africa, a significant proportion of South African people with amputations may be suffering from PLP. Based on this idea, we conceived the current study with the aim of exploring the prevalence of PLP and identifying associated risk factors in a sample of African people with amputations.

3.3 Aims and objectives.

3.3.1 Aim

The aim of this cross-sectional study was to determine the prevalence of PLP in adults who have undergone limb amputations at Groote Schuur Hospital in Cape Town, South Africa.

3.3.2 Objectives

- To determine the prevalence of PLP at different time-points.
- To identify pre-operative, peri-operative and post-operative risk factors associated with PLP.

3.4 Summary of main findings

- The study included 106 participants [male (n=66); female (n=40)] with lower limb amputations and a median [IQR] age of 59 [53 – 67]. Data were analysed using 129 amputation cases because 23 participants had double amputations.
- The indication for amputations were complications due to uncontrolled diabetes, infection, limb ischaemia, and cancer.
- The overall prevalence of PLP during the week preceding data collection was 50.78% [95% CI: 41.80 – 59.72].

- The prevalence of PLP varied between different time-points after limb amputations. Phantom limb pain prevalence was 41% [95%CI: 20.7 – 63.67] in people who had been amputated within the previous six months, 67% [95%CI: 49.8 – 80.9] in people who had been amputated seven to 12 months previously, 29% [95%CI: 11.3 – 52.12] in people who had been amputated 13 to 18 months previously, 65% [95%CI: 38.3 – 85.8] in people who had been amputated 19 to 24 months previously, and 46% [95%CI: 27.5 – 66.1] in people who had been amputated 25 to 32 months previously.
- Persistent pre-operative pain was the only risk factor positively associated with PLP in the univariate logistic regression analysis [OR 2.4 (1.12 – 5.0); P=0.02]. This association was confirmed in the multivariate logistic regression analysis [OR 2.3 (1.0 – 5.1); P=0.04].

"The manuscript presented below has been prepared for submission to the European Journal of Pain"

3.5 Manuscript prepared for submission to the European Journal of Pain

Title: The prevalence of, and risk factors for, phantom limb pain in amputees living in South Africa: a cross-sectional survey.

Running head: Phantom limb pain prevalence and risk factors.

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Research category: Original article

Funding sources: Start-up Emerging Researcher Award, University of Cape Town.

Conflict of interest: The authors declare no conflict of interest.

Significance: This is the first study to report on the prevalence of, and risk factors for, Phantom Limb Pain in a sample of African participants with amputations. The results of this study may help to strengthen efforts to optimise recovery from amputation surgery, and to reduce suffering and disability in people with amputations. The knowledge of the risk factors for PLP in this population may yield more effective and targeted pre- and post-amputation care, leading to reduced health care utilisation and improved quality of life.

3.5.1 Abstract

Background: We previously performed a systematic review and meta-analysis which showed that 64% [95% CI: 60.01 – 68.1] of people with amputations worldwide are affected by Phantom Limb Pain (PLP). The prevalence estimates varied significantly between developed and developing countries. Remarkably, no studies could be found that were conducted to determine the prevalence of PLP in an African population.

Methods: A cross-sectional study was conducted using 129 amputation cases. Patients who had undergone limb amputations between January 2018 and October 2020 were identified from the ethics-approved registry held in the acute care surgery unit at Groote Schuur Hospital. Data on the prevalence and risk factors for PLP were collected telephonically from consenting and eligible participants. The prevalence of PLP was expressed as a percentage with a 95% confidence interval. The associations between PLP and risk factors for PLP were tested using univariate and multivariate logistic regression analyses. The strength of association was calculated using the Odds Ratio where association was confirmed.

Results: The overall PLP prevalence was 51% [95% CI: 41.8 – 59.7]. The prevalence of pain varied at different time-points post amputation. However, there was no significant difference in prevalence over time. Persistent pre-operative pain was identified as a risk factor for PLP.

Conclusion: This study revealed a high prevalence of PLP. The use of effective treatments targeting pre-amputation pain may yield more effective and targeted pre-amputation care, leading to improved quality of life after amputation.

1. Introduction

The prevalence of phantom limb pain (PLP) – painful sensations felt in the amputated part of a limb, is high (119). Limb amputations contribute to disability, loss of financial income, and increased healthcare utilisation and related costs (127, 128). Approximately 356 million limb amputations are conducted globally every year (129). The sharp increase in the number of amputations in the past 10 years, primarily due to uncontrolled diabetes, has contributed to an increase in the prevalence of post-amputation complications including PLP (130).

Phantom limb pain is a common complication in people who have undergone limb amputations. We previously performed a systematic review and meta-analysis of the literature which showed that 64% [95% CI: 60.0 – 68.1] of people with amputations worldwide are affected by PLP (119). This is a high and important statistic indicating that efforts should be made to adequately understand the mechanisms underlying PLP.

The current evidence points to spontaneous nociceptive firing of the severed nerve and maladaptive cortical reorganisation as important drivers of PLP (98, 131). It is hypothesised that spontaneous nociceptive firing of the afferent nerve is primarily responsible for the onset of acute PLP, and that maladaptive cortical reorganisation is involved in the maintenance of pain in the long-term (98). Our systematic-review evidence suggests that these mechanisms may be predicted by undergoing amputation as a result of uncontrolled diabetes, and having persistent pre-amputation pain, an amputation of a lower limb, above-knee amputation, residual limb pain, phantom sensations, and not receiving pre-amputation counselling (119).

Remarkably, our systematic review and meta-analysis found no studies that reported on the prevalence of PLP and associated risk factors in African populations (119). Therefore, the burden of pain and potential targets for treatment in this patient group are not clearly understood.

In addition, it may be inappropriate to extrapolate the current evidence to the African context because of disparities in patient demographics and socioeconomic determinants of pain in developing and developed countries (132, 133). The differences in these key determinants of pain indicate that a relevant study focusing on the African population is warranted. Therefore, we conceived the current study with the aim to explore the prevalence of PLP and associated risk factors in African people with lower limb amputations. The results of this study may help to strengthen efforts to optimise recovery from amputation surgery in diverse populations, and to reduce suffering and disability in people with amputations. In addition, increased knowledge of the risk-factors for PLP in this patient-group may yield more effective and targeted post-amputation care.

2. Methods

This study was designed using the STROBE checklist for observational studies (134). Ethical approval for this study was granted by the Faculty of Health Sciences Human Research Ethics Committee of the University of Cape Town [ref: 066/2020] (Appendix 2). Permission to conduct the study at Groote Schuur Hospital (GSH) was granted by the hospital's research and ethics committee.

2.1 Study design

We conducted a cross-sectional study using random sampling. The random-sampling technique provides participants with an equal chance of being included in the study. This technique addresses the sampling bias often seen in prevalence studies that use convenience sampling (135).

2.2 Research setting

The study was conducted at GSH - a tertiary healthcare facility providing services to people living in and outside of Cape Town, South Africa. Most of the patients at GSH are from low-middle income households (136), and they commonly present with comorbidities (e.g. diabetes, peripheral vascular disease) that often result in complications leading to a limb amputation (130).

2.3 Recruitment

We recruited the participants for this study from a pre-existing ethics-approved database held by the acute care surgical unit [Acute care surgery online database- HREC 020/2018; Valid until 30 Sep 2021] (Appendix 5). This registry includes patients who have undergone limb amputations and provided consent to be contacted for research purposes. The names and contact details of patients who had undergone limb amputations between January 2018 and October 2020 were retrieved and entered into an excel spreadsheet in date order from the first surgery performed in 2018 to the last surgery performed in October 2020. The registry was developed in January 2018, hence only the patients who had limb amputations from this point could be identified. The list was then rearranged using a random sequence generator available on https://www.random.org/sequences/. Patients were contacted telephonically starting with the first allocated number to inform them (in the language they comprehended best) about the study and to invite participation (Appendix 6). Those who verbally consented to participation were screened for eligibility against the inclusion/exclusion criteria. We included adults (≥18 years) who had undergone surgical or traumatic lower limb amputations between January 2018 and October 2020 at GSH, and were able to speak English, isiXhosa or Afrikaans - the most commonly spoken languages in Cape Town. Patients were excluded if they had auditory or speech impairments in such a way that they were unable to hear or speak clearly via telephone. In addition, we excluded patients who could not be reached via telephone after being contacted for three consecutive days at different times.

2.4 Sample size determination

The sample size was calculated using the formula [$n = \frac{Z^2\ P(1-P)}{d^2}$] developed by Daniel (137) for calculating a sample size in prevalence studies. "Z" represents the Z statistic for a level of confidence, "P" the expected prevalence and "d" the precision of the 95% confidence interval.

Using the Z statistic of 1.96 (for 95% CI), an expected prevalence of 64% (based on the pooled prevalence estimate in our meta-analysis) and precision of 0.053 (based on the 95% CI of the pooled prevalence estimate in our meta-analysis), a sample of 316 participants was required for a 95% confidence level (Appendix 7).

2.5 Outcomes

The presence of PLP was assessed using the pain severity scale of the Brief Pain Inventory (BPI) (Appendix 8) (138). The first question of the BPI was modified to "Many people who have had amputations report that they can still feel their limb or have pain in the limb which is no longer there. Being able to feel the limb is called phantom limb sensation. Having pain in the limb which is no longer there is called phantom limb pain. In the past week, have you experienced phantom limb pain – pain in your limb which is no longer there?" The pain severity scale of the BPI was also used to assess the participant's worst, average and lowest PLP in the previous week, and their current PLP on a scale of zero to 10, where zero represents "no PLP" and 10 represents "worst PLP they could possibly imagine". The pain severity score was calculated as the average of the four ratings. The BPI has been validated for use in South Africa in all three of the languages used in this study (139).

Data on the characteristics and risk factors for PLP were collected using a pre-piloted customised tool (Appendix 9) and were score dichotomously as either "Yes" or "No". The tool included the risk factors that were identified in our recent systematic review to be consistently positively correlated with PLP: persistent pre-amputation pain, pre-amputation depression, diabetic cause of amputation, traumatic cause of amputation, not receiving pre-amputation counselling, above-knee amputation, bilateral amputation, post-amputation depression, residual limb pain, non-painful phantom sensations, and using a cosmetic prosthetic limb (119). In addition, the tool assessed the characteristics of PLP: nature, number of episodes, and duration of each episode of pain. The characteristics included in this tool have been identified in the literature as important items to include in the assessment of PLP in people with amputations (14).

2.6 Piloting

The random selection process and data collection forms were piloted in a small-scale study of 10 participants. This sample size is appropriate for pilot-testing the study procedure (140). We used the first 10 records retrieved from the random selection process. These pilot participants were excluded from the main study. The piloting process was conducted to consider the time to complete data collection with each participant and to determine the feasibility of using the questionnaires telephonically. The pilot data were used to pre-test and adapt the planned data import, tidying, and analysis processes. The data collection process was revised to separately collect data for each amputated limb instead of focusing only on the most recently amputated limb in people with double amputations. As a result, the data analysis plan was revised in such a way that the prevalence of PLP was calculated by dividing the number of PLP cases with the number of amputation cases.

A trained healthcare professional fluent in the English, isiXhosa and Afrikaans languages contacted the patients telephonically for data collection. The patient demographics questionnaire was used to collect demographic data including the number of amputated limbs per participant. In a case where the participant had multiple amputated limbs, outcome data on each amputated limb were collected. The participants were screened for PLP in the amputated limb by asking them the adapted first question of the BPI. Only the participants who responded with a ‘’yes” to this question were asked to complete the pain severity scale of the BPI and provide details of the pain characteristics (i.e. nature and duration of pain, and frequency of pain episodes) specific to the affected limb. Participants with and without PLP were then screened for risk factors associated with PLP. The interview for patient participation and data collection took approximately 30 minutes.

2.7 Statistical analysis

Data were analysed using 'R'- a statistical tool available on www.R-project.org. The prevalence of PLP was calculated by dividing the number of PLP cases with the number of amputation cases. For example, if the participant had two amputated limbs but had PLP in one of them, we recorded this as one PLP case and two amputation cases. The overall prevalence of PLP was expressed as a percentage with a 95% confidence interval. In addition, we conducted sub-group analyses of the prevalence of PLP in people who had been amputated 0 to six months (n=22), seven to 12 months (n=39), 13 to 18 months (n=21), 19 to 24 months (n=17), and 25 to 32 months previously (n=30). We conducted the sub-group analyses to determine the distribution of this outcome over time (141). Because of the small sample size and skewed distribution of data, a Kruskal-Wallis test was conducted to test for a significant between-group difference PLP prevalence over time (142). Regression analyses were conducted to determine the number and duration of episodes, and pain severity scores over time. The associations between risk factors and PLP were tested using univariate logistic regression analyses. This method is appropriate when the dependant variable is binary (143). In addition, it informs us not only about the size of the association between two variables, but also the direction of such association (144). Hundred and twenty-nine amputation cases were entered into the univariate and multivariable model. For example, if one person with double amputations had experienced persistent pre-amputation pain in both limbs, we entered these as two cases of pre-amputation pain. Covariates found to be associated with PLP after the univariate analysis were entered into the multivariable logistic regression analysis. In addition, we entered independent variables that are consistently positively associated with PLP in the literature but showed no significance after the univariate analysis. We used this approach to explore the adjusted effects of the variables on the association between covariates and PLP (145). We excluded interrelated independent variables (e.g. pre-amputation depression and post-amputation depression) to increase the robustness of the multivariable model. The associations between covariates and PLP were reported as Odds Ratios with a 95% confidence interval (146). The median and Inter-Quartile Range

(IQR) were used to analyse numerical baseline data. Characteristics of PLP were reported descriptively. Statistical significance was set at $p<0.05$ for all analyses.

3. Results

The results of the recruitment process are illustrated in Figure 3.1. The study included 106 participants [male (n=66); female (n=40)] with a median [IQR] age of 59 [53 – 67] (Table 3.1). However, we analysed data from 129 amputation cases because 23 participants had double amputations. All the participants had lower limb amputations, with most having amputations above the knee (57%). The participants had undergone amputation surgery a median of 13 [8 – 23.5] months prior to recruitment. The indications for amputation were complications due to uncontrolled diabetes, infection, limb ischaemia, and cancer. The terms that were commonly used to describe the PLP were sharp, burning, and shooting (Table 3.2).

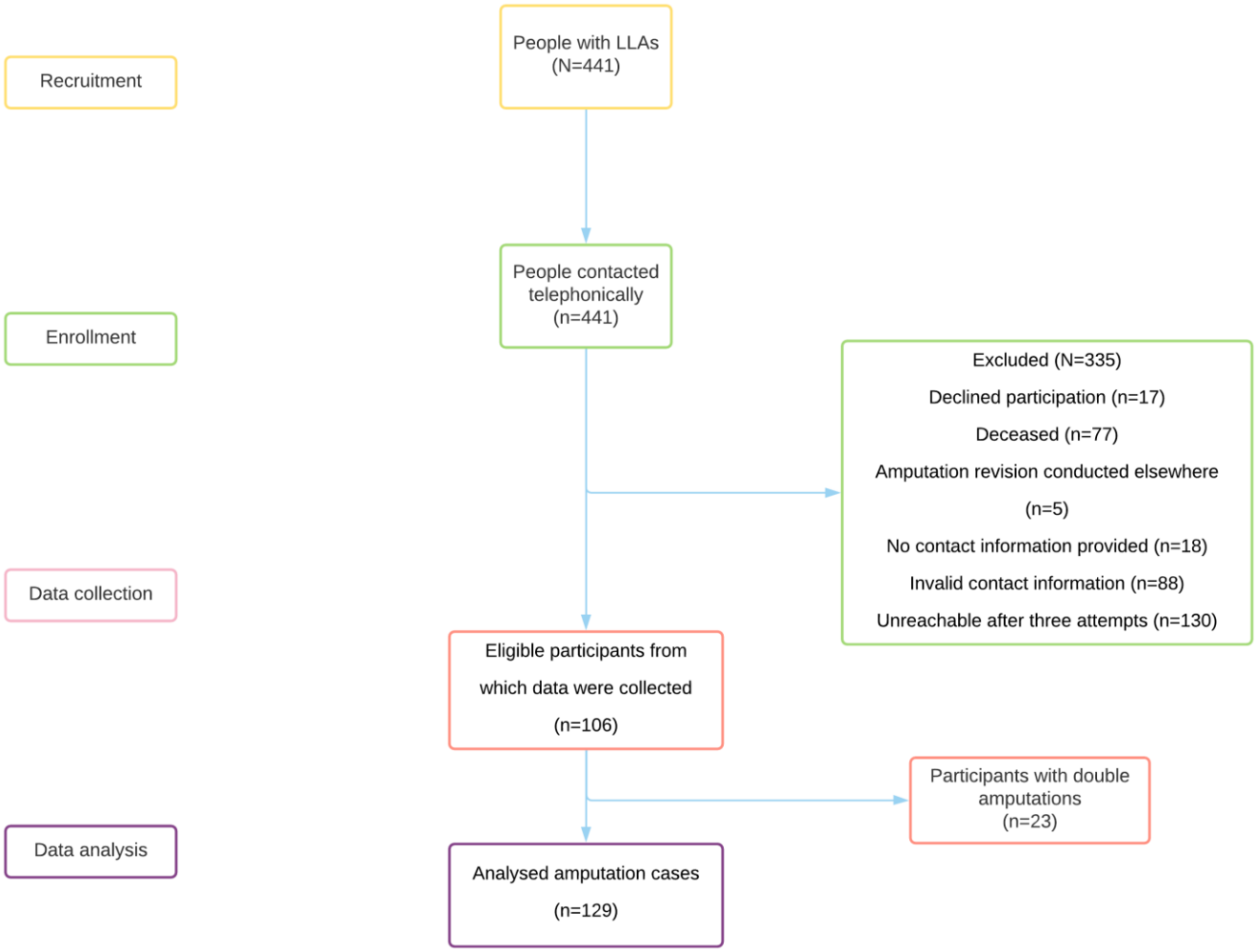

Figure 3.1: The STROBE flow diagram illustrating the recruitment, data collection, and data analysis processes.

Table 3.1: A summary of the demographic characteristics of the participants (n=106).

Variable	Measure
Number of participants [n (%)]	
All the participants	106 (100)
Male	66 (62)
Female	40 (38)
Age [median (IQR)]	
All the participants	59 (53 – 67)
Male	58.5 (53 – 68)
Female	59.5 (55 – 66)
Level of amputation [n (%)]	
Above knee amputation	73 (56.50)
Below knee amputation	56 (43.50)
Months since amputation [median (IQR)]	
All the participants	13 (8 – 23.5)
Indications for amputation [n (%)]	
Diabetic complications	99 (76.74)
Infection	16 (12.40)
Limb ischaemia	13 (10.10)
Cancer	1 (0.80)
Employment status [n (%)]	
Employed	9 (8.5)
Unemployed	97 (91.5)

3.1 Prevalence and characteristics of PLP

The overall prevalence of PLP during the week preceding data collection was 51% [95% CI: 41.8 – 59.7]. The prevalence of PLP varied between different time-points after limb amputations. Phantom limb pain prevalence was 41% [95%CI: 20.7 – 63.67] in people who had been amputated within the previous six months; 67% [95%CI: 49.8 – 80.9] in people who had been amputated seven to 12 months prior; 29% [95%CI: 11.3 – 52.2] in people who had been amputated 13 to 18 months prior; 65% [95%CI: 38.3 – 85.8] in people who had been amputated 19 to 24 months prior; and 46% [95%CI: 27.5 – 66.1] in people who had been amputated 25 to 32 months prior (Figure 3.2). There were no significant changes in PLP prevalence over time [H=7.78; p=0.1].

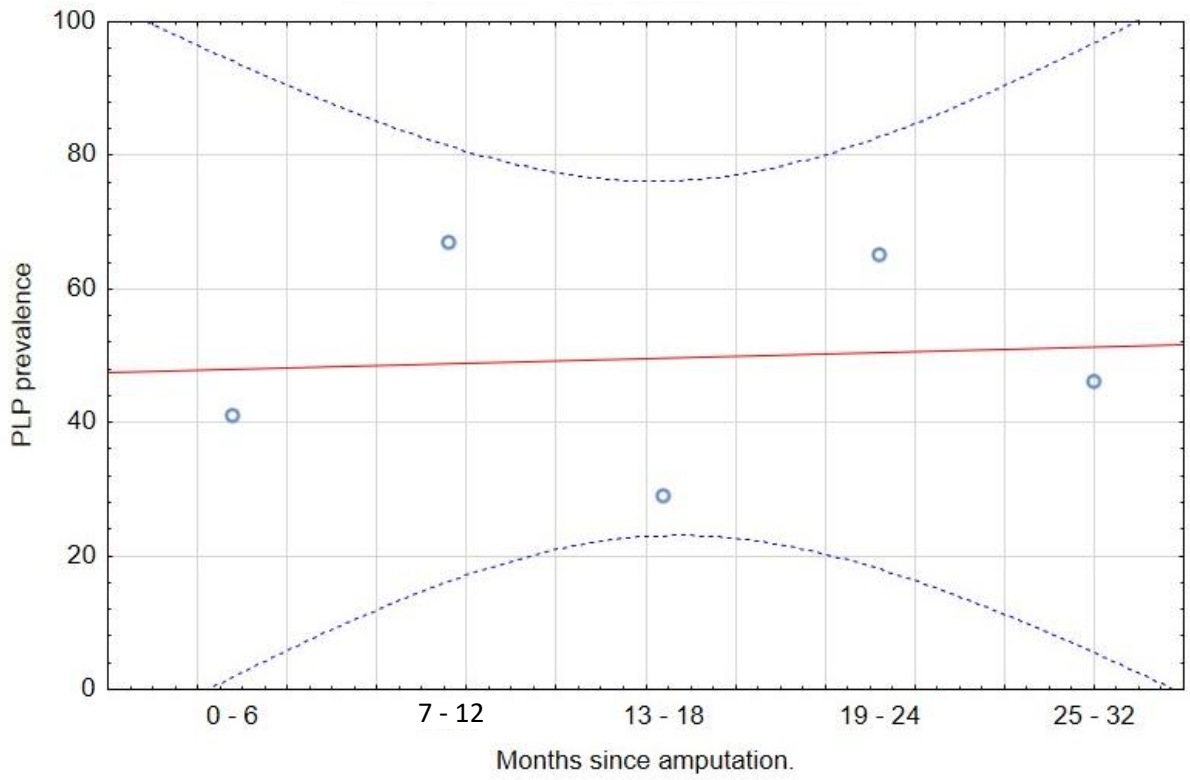

Figure 3.2: The prevalence of PLP by number of months since amputation.

The participants with PLP had a median [IQR] pain severity score of 2.5 [1.75 – 2.5] out of 10. The pain severity scores were consistent at different time-points (Figure 3.3). There was no significant change in pain severity over time [df=62; r^2=-0.02; p=0.96]. The participants had a median [IQR] of 3

[2 – 4] PLP episodes per week. There was no significant difference in the number of weekly pain episodes at different time-points (Figure 3.4) [df=62; r^2=-0.004; p=0.4].

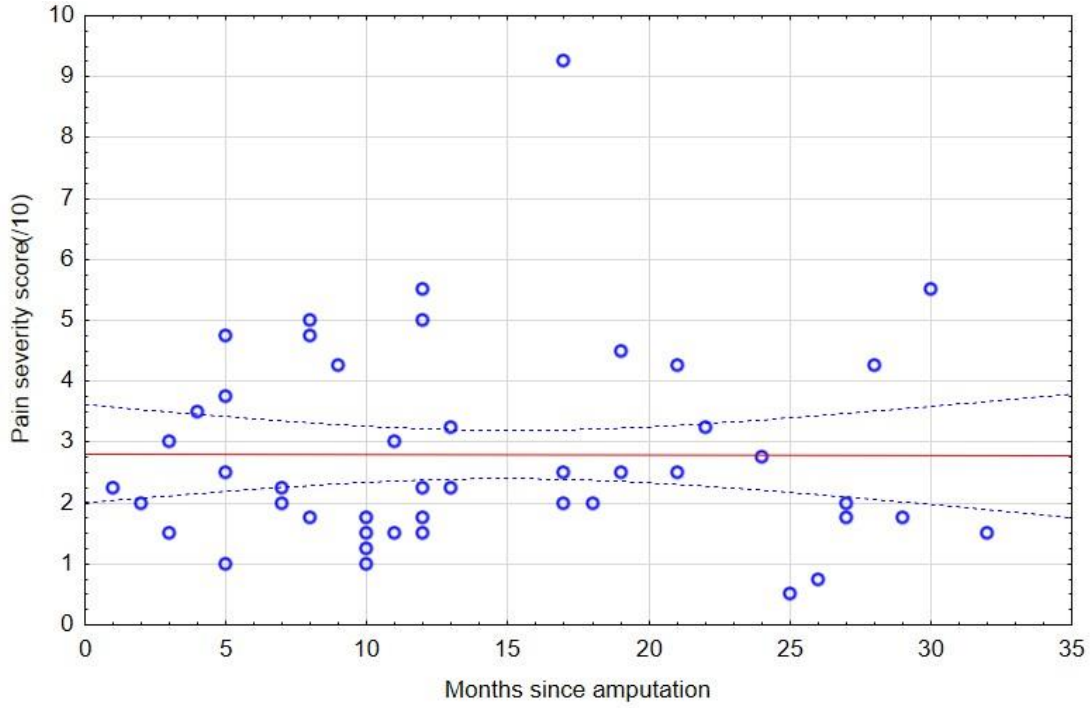

Figure 3.3: The severity of PLP by number of months since amputation.

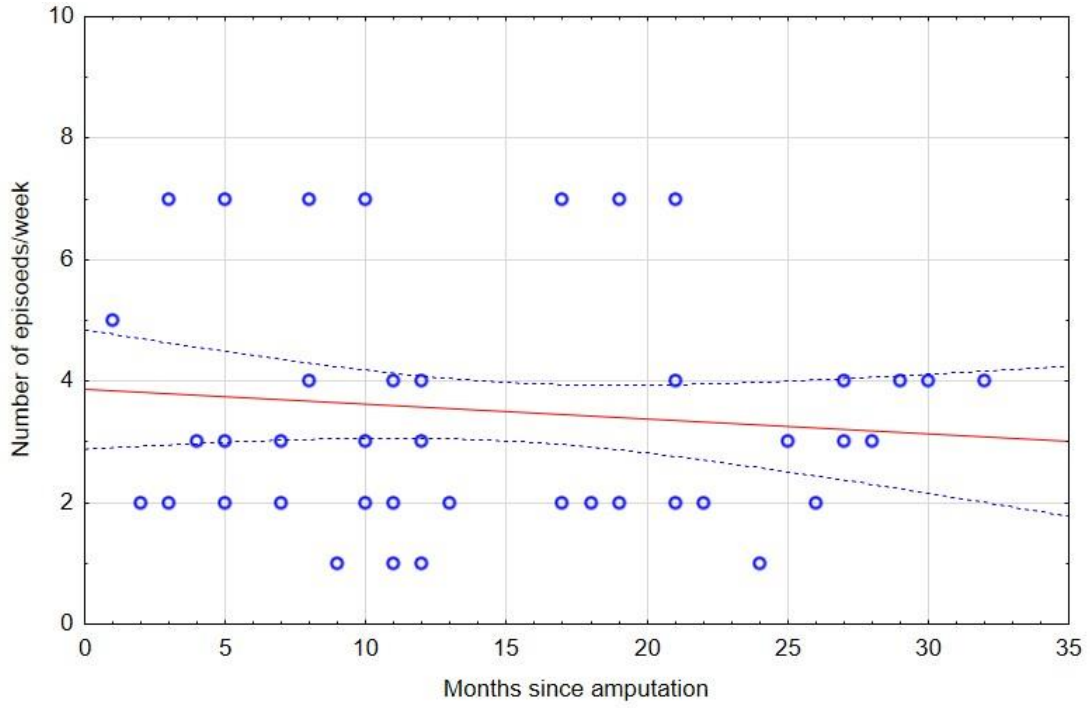

Figure 3.4: The number of episodes of PLP per week by the number of months since amputation.

The weekly pain episodes lasted for a median [IQR] of 20 [6 – 80] minutes. There was no significant difference in the duration of weekly episodes of pain at different time-points (Figure 3.5) [df=62; r^2=-0.01; p=0.6].

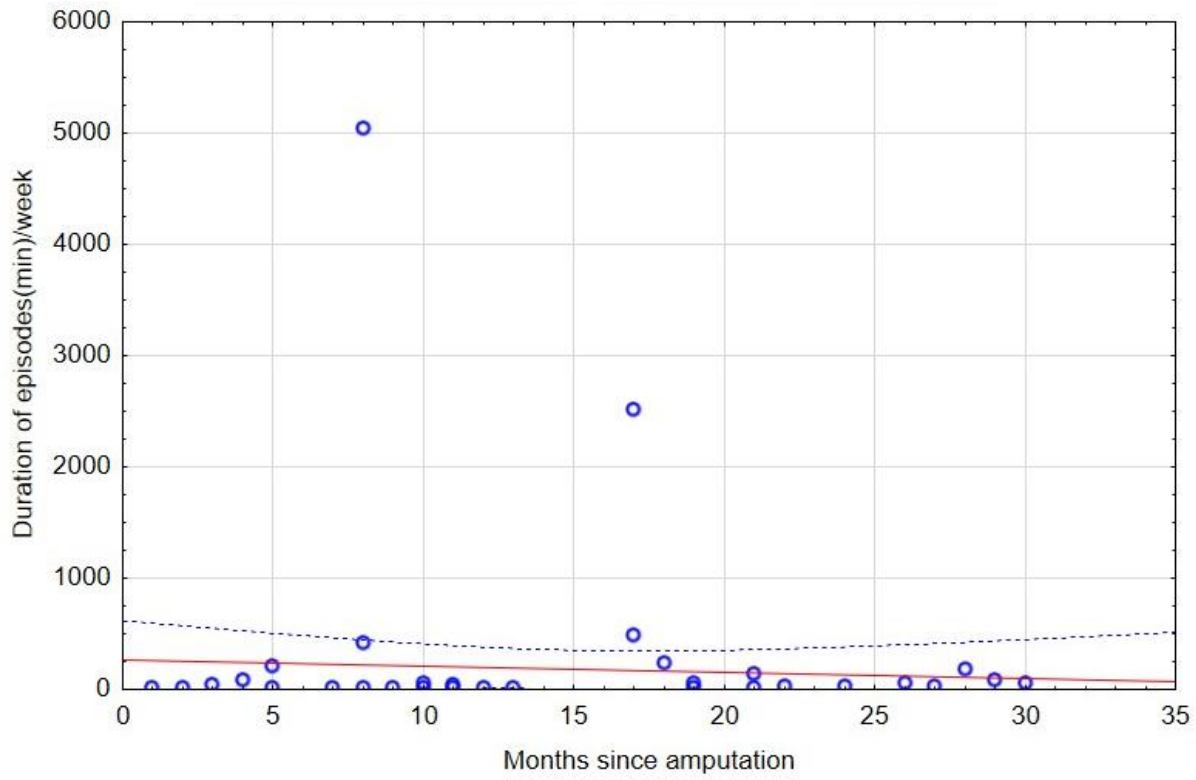

Figure 3.5: The duration of PLP episodes per week by number of months since amputation.

3.2 Phantom limb pain risk factors

Phantom limb pain risk factors which were explored in this study are presented in Table 3.3.

Persistent pre-operative pain was the only risk factor positively associated with PLP in the univariate logistic regression analysis [OR 2.4 (1.2 – 5.1); p=0.02]. This association was confirmed in the multivariable logistic regression analysis [OR 2.23 (1.0 – 5.1); p=0.04]. The univariate logistic regression analysis revealed a negative association between being male and PLP [Univariate: OR 0.5 (0.2 – 1.0); p=0.04], i.e. being male reduced the risk of developing PLP. However, no firm association was confirmed in the multivariable logistic regression analysis (OR 0.5 [0.2 – 1.2]; P=0.10]). No associations were shown between other variables and PLP.

Table 3.2: The symptoms of PLP and number of people experiencing them.

PLP symptoms	People experiencing PLP symptoms [n (%)][*]
Sharp	22 (33.8)
Shooting	16 (24.6)
Burning	15 (23.1)
Cramping	5 (7.7)
Dull	5 (7.7)
Itchiness	3 (4.6)
Stabbing	3 (4.6)
Shocking	3 (4.6)
Pinching	2 (3.1)
Pins and needles	2 (3.1)
N**umbness**	2 (3.1)
Piercing	1 (1.5)
Throbbing	1 (1.5)

[*] The percentage does not add up to 100% because some participants reported more than symptom.

Table 3.3: The univariate and multivariable analyses of risk factors for PLP (n=129).

Risk factors	Univariate analysis: OR [95% CI]	P-value	Multivariable analysis: OR [95% CI]	P-value
Pre-operative				
Persistent pain	2.37 [1.15 – 5.02]	0.02	2.25 [1.03 – 5.05]	0.04[†]
Diabetic indication for amputation	1.28 [0.64 – 2.58]	0.49	1.33 [0.50 – 3.62]	0.56
Depression	0.77 [0.30 – 1.94]	0.58	0.63 [0.22 – 1.74]	0.38
No pre-operative counselling	0.57 [0.24 – 1.29]	0.18	0.62 [0.25 – 1.50]	0.29
Peri-operative				
Bilateral amputation	1.02 [0.50 – 2.10]	0.96	—[‡]	—
Above-knee amputation	1.45 [0.72 – 2.96]	0.30	1.27 [0.58 – 2.76]	0.55
Post-operative				
Depression	1.29 [0.45 – 3.83]	0.64	—[§]	—
Residual limb pain	1.67 [0.76 – 3.74]	0.20	1.27 [0.54 – 3.02]	0.58
Non-painful phantom limb sensations	1.55 [0.77 – 3.17]	0.22	1.52 [0.69 – 3.37]	0.30
Use of a prosthesis	0.56 [0.11 – 2.39]	0.44	—[**]	—

[†] Indicates a significant result.
[‡] Variable was excluded due to a lack of significance in univariate analysis and a lack of literature indicating its role on PLP.
[§] Variable was excluded because it is associated with pre-amputation depression.
[**] Variable was excluded due to a lack of significance in univariate analysis and a lack of literature indicating its role on PLP.

4. Discussion

To our knowledge, this is the first study to evaluate the prevalence and characteristics of PLP and associated risk factors in a cohort of South African people with limb amputations. The findings of this study revealed a PLP prevalence estimate of 51% [95% CI: 41.8 – 59.7]. In addition, this study revealed persistent pre-operative pain as an important risk factor for PLP.

4.1 PLP prevalence

The prevalence estimates in this study suggest that approximately half of people in this population with amputations experience PLP. These estimates are consistent with the results of similar studies conducted in developing countries (7, 56, 72, 147), but substantially lower than those of studies conducted in developed nations (48, 84, 148). This finding is further supported by our recent meta-analysis which showed a significantly lower pooled PLP prevalence estimate from studies conducted in developing countries [54% (95%CI: 44.8 – 63.1)] compared to those conducted in developed countries [67% (95%CI: 62.0 – 71.6)]. Nevertheless, the prevalence of PLP was high, and strategies including patient and healthcare provider education need to be implemented effectively to improve the patient-centred prevention and management of PLP in people with limb amputations (119).

The significant differences in the prevalence of PLP could be an artefact of biased recruitment processes and the fear of PLP-related stigma commonly seen in developing countries. The social stigma associated with chronic pain is common in South Africa (149), and participants may not report their PLP due to the fear of being stigmatised as mentally ill (39, 150). Another consideration is that all the studies in our systematic review that were conducted in developing countries recruited participants from patients continuing with medical care (119). The process of recruiting patients from amongst those continuing with medical care suggests people with PLP who have been discharged from acute hospital care are unaccounted for in the prevalence reports.

In addition, all the studies in our systematic review that were conducted in developing countries had a high risk of bias for having a recruitment response rate of less than 75%. Similarly, a very low response rate of 25% was obtained in this study. Selection and non-response biases in this study could have resulted in the underestimated prevalence of PLP if patients without continuing medical care and those who did not respond to the study's invitation had PLP. The lack of robust recruitment processes raises the need to adapt current recruitment practices specifically to people in developing countries to increase the rigour of prevalence estimates in future studies.

Several studies indicates that a considerable number of people with amputations develop pain and experience suffering during this period (7, 14). This evidence highlights the importance of addressing pain early to prevent pain chronicity and disability. Interestingly, a lower PLP prevalence was seen in people who had limb amputations for more than a year. This observation is supported by the results of another study that showed a gradual decrease in PLP prevalence over time (151). The participants in the previous study had undergone amputation an average of 4 years prior to data collection. This duration may have been sufficient for participants who had limb amputations over a year prior to seek and receive treatment or develop coping strategies that may have resulted in pain relief. On the contrary, the study had recall bias in that participants were asked to recall their experience of pain at 6 months, year 1, year 2, and year 5. Another consideration is that a relatively lower PLP prevalence may be partly explained by the fact that patients with comorbidities (who usually present with PLP) die sooner and have less presentation in the subgroup of people who had been living with an amputation for more than a year (152). It would have been interesting to track PLP prevalence estimates in people with late-stage amputations. However, because we recruited participants from a registry that only started in 2018, this was not possible because none of the participants in this study had had amputations for more than two and half years. Therefore, a large nation-wide prospective longitudinal follow-up study will be conducted to further explore the factors and mechanisms associated with PLP prevalence over time.

We found it interesting that participants with PLP in this study reported pain severity scores below the threshold (of 5 out of 10 on a VAS scale) that is typically associated with a negative impact on function (153). The low pain severity scores and the intermittent nature of PLP suggest that some participants may be coping with pain. However, studies suggest that high 'worst pain' scores on the BPI and the unpredictable nature of pain inform us better about the bothersomeness of pain (154, 155). In consideration of this, we conducted a post-hoc analysis of the 'worst pain' scores in people with PLP. The results showed a median [IQR] pain severity of 5 [4 – 7]. In addition, the words used to describe PLP in this study (e.g sharp, shooting) are commonly associated with the spontaneous and unpredictable nature of pain (156). Further, considering that participants experienced an average of three PLP episodes lasting for approximately 20 minutes during the week prior to data collection, the compounded effects of pain on function and mental health could be disabling over time. Therefore, more patient-centred research is recommended to inform us about the extent of the interference of pain with function and care priorities in this patient-group. Our results on patient care priorities after lower limb amputations are presented in Chapter 5.

It was not surprising that complications due to uncontrolled diabetes was the most common reason for amputations in this study. The International Diabetes Federation estimated that approximately 4.5 million people in South Africa had diabetes in 2019 (124). Considering the steady rise in cases reported since 2009, the prevalence of diabetes is predicted to rise significantly in the future (130, 157). This chronic disease of lifestyle largely affects people in low-income households, who are less educated about the condition and have difficulty maintaining healthy eating habits due to the perceived high cost of healthy food (158). It has been shown that low health-literacy levels are common among diabetic patients (159). A recent study showed that 47% of people with diabetes had an average score of 13.2 on a 0-100 test of functional health literacy in adults (160).

Low health-literacy is associated with poor self-management strategies, deterioration in health status and increased chances of hospitalization, and several complications that may result in the surgical amputation of a limb (161). Altogether, these findings motivate for the design and implementation of evidence- and population-based education programmes focusing on the chronic diseases of lifestyle, including diabetes, and strategies for prevention and self-management.

4.2 Risk factors

Persistent pre-amputation pain was the only co-variate shown as a risk factor for PLP in the univariate logistic regression analyses. Likewise, when adjusted for each independent variable in the multivariable logistic regression analysis, the results showed that people with PLP were two times more likely to have experienced persistent pre-amputation pain than those without PLP. Persistent pre-amputation pain is consistently positively associated with PLP in the literature (46, 53, 83). Studies conducted elsewhere indicate that people with PLP are three to ten times more likely to have experienced persistent pre-amputation pain (7, 49). The strong association between pre-amputation pain and PLP may be explained by central sensitization – a physiological mechanism where persistent pain prior to amputation contributes to the hyperexcitability of the central nervous system that may continue to upregulate nociceptive activity after amputation, thus resulting in PLP with similar characteristics. This causal mechanistic relationship between PLP and pre-amputation pain was first suggested by Jensen et al (101) after revealing striking similarities in the characteristics (nature, quality and severity) of pre-amputation pain and PLP. This idea has since been supported by other studies showing that over 60% of the people who experienced persistent pre-amputation pain experience PLP with similar characteristics (17, 102). The strong association between pre-amputation pain and PLP also highlights the need to optimise perioperative pain management using multimodal analgesia, particularly in patients with uncontrolled diabetes and limb infections, who may have experienced pre-amputation pain (162, 163).

The results of the univariate analysis suggest that males in this study were at a lower risk of developing PLP than females. The results showed a lower prevalence in males (male: 44% [95%CI: 32.4 – 55.3] versus females: 62% [95%CI: 47.6 – 75.4]), although they represented a significantly higher proportion of the entire sample. These findings are supported by a small study of 85 participants showing that males had a significantly lower risk of developing PLP than females [OR: 0.1 (0.03 – 0.5)] (148). In that study, females had over 30% higher PLP prevalence at 6-months after amputation. Interestingly, the results were maintained at 42 months. The factors contributing to differences in the overall experience of pain in males versus females are well documented in the literature. Biological factors unique to women including a drop in plasma levels of oestrogen during a menstrual cycle or after trauma, and lowered firing threshold of the nerve put them at a higher risk of developing chronic pain than men (164). Moreover, several psychosocial factors common to women in South Africa including being victims of physical and emotional abuse have been identified as significant contributors to chronic pain (165, 166), with a recent nation-wide survey showing a significantly higher prevalence of chronic pain in South African females than males (32). Another important consideration is that African males tend to underreport pain as it is perceived to reduce their masculinity (167). Further, a recent review of the literature revealed that men were less likely to report chronic pain when assessed by a female health professional (168). We suspect this could have been a contributing factor in our study as the research assistant in this study is female. In consideration of this, pain awareness initiatives tailored specifically for men with chronic pain may improve the accuracy of pain reports in this patient-group.

4.3 Limitations

We could not recruit more participants beyond the attained sample size (of 129 amputation cases) to fulfil the required sample size because we had exhausted the list of patients who had given consent to be contacted for research purposes. In preparation for publication of this study, further data will be collected and re-analysed to adequately address the aim and objectives of the study.

We had hoped to randomly select the required number of participants from the database of people with amputations to minimise selection bias and to have sample that is representative of the amputee population. However, a small pool of patients in this database meant we had to use a convenience sample. Lastly, this study used a cross-sectional design to evaluate risk factors for PLP. This design (compared to a cohort design) is subject to recall bias in that patients may not accurately recall their exposure to some risk factors prior to the onset of PLP. We recommend that further studies use a prospective longitudinal cohort design to provide robust results on important risk factors for PLP in the African population.

5. Conclusion

Our results indicate that 5 out of 10 people who have undergone limb amputations at GSH report PLP. These results are consistent with the prevalence estimate of our recent meta-analysis of PLP prevalence studies conducted in developing countries (119). Within the constraints of the study the prevalence of PLP was high in respondents, and healthcare professionals ought to implement effective screening procedures for pre-operative pain to identify patients who are at high risk of developing PLP after amputation. The identification of persistent pre-amputation pain as a modifiable risk factor for PLP in this patient-group may yield more effective and targeted pre-amputation care, leading to improved quality of life after amputation. In addition, healthcare professionals ought to implement effective post-operative screening processes for PLP and ask for patient's input on priorities for treatment. The use of effective patient-centred post-operative management may strengthen efforts to reduce the burden of PLP.

6. Acknowledgements

The authors would like to thank Ms Bonolo Mafojane for collecting data in this study who recently passed away. We will remember her gentle character, and hard work and dedication to improving pain research in South Africa. May her soul rest in God's peace.

Chapter 4: Treatment recommendations for phantom limb pain in people with amputations: an expert consensus Delphi study

4.1 Publication reference

Limakatso K, Parker R. Treatment recommendations for phantom limb pain in people with amputations: an expert consensus Delphi study. PM&R. 2021 Jan 18.

https://doi.org/10.1002/pmrj.12556

4.2 Declaration from author and co-authors:

4.2.1 Declaration from author

The following co-author contributed to the manuscript: Romy Parker. The contribution of the authors for this manuscript is as follows: Katleho Limakatso conceptualised the study with the input from Romy Parker and Victoria J. Madden. Katleho Limakatso recruited participants. Katleho Limakatso collected and curated data. Katleho Limakatso conducted the formal analysis of the data with the input from Romy Parker. Katleho Limakatso wrote the original draft of the manuscript. All the authors reviewed and edited the manuscript and approved it for submission for examination.

Extent of contribution:

- Katleho Limakatso: 75%
- Prof Romy Parker: 15%
- Dr Victoria J. Madden: 10%

_____

Signed by Katleho Limakatso Date: 25/11 /2021

4.2.2 Declaration of co-authors

Undersigned hereby certifies that:

1. The above declaration correctly reflects the nature and extent of the candidate's contribution to this work and the nature of the contribution of each of the co-authors.
2. They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise.
3. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication.
4. There is no other author of the publication according to these criteria.
5. Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit.
6. The original data are stored at the following location and will be held for 10 years from the date of the study's completion.

Location of stored data: Data were stored on a password-protected computer. Back-up data were stored on an external hard drive and shared on a secure online data repository (https://Zenodo.org/DOI:10.5281/zenodo.6355501). Data will be securely kept for 10 years after the completion of the study. Deidentified data will be made public in perpetuity according to Open Science principles (29). The peer-reviewed manuscript developed from this study was shared on OpenUCT (www.open.uct.ac.za/katleho_limakatso) according to the Open Access Policy at UCT.

Romy Parker Date: 25/11/2021

4.3 Background and motivation

The results in chapters two and three indicate that the prevalence of PLP is consistently high in various parts of the world. Exposure to multiple pre-operative, peri-operative and post-operative risk factors is proposed to contribute significantly to a high prevalence of PLP. Several risk factors including persistent pre-operative pain, pre-operative depression, residual limb pain and having a lower limb amputation have been reported and consistently correlated with the onset of PLP after amputation. The high prevalence of PLP adds to the already existing burden of post-surgical complications seen in people who have undergone limb amputations.

The debilitating effects of PLP on function and health-related quality of life have previously been reported. Depression, anxiety, distorted body-image and loss of self-esteem are common problems seen in people with amputations, and these problems may be long lasting. It is hypothesised that these problems may instigate or contribute further to suicidal ideation, alcoholism, violence, and drug abuse. These dreadful complications are often overlooked, mainly because they are under-reported for various reasons including the fear of stigma (169). This raises the need for strengthening strategies for creating awareness about PLP and associated complications, and for developing guidelines for effective patient-centred management of PLP.

The first-line management for PLP is currently uncertain. Pharmacological treatments such as pregabalin, ketamine and amitriptyline are used in accordance with the National Institute for Health and Care Excellence (NICE) guidelines for neuropathic pain (170). However, systematic-review evidence has consistently shown that these treatments are marginally effective at best and show no clear benefit over placebo (23). Conversely, the evidence is promising and growing for non-pharmacological interventions including Graded Motor Imagery (GMI), mirror therapy, and limb training using augmented reality (30, 171, 172). However, variations in study designs and treatment protocols make it challenging to generate the best evidence on these treatments using systematic review and meta-analysis methods.

Systematic reviews and meta-analyses play an integral role in evidence-based practice. Evidence-based practice is the integration of individual clinical expertise with patient's values and expectations, and the best available evidence from systematic research. Systematic reviews and meta-analyses provide us with the best form of evidence on a topic of interest because their approach to data analysis is more comprehensive, rigorous, and robust compared to approaches used in other study designs. Systematic reviews are thus preferably used to reach consensus on medical practice guidelines (173).

The current NICE guidelines for the management of neuropathic pain conditions may not be suitable for PLP due to a lack of positive results for the recommended treatments. The weak evidence for pharmacological treatments and the inability to conduct meta-analyses for non-pharmacological interventions (due to use of varying treatment protocols and study methodologies) means the consensus on the best management of PLP needs to be generated using an alternative approach. The Delphi method is applicable when there is limited evidence on a specific topic of interest and recommendations could be derived from the collective subjective judgements of experts (174).

4.4 Aim

The aim of this study was to reach expert consensus and make recommendations on effective treatments for PLP in people with limb amputations.

4.5 Summary of main findings

- Twenty-seven experts participated in the study, and 20 (74%) completed the final round. The experts who completed the study were anaesthesiologists (n=3), physiatrists (n=3), psychologists (n=2), neurologists (n=2), physiotherapists (n=8), nurse (n=1) and occupational therapist (n=1).
- Fifteen of the experts who completed the study described themselves as clinician-researchers, three described themselves as full-time researchers and two described themselves as full-time clinicians.

- The experts who participated were based in Europe (n=12), Africa (n=8), Asia (n=5) and North America (n=2) at the time of the study.
- Consensus was reached on seven treatments that were considered effective for managing PLP, and on two treatments [citalopram (60%) and Pulsed Radiofrequency Stimulation (PRFS) of the dorsal root ganglion (70%)] that were considered ineffective because of a lack of scientific evidence supporting their efficacy in people with PLP.
- Graded Motor Imagery, mirror therapy and amitriptyline were endorsed by most experts because of the available supporting scientific evidence and their reported efficacy in clinical practice. Cognitive Behavioural Therapy, virtual reality training and use of a functional prosthesis were endorsed by most experts because of their reported efficacy in clinical practice. However, this group of experts indicated that there is essentially no scientific evidence supporting the use of these treatments for PLP. The rationales for endorsing sensory discrimination training were evenly distributed across the three domains.

"The content of the manuscript from which these summarised results were extracted is presented below"

4.6 Manuscript published in Physical Medicine and Rehabilitation

Title: Treatment recommendations for phantom limb pain in people with amputations: an expert consensus Delphi study**.**

Short title: Treatments for phantom limb pain in amputees.

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Sources of financial support: Start-up Emerging Researcher Award, University of Cape Town.

Acknowledgements: We thank the experts for their time and commitment to providing constructive input in this study. We thank Victoria J. Madden for her contribution in designing this study. We thank Gillian J Bedwell for reviewing and editing this manuscript.

Conflict of interest: The authors declare no conflict of interest.

Ethical approval to conduct this study was granted by the University of Cape Town, Faculty of Health Sciences, Human Research Ethics Committee (HREC ref: 355/2019).

4.6.1 Abstract

Introduction: Phantom limb pain (PLP) is common and often accompanied by serious suffering. Current systematic-review evidence suggests that recommended treatments are no more effective than placebo for reducing PLP. Given the difficulty in conducting a meta-analysis for non-pharmacological treatments and the weak evidence for pharmacological treatments for PLP, consensus on the first-line management of PLP needs to be reached using alternative methods.

Objective: To reach expert consensus and make recommendations on the effective management of PLP.

Design: A three-round Delphi design was used.

Setting: The study was conducted using e-mail and Google survey tool as main methods of communication and providing feedback.

Participants: The study included 27 clinicians and researchers from various health disciplines who are experts in PLP management.

Method: Data were collected using three sequential rounds of anonymous online questionnaires where experts proposed and ranked the treatments for PLP. A consensus was reached on the treatments that were endorsed by 50% or more of the experts.

Results: Thirty-seven treatments were proposed for the management of PLP at the beginning of the study. Consensus was reached on seven treatments that were considered effective for managing PLP, and on two treatments that were considered ineffective. Graded Motor Imagery, mirror therapy, amitriptyline, sensory discrimination training and use of a functional prosthesis were endorsed by most experts because of the available backing scientific evidence and their reported efficacy in clinical practice.

Cognitive Behavioural Therapy and virtual reality training were endorsed by most experts because of their reported efficacy in clinical practice despite indicating a dearth of scientific evidence to support their ranking. Citalopram and dorsal root ganglion pulsed radiofrequency were rejected due to a lack of relevant scientific evidence.

Conclusion: The results of this study suggest that the non-pharmacological treatments endorsed in this study may have an important role in the management of PLP.

Key words: Phantom limb pain; amputation; treatment.

1. Introduction

Phantom limb pain (PLP) – pain felt in the missing portion of the amputated limb – is a common phenomenon (175, 176). A recent systematic review and meta-analysis indicates that PLP affects approximately 64% [95% CI: 60.0 – 68.1] of people with amputations, thus making it the most common chronic pain condition in people with limb amputations (119). Phantom limb pain is associated with personal suffering, interference with general daily activities, disability, and reduced health-related quality of life (177, 178).

Previous studies have argued that PLP is driven by ectopic-impulse discharges from neuromas located in the residual limb i.e. peripheral mechanisms (98, 179). However, there are reports of persisting PLP despite the anaesthetising of the neuroma (180). In addition, PLP has been reported in congenital amputees who typically do not present with any nerve damage, and in whom the development of a neuroma is unlikely (181). This evidence suggests that peripheral mechanisms alone are not sufficient to explain PLP. Recent fMRI studies show that PLP may be maintained by maladaptive reorganization in the somatosensory and motor areas of the brain (106, 108, 111). Maladaptive reorganisation is the process whereby the adjacent cortical areas take over the functional activity of the cortical area that previously innervated the amputated limb (182). These studies suggest that treatments aimed at addressing maladaptive reorganisation in the brain may provide pain relief.

Phantom limb pain is classified as a neuropathic pain disorder in the International Classification of Diseases (ICD-11), and its pharmacological management is based on recommendations for neuropathic pain syndromes (183, 184). The National Institute for Health and Care Excellence (NICE) guidelines for neuropathic pain were developed to align the assessment and management of neuropathic pain conditions to the best available evidence and to improve the quality and appropriateness of care (170). However, current systematic review evidence suggests that three recommended pharmacological treatments (amitriptyline, duloxetine, and pregabalin) are

marginally effective in the short term, and present with various negative side-effects including nausea, vomiting, and dizziness (185). The lack of effectiveness of these treatments may be because they do not target maladaptive cortical reorganisation which has been shown to be strongly associated with the maintenance of PLP (106, 108-111, 186).

Few studies have evaluated the effectiveness of non-pharmacological treatments for reducing PLP in the last decade. However, the early evidence is promising for treatments such as Graded Motor Imagery (GMI) and mirror therapy (187, 188). Given the difficulty in conducting a meta-analysis of the non-pharmacological and interventional treatments for PLP (due to variations in study methodology, sample characteristics, treatment protocols and the levels of risk of bias) and the weak evidence for pharmacological treatments for PLP, consensus on the first-line management of PLP needs to be reached using alternative methods.

1.1 Aim

The aim of this study was to reach expert consensus and make recommendations on the effective treatments for PLP in people with limb amputations.

2. Methods

Ethical approval for this study was granted by the Faculty of Health Sciences Human Research Ethics Committee of the University of Cape Town [ref: 771/2020] This study was conducted in accordance with the ethical principles of human research outlined in the Declaration of Helsinki (189).

2.1 Research design

An expert-consensus Delphi study using three sequential rounds of anonymous online questionnaires was conducted to identify expert-recommended treatments for reducing PLP in people with limb amputations. The Delphi method is applicable when there is limited evidence on a specific topic of interest, allowing recommendations to be derived from the collective judgements of experts (174).

2.2 Research setting

The study was conducted online, using e-mail and the Google survey tool (https://www.google.com/forms) as the main methods of communication and providing feedback.

2.3 Participants

We targeted clinicians and researchers from developing and developed countries who are experts in PLP and who represented a range of health disciplines such as physiotherapy, psychology, occupational therapy, chiropractic, nursing, and medicine (e.g., general practitioners and anaesthesiologists). These disciplines are directly involved in pain management after amputations and would benefit from clinical practice guidelines and recommendations (28). Experts were identified by screening the authors of published articles on PLP and seeking peer recommendations on leaders in PLP research and clinical practice. Currently there are no standardised criteria for defining an "expert" in Delphi studies (174). However, the number of years of clinical experience and number of research publications have commonly been used as a proxy for participants' level of expertise (190). Experts were considered eligible for inclusion in this study if they were 18 years or older at the time of recruitment and could communicate in the English language. Researchers were included in the study if they were the first author of at least one publication or co-author of at least two publications on PLP. Clinicians were included if they had managed over 100 patients with PLP or had clinical experience of at least 2 years in PLP management. Only one list of criteria for either subgroup was required because the intention was to include both researchers and clinicians from different health disciplines.

2.4 Sample size determination

Currently, there are no guidelines or recommendations on the appropriate sample size for expert-consensus Delphi studies, nor a standardised definition of a small or large sample size (191). However, it is established that a minimum sample size of 10 experts who are representative of at least three disciplines is adequate for content validity (192).

In consideration of this, we targeted a purposive sample of all experts with the aim of obtaining a minimum sample of 20 experts (who were representative of at least three disciplines) at the end of the study. This sample size was chosen to ensure a fair representation of various health disciplines in this study and consequently generate a full spectrum of views on the topic (193, 194).

2.5 Recruitment

An invitation outlining the details of the study and the eligibility criteria was sent to the identified experts (n=63) via email (Appendix 10). Experts who fulfilled the eligibility criteria and agreed to participate in the study were sent an electronic link to the survey where they completed the first round of the Delphi. In addition to the purposive sampling technique, we used snowball sampling where experts initially recruited by the researcher were encouraged to invite other experts meeting the study's inclusion criteria from their professional circles to participate in this study (195). The snowball sampling technique is appropriate for finding additional experts who might not be known by the researcher (196). Furthermore, this sampling approach is thought to strengthen panellist retention, thus limiting the number of participants lost at follow up (197).

2.7 Instruments

We used a 5-point Likert scale ranging between 1 and 5 [1=Strongly agree; 2=Agree; 3=No opinion; 4=Disagree; 5=Strongly disagree] for experts to indicate their rating for statements provided during the second and third rounds of the Delphi (198). This scale is efficient and easy to use, and has been validated to facilitate the expert's rating of items in Delphi studies (28, 199).

2.8 Data collection

During the first round, each expert was sent an email asking them to propose all effective treatments for reducing PLP. Responses to the first question were used to design a standardised questionnaire (listing all the proposed treatments) that formed the basis of the second round of the Delphi.

During the second round, experts were asked to rank (on the 5-point Likert-type scale) whether each of the proposed treatments is effective for reducing PLP. We generated a variety of rationales for endorsing or rejecting each treatment, from which each expert was asked to select the rationale that best reflected their viewpoint (Table 4.1).

Table 4.1: Questions and instructions sent to participants for each round of the Delphi study

<table>
<tr><th colspan="5">First round</th></tr>
<tr><td colspan="5">1. What treatments would you propose for the management of PLP in people with limb amputations?</td></tr>
<tr><td colspan="5">Second Round</td></tr>
<tr><td colspan="5">1. Would you say these treatment approaches are effective for reducing PLP in people with amputations? Please indicate your response by selecting one number on a scale of 1-5.</td></tr>
<tr><td>1=Strongly agree</td><td>2=Agree</td><td>3=No opinion</td><td>4=Disagree</td><td>5=Strongly disagree</td></tr>
<tr><td colspan="5">2. Please select from the provided list a rationale that best reflects your viewpoint for endorsing or rejecting each treatment.</td></tr>
<tr><td>There is some scientific evidence supporting the effectiveness of the treatment</td><td>The treatment is effective in clinical practice</td><td>There is some scientific evidence supporting the effectiveness of the treatment and the treatment is effective in clinical practice</td><td>There is a lack of scientific evidence supporting the effectiveness of the treatment</td><td>The treatment is not effective in clinical practice</td></tr>
<tr><td colspan="5">Third Round</td></tr>
<tr><td colspan="5">1. Here are the results of the second round of the Delphi. Considering the group’s opinion, please review (If necessary) your ratings from the second round.</td></tr>
</table>

Treatments that were considered effective (rated 4 or 5 on a 0 – 5 Likert scale) by 50% or more of the experts were carried into the final round and the remainder were excluded. In the final round, experts were sent a summary of the responses and the list of treatments endorsed for managing PLP. Experts were asked to review their responses in light of the group's opinion, following which a final decision on endorsed treatments for PLP was reached.

3. Data analysis

Data were coded and entered into an Excel spreadsheet for analysis (200). Numerical demographic data were analysed by calculating the median and ranges. We opted for this method of analysis because of the small study sample size (201). The level of agreement on each treatment was expressed as a percentage. Consensus on each treatment was reached when 50% or more of the experts were in agreement (202). The level of consensus was presented as low (≥50% - 60%), moderate (>60% - 70%) and high (>70%) (203). The ratings of the participants who neither agreed nor disagreed with the effectiveness of the treatment were excluded in these calculations. The remaining data were synthesised descriptively.

4. Results

Twenty-seven experts participated in the study (response rate: 43%), and 20 (74%) completed the final round. Only two participating experts were recruited using snowball sampling. The experts who completed the study were anaesthesiologists (n=3), physiatrists (n=3), psychologists (n=2), neurologists (n=2), physiotherapists (n=8), nurse (n=1) and occupational therapist (n=1). Of these, 15 described themselves as clinician-researchers, three described themselves as full-time researchers and two described themselves as full-time clinicians. Full-time researchers had a median of 8 (range: 2-6) years of PLP research experience. Full-time clinicians had a median of 2 (range: 2-2) years of PLP clinical experience. Clinician-researchers had a median of 8 (range: 2-8) years of PLP clinical experience and 8 (range: 2-8) years of PLP research experience. The countries in which the experts were based during data collection are presented in Figure 4.1.

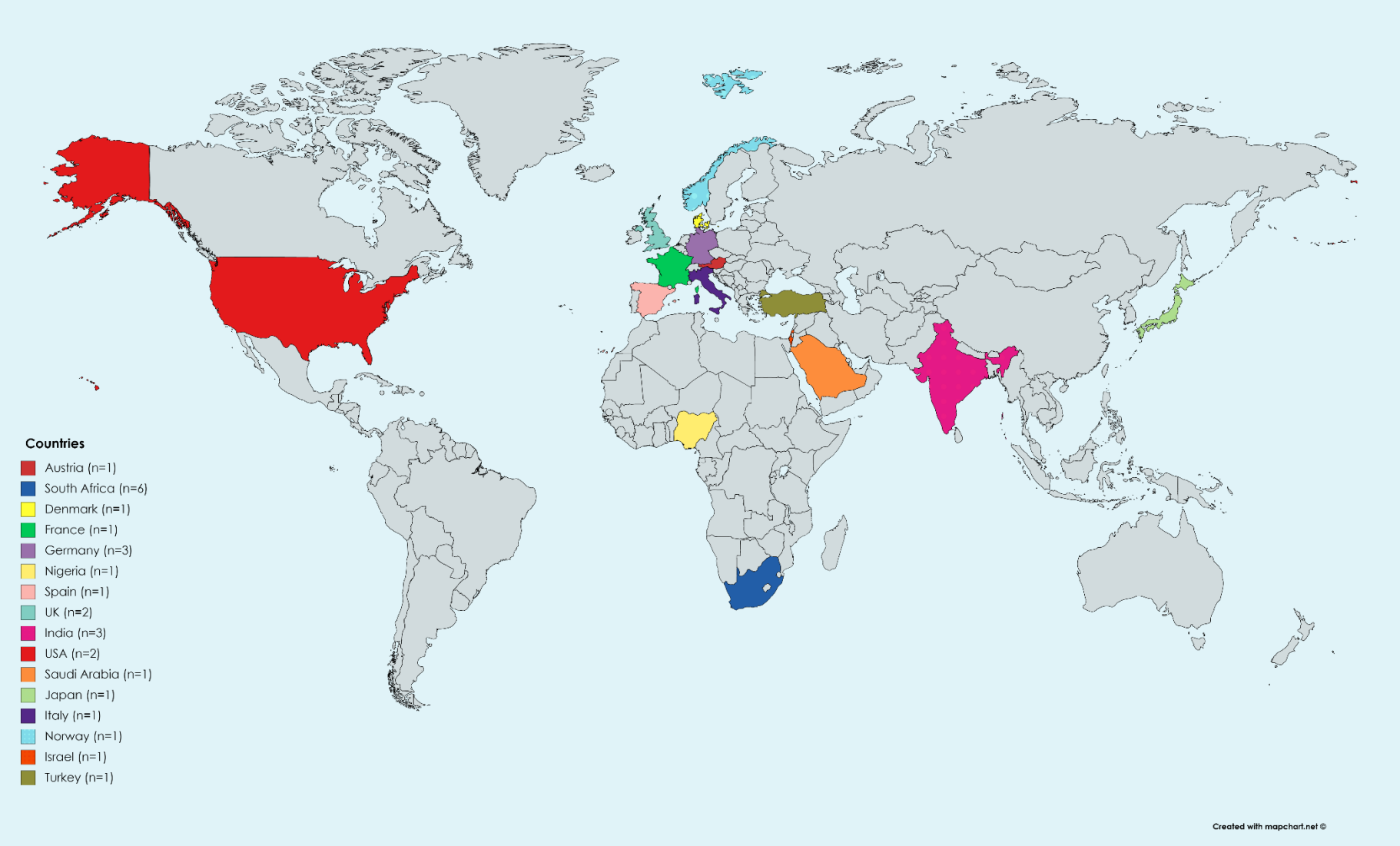

Figure 4.1: A representation of the countries in which the experts were based during data collection.

4.1 Treatments for managing PLP

Treatments proposed by this group of experts for the management of PLP are presented in Table 4.2. Thirty-seven treatments were proposed for the management of PLP at the beginning of the study. Consensus was reached on seven treatments that were considered effective for managing PLP, and on two treatments [citalopram (60%) and Pulsed Radiofrequency Stimulation (PRFS) of the dorsal root ganglion (70%)] that were considered ineffective because of a lack of scientific evidence supporting their efficacy in people with PLP. Consensus was not reached on the remaining 28 treatments. The rationales and the number of experts who indicated their rationales for supporting each treatment are presented in Table 3. Graded Motor Imagery (GMI), mirror therapy and amitriptyline were endorsed by most experts because of the available supporting scientific evidence and their reported efficacy in clinical practice. Cognitive Behavioural Therapy (CBT), virtual reality training and use of a functional prosthesis were endorsed by most experts because of their reported efficacy in clinical practice. However, this group of experts indicated that there is essentially no scientific evidence supporting the use of these treatments for PLP. The rationales for the effectiveness of sensory discrimination training were evenly distributed across the three domains (Table 4.3)

Table 4.2: Treatments proposed by experts for the management of PLP.

Proposed treatments	Percentage of experts who endorsed each treatment in round 2.	Percentage of experts who endorsed each treatment in round 3.[6]	Consensus reached? (Yes/No)	Level of consensus[7]
Non-pharmacological treatments				
Mirror therapy	75	80	Yes	High
Graded Motor Imagery	70	75	Yes	High
Cognitive Behavioural Therapy	70	75	Yes	High
Use of a functional prosthesis	70	75	Yes	High
Sensory discrimination training	60	60	Yes	Low
Virtual reality training	60	75	Yes	High

6 Endorsed = rated the treatment as effective on a 0 – 5 Likert scale.

7 The level of consensus is presented as low (≥50% - 60%), moderate (>60% - 70%) or high (>70%).

TENS[8]	45	-	No	-
Stump muscle exercises	45	-	No	-
Acceptance and Commitment Therapy	45	-	No	-
Mindfulness	40	-	No	-
Pain Neuroscience Education	40	-	No	-
Imagined limb-movement exercises	40	-	No	-
Stump massage	40	-	No	-
Post-amputation counselling	35	-	No	-
Active listening	35	-	No	-
Peripheral nerve stimulation	35	-	No	-

8 TENS= Transcutaneous Electrical Nerve Stimulation.

Targeted muscle reinnervation	30	-	No	-
Stump bandaging	30	-	No	-
Sympathetic nerve block	30	-	No	-
Left/right judgements	25	-	No	-
Dorsal root ganglion stimulation	25	-	No	-
Prosthesis electromagnetic shielding	25	-	No	-
Electromyogram biofeedback training	20	-	No	-
Progressive stump-muscle relaxation	15	-	No	-
Spinal cord stimulation	15	-	No	-
Pharmacological treatments				
Amitriptyline	50	65	Yes	Moderate

Pregabalin	45	-	No	-
Gabapentin	40	-	No	-
Morphine	35	-	No	-
Ketamine	30	-	No	-
Intraforaminal infusion of dilute lidocaine	30	-	No	-
Fluoxetine	15	-	No	-
NSAIDs	15	-	No	-
Surgery				
Peripheral surgeries	35	-	No	-
Stump surgical revision	15	-	No	-

Table 4.3: The rationales and percentage of experts who provided supporting rationale for each treatment.

Treatment	The percentage of experts who provided a rationale for supporting each treatment			Total percentage of experts who provided supporting rationale for treatment
	There is some scientific evidence supporting the effectiveness of the treatment	The treatment is effective in clinical practice	There is some scientific evidence supporting the effectiveness of the treatment and the treatment is effective in clinical practice	
Mirror Therapy	21.1	15.8	57.9	94.8
Graded Motor Imagery	26.3	26.3	42.1	94.7
Cognitive behavioural therapy	5.3	36.8	36.8	78.9
Sensory discrimination training	21.1	21.1	26.3	68.5
Virtual reality treatment	10.5	36.8	21.1	68.4
Use of functional prosthesis	22.2	16.7	27.8	66.7
Amitriptyline	23.5	5.9	35.3	64.7

5. Discussion

Considering the lack of robust evidence on the management of PLP, we used a Delphi approach to reach expert consensus on the effective treatments for PLP in people with limb amputations. Expert consensus was reached on seven treatments that were considered effective for reducing PLP, and on two treatments that were considered ineffective. Treatments which were endorsed in this study are: mirror therapy; GMI; CBT; virtual reality training; sensory discrimination training; amitriptyline; and a use of a functional prosthesis. An important consideration is that the experts included in this study were highly experienced and part of a well-representative panel of health care professionals involved in the management of patients with PLP. The representation of a variety of pain-treatment classifications in this study indicates an interdisciplinary approach to the management of PLP (204). To the best of our knowledge, this is the first Delphi study to reach expert consensus on the effective treatment strategies for PLP in people with amputations.

Six of the seven treatments endorsed by experts in this study are non-pharmacologically based. This is perhaps not surprising because of the available strong evidence negating the efficacy of currently available pharmacological treatments in managing PLP, as well as the growing evidence of the positive effects of the non-pharmacological interventions endorsed in this study (185, 205). The results of this study support the role of non-pharmacological treatments in PLP management.

A high level of expert-consensus was reached on mirror therapy. Mirror therapy is a movement representation technique that uses the reflection of voluntary movements of the intact limb to provide an illusion that movement of an amputated limb was performed without pain or hindrance (206). Mirror therapy is proposed to address maladaptive cortical reorganisation in the corresponding primary motor cortex. The maladaptive cortical reorganisation is theorised to trigger a protective pain response because of a mismatch between movement intent, proprioception, and visual feedback from the amputated limb (108, 109, 111, 207).

The visual feedback provided by mirror therapy appears to be a key component in reducing PLP, since pain reductions are not seen when limb exercises are conducted with a covered mirror or without a mirror (172, 208-210). It is hypothesized that the firing of mirror neurons while observing movement provides the perception of movement in the amputated limb, consequently resolving the conflict between movement intent, proprioception, and visual feedback (211, 212). A substantial amount of the literature on mirror therapy is based on case studies, most of which show positive outcomes (213-218). The most recent systematic review on mirror therapy identified four controlled trials and all reported statistically significant improvements in PLP (219). However, only one of these showed clinically significant reductions in pain (of 3 or more points on a 0-10 VAS) at the conclusion of treatment (220). Interestingly, a three-arm multicentre randomized controlled trial published after this review did not show a significant difference between mirror therapy and sensorimotor exercises (without a mirror) in reducing PLP severity (172). However, mirror therapy showed superior effects in reducing the duration and frequency of PLP episodes. Further, a subgroup analyses in that study revealed that women, and participants experiencing telescoping of the phantom limb and those who felt their limbs stuck in an unnatural position had significant reductions in PLP severity compared to those without these characteristics. This suggests that some patients are more likely to benefit from mirror therapy than others. One common reason is that some patients struggle with the embodiment of the mirror image (221). For example, one patient said, “I perceived my phantom leg behind the mirror as being strutted apart and this didn't match with the mirror image. I rather had the feeling of having 3 legs.” (221). In consideration of this evidence, efforts should be focused on identifying the characteristics of patients suitable for mirror therapy, who are most likely to benefit from the treatment.

The expert-recommendations provided in this study align with the supporting evidence and reported effectiveness of mirror therapy in clinical practice. However, it is worth cautioning that a few patients may experience increased pain severity following mirror therapy (218, 222).

Initiating mirror therapy prior to progressively addressing the maladaptive changes in the sensory and pre-motor cortices is theorised to trigger a protective pain response that results in increased pain severity during or after treatment (223). Based on the theory of alterations in the sensory, pre-motor and motor cortex representation of the amputated limb contributing to PLP, GMI may be a viable alternative with a lower risk of pain exacerbation.

Graded motor imagery, a three-step programme that purportedly addresses maladaptive changes in the sensory, pre-motor and primary motor cortices using a graded sequence of left/right limb judgements, imagined limb movements and mirror therapy (223), was also supported by a high level of expert-consensus. Maladaptive changes in these cortical areas have been positively associated with pain severity in people with limb amputation (108). Targeting these changes using mirror therapy (224) and mental imagery (109), both components of the GMI programme, has been shown to result in pain reduction. It is hypothesised the progressive activation of the somatosensory and motor networks using GMI may prevent the triggering of a pain response reported by some patients undergoing mirror therapy only (223). It would be valuable to determine whether there is a significant difference in the efficacy of GMI and mirror therapy. However, to date, there is no published study comparing these treatments. The only three randomised controlled trials on GMI for PLP showed clinically significant pain reductions at the end of treatment and at 6-month follow up (223, 225, 226). The high level of expert consensus in this Delphi study and the promising body of literature on GMI provide the basis for recommending GMI for managing PLP. However, further rigorous studies with a larger sample size are required to build upon the existing literature.

Virtual reality training is another treatment that utilises visuo-proprioceptive feedback from a virtual reality headset to manage PLP (227) which had high support from the expert panel. Virtual reality training may be preferable over traditional mirror therapy because of its utility during functional tasks (e.g. walking) (227). In addition, virtual reality training enables patients to perform unsynchronized limb movements which are realistic and may provide richer somatosensory

feedback essential for reducing pain (228). The study of virtual reality in people with PLP is in its infancy, and the quality of evidence for this intervention is low; the evidence is based mostly on case-control and case-series studies, and no RCTs could be found (229). Another study showing promising results investigated the efficacy of phantom motor executions facilitated by machine learning and augmented reality (171). The study showed significant reductions in pain severity, interference of pain with ADL and sleep, and medication intake. Currently, there is no standardised protocol for virtual reality and its long-term effects are unknown. However, the high level of expert consensus for the effectiveness of virtual reality training in clinical practice may warrant further studies to elucidate the effectiveness of virtual reality training in PLP management.

We found it interesting that a high level of expert consensus was reached on CBT because of its reported efficacy in clinical practice, although the experts indicated a dearth of scientific evidence to support their ranking. Indeed, we could not find any published studies that examined the efficacy of CBT for reducing PLP in people with amputations. However, there is adequate evidence to support the use of CBT in the management of other chronic pain conditions (230-234). At this time, the mechanisms by which CBT reduces pain are unclear (234). It appears that the treatment principles of CBT are in line with the Neuromatrix theory of pain, that emphasises the role of cognitive, affective and behavioural influences in the development and maintenance of chronic pain (235). Cognitive Behavioural Therapy generally improves clinical outcomes by modifying dysfunctional emotions, thoughts and behaviours (236). Given that amputees with PLP often present with risk factors such as depression, feelings of helplessness, and debilitating passive coping strategies (7, 82), it is likely that CBT targets these factors with a secondary improvement in PLP severity. The precise mechanism of action needs to be confirmed in future studies.

The use of a functional prosthesis also had high support for its reported efficacy in clinical practice despite the experts indicating a lack of scientific evidence to support the use of the treatment.

However, unlike CBT, the benefits of using a functional prosthesis that provides proprioceptive feedback to the residual limb during functional activities (e.g. walking, lifting a cup) have been repeatedly documented in the last decade (105, 237-242). The literature shows that using a functional prosthesis is more effective than a cosmetic prosthesis for improving pain and function (104, 105, 237, 243-246). These findings suggest that ongoing stimulation, muscular training, and visual feedback provided by a functional prosthesis may have an important role in addressing the mechanisms proposed to maintain PLP (105, 242). In fact, a mechanistic neuroimaging study (247) revealed cortical reorganisation in patients after starting to use a functional prosthesis which provided somatosensory feedback. The neuroimaging revealed a normalization of the cortical representation of the amputated limb which was positively associated with a reduction in PLP (247). Furthermore, patients using prostheses with proprioceptive feedback reported improved embodiment (feeling of bodily ownership and control) of the prosthesis. The improved embodiment is thought to be essential in the improvement of PLP and function after limb amputation (104, 246). The high level of expert consensus for the use of a functional prosthesis in this study is in line with the positive findings in the literature. These findings provide a basis for recommending the use of a functional prosthesis which provides somatosensory feedback in the rehabilitation of people with amputations.

Sensory discrimination training is the only non-pharmacological treatment that had a low level of expert consensus on its effectiveness for reducing PLP in this study. Sensory discrimination training is a technique that uses fabrics of different softness/harshness (e.g. cotton vs velcro) to provide sensory input to areas adjacent to the distal part of the residual limb (248, 249). The treatment is proposed to normalise cortical reorganisation by addressing a mismatch between the brain's sensory output and sensory feedback from the amputated limb (206, 250-252). The pain-relieving effects of sensory discrimination training have been reported in only three available studies (248, 249, 253). Therefore, a definitive conclusion on the efficacy of this treatment cannot be drawn due to a lack of evidence.

However, the results of a recent study (253) suggest that home-based sensory discrimination training may be a useful supplement to already existing therapies, such as GMI and mirror therapy.

The appropriateness of pharmacological treatments in the management of PLP have been placed in doubt because they are typically ineffective (254). This is possibly reflected by amitriptyline being the only pharmacological treatment endorsed in this study despite almost half of the participant in this study being prescribers. Although amitriptyline is commonly used in the management of PLP, studies investigating its efficacy for reducing PLP are essentially non-existent (255). The most recent systematic review on pharmacological treatments for PLP identified only one relevant study (185). The study investigated amitriptyline (titrated up to 125mg/day for 6 weeks) versus active placebo (benztropine mesylate) for reducing chronic PLP (PLP persisting for more than three months) (255). The results showed that amitriptyline was no more effective than placebo for reducing chronic PLP. Overall, the rating for the effectiveness of amitriptyline for reducing PLP in this study indicates the dissonance between clinical practice guidelines and the available scientific evidence for PLP (256). It is worth noting that two treatments (citalopram and PRFS of the dorsal root ganglion) had moderate – high level expert consensus *rejecting* their efficacy for reducing PLP. Pulsed radiofrequency stimulation of the dorsal root ganglion is an invasive procedure with known adverse effects such as neurological fallout and increased pain (257). Considering that there are safer and effective interventions for PLP, it may not be ideal to use this treatment in a vulnerable group of people with amputations. Likewise, considering that citalopram has similar mechanisms to those of amitriptyline (i.e. inhibiting the re-uptake of serotonin at the synapse), it is likely that it may not yield clinically significant improvements in PLP (258).

6. Limitations

A withdrawal of seven experts after the first round may have been precipitated by the requirement to comment on treatments not within their scope of practice. This may have led to a non-response bias, in that, experts who did not complete the study may have different viewpoints from those who

completed the study. However, the descriptive analysis of responses generated in Round 1 showed no outlier views. The rating of treatments in this study could have been improved by clarifying the contents of the intervention so that the experts hold the same understanding on each treatment. We generated a variety of rationales for endorsing or rejecting each treatment, from which each expert selected the rationale that best reflected their viewpoint. We acknowledge that this might have limited the experts to fully express their opinions on the efficacy of each treatment. It would have been valuable to report on treatments endorsed by each profession. However, we could not perform subgroup analyses by profession because of the small sample size in each professional category. The level of expertise that informed the rating of treatments (pharmacological *vs* non-pharmacological) varied between experts. Therefore, this variation may have influenced the results. We included option three of the Likert scale ('No opinion') for experts to select if they had insufficient knowledge to inform their decision on a specific treatment. Using the option 'no expertise in this area' instead would have provided more clarity. Injectates (e.g. phenol, botulinum & etanercept) were not proposed in this study. This may have limited the experts' opinion on the efficacy of these treatments for reducing PLP. The list of effective treatments in this study was generated based on the contributions of health care professionals only, who may not always prioritise the elements of treatment that are important to the patient (259). Therefore, relevant future studies should make efforts to include patients in the generation of treatment guidelines and recommendations. Lastly, this study does not provide any suggestions on the dosage and methods of administration as this was not the aim. Follow-up studies are indicated to explore dosage recommendations.

7. Conclusion

The results of this study suggest that non-pharmacological and non-interventional treatments: GMI; mirror therapy; CBT; virtual reality training; use of a functional prosthesis; and sensory discrimination training may have an important role in the management of PLP.

There is evidence showing that these endorsed treatments reduce PLP by addressing neural mechanisms in the brain, emphasizing the dominant role of cortical reorganisation in PLP. We found it interesting that experts proposed CBT as an effective treatment for PLP despite a paucity of scientific evidence to support its use in people with PLP. Given that pain is a biopsychosocial construct, it might be beneficial to examine the effects of psychological treatments and their specific mechanisms for reducing PLP. Some of the experts in this study provided additional feedback suggesting that most of the presented treatments have a meaning effect and thereby may work directly through meaning responses or that their effect may be augmented by a meaning response. Proving that a treatment has active efficacy (efficacy beyond meaning), requires the use of valid shams, which are often expensive, and sometimes impossible. Therefore, we recommend that future studies must fully engage with developing valid sham treatments to explore the direct effect of the treatment and the meaning response. In this study, expert consensus was reached to support the use of GMI, mirror therapy, CBT, virtual reality training, use of a functional prosthesis, sensory discrimination training and amitriptyline in the management of PLP. The evidence on treatments for PLP is lacking, and further research on the treatments recommended based on their clinical efficacy is warranted.

Chapter 5: Care priorities for patients with lower limb amputations: a patient Delphi study.

5.1 Declaration from author and co-authors:

5.1.1 Declaration from author

The following co-authors contributed to the manuscript: Tholoana Limakatso and Romy Parker. The contribution of the authors for this manuscript is as follows: Katleho Limakatso conceptualised the study with input from Romy Parker. Katleho Limakatso recruited participants. Katleho Limakatso collected and curated data. Katleho Limakatso and Tholoana Limakatso conducted the formal analysis of the data with input from Romy Parker. Katleho Limakatso wrote the original draft of the manuscript. All the authors reviewed and edited the manuscript and approved it for submission for examination.

Extent of contribution:

- Katleho Limakatso: 75%
- Tholoana Limakatso: 10%
- Prof Romy Parker: 15%

_____

Signed by Katleho Limakatso Date: 25/11/2021

5.1.2 Declaration of co-authors

Undersigned hereby certifies that:

1. The above declaration correctly reflects the nature and extent of the candidate's contribution to this work and the nature of the contribution of each of the co-authors.
2. They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise.
3. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication.
4. There is no other author of the publication according to these criteria.
5. Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit.
6. The original data are stored at the following location and will be held for 10 years from the date of the study's completion.

Location of stored data: Data were stored on a password-protected computer. Back-up data were stored on an external hard drive and shared on a secure online data repository (https://Zenodo.org/DOI:10.5281/zenodo.6355501). Data will be securely kept for 10 years after the completion of the study. Deidentified data will be made public in perpetuity according to Open Science principles (29). The peer-reviewed manuscript developed from this study was shared on OpenUCT (www.open.uct.ac.za/katleho_limakatso) according to the Open Access Policy at UCT.

Romy Parker Date: 25/11/21

Tholoana Limakatso Date: 25/11/21

5.2 Background and motivation

The global incidence of lower limb amputations (LLAs) is high. Approximately 455 per 100 000 people undergo LLAs annually (125). Based on our results presented in Chapter 2, an estimated 64% of these may experience PLP in addition to a plethora of debilitating consequences of amputations including depression, loss of function and income, and suicidal ideation (260). In consideration of this, efforts have been made towards optimising the care of patients with amputations and to restore them to their previous level of function (261). However, the consistently high levels of disability and low treatment satisfaction scores in people with amputations suggests that these efforts are insufficient (261).

The lack of success in effectively managing patients with amputations is possibly an artefact of a mismatch of care priorities between patients and healthcare providers. The current treatment guidelines for people with amputations primarily address their biomedical needs and overlook various psychosocial and economic determinants of disability in this patient group (262). In addition, the guidelines were generated by healthcare professionals who may not be aware of individual patient needs at a specific time point. Another important consideration is that care priorities are context-specific (263). Therefore, guidelines generated in developed parts of the world may not be suitable for people living in less developed areas. The discrepancy in contexts raises need to develop patient-derived guidelines addressing biopsychosocial needs that contribute towards the recovery and improved functioning of people with LLAs living in developing countries.

Involving patients in clinical decision making promotes patient-centred care that facilitates a partnership between the patient and healthcare provider and acknowledges the patient as the expert of their ailment, and takes into consideration their values and treatment preferences (264). It has been shown that involving patients in clinical decision making improves adherence to treatment and yields good clinical outcomes including improved patient satisfaction with clinical care (265, 266). Based on these positive findings, we conceived the current study with the aim of generating patient consensus on care priorities for African people with LLAs.

5.3 Aims and objectives

5.3.1 Aim

The aim of this Delphi study was to generate patient consensus on care priorities for people who have undergone LLAs.

5.3.2 Objectives

- To generate consensus on care priorities for people who have undergone a LLA in the previous year.
- To generate consensus on care priorities for people who have undergone LLAs more than a year ago.
- To understand the reasons the participants identify for needing help with each of the short- and long-term care priorities after LLA

5.4 Summary of main findings

- The study included 20 participants [Male (n=16); Female (n=4)] with a median [IQR] age of 65.5 [50 – 71].
- All the participants had lower limb amputations, with most having amputations above the knee (55%).

- The participants had undergone amputation surgery a median of 16 [11.5 – 31] months prior to the time of recruitment. The participants who had been amputated for less than a year (n=54) had undergone surgery a median of 7 [1 – 11] months, and those who had been amputated for a year or more (n=75) had undergone surgery a median of 21 [12 – 32].
- The indications for amputations were complications due to uncontrolled diabetes, peripheral vascular diseases, infection, and trauma.
- All the participants were unemployed, and most presented with comorbidities including diabetes, hypertension, and hypercholesterolaemia.
- Consensus was reached on 24 short-term care priorities and 12 long-term care priorities in the biomedical, psychological and social domains.
- Rationales for endorsing the care priorities generated three themes: (1) Mental health, and psychological and spiritual well-being, (2) preparedness, and (3) participating in life, with respect and dignity.

"The manuscript presented below has been prepared for submission to Pain Medicine"

5.5 Manuscript prepared for publication in Pain Medicine

Title: Care priorities for patients with lower limb amputations: a patient Delphi study.

Running head: Care priorities after lower limb amputations.

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Research category: Original article

Funding sources: Start-up Emerging Researcher Award, University of Cape Town.

Conflict of interest: The authors declare no conflict of interest.

Significance: This is the first study to report on the short- and long-term care priorities of people with lower limb amputations. Understanding patients' priorities for care will enable health care professionals to provide patient-centred treatment while optimising recovery from amputation surgery, and reducing suffering and disability in people with amputations. This may result in better adherence to treatment and improved treatment outcomes that may contribute to a higher health-related quality of life.

5.5.1 Abstract

Background: Clinical practice guidelines for the rehabilitation of people with lower limb amputations (LLAs) have previously been published. However, the formulation of these guidelines was based on the contribution of health care professionals only, who may not always prioritise the elements of care that are important to the patient at a specific time-point. To date, there are no published literature on patient-generated care priorities for people with LLAs.

Methods: A three-round Delphi study was conducted using a convenience sample of 20 participants who had undergone LLAs at Groote Schuur Hospital. The participants proposed and ranked the care priorities for people with LLAs. Consensus on each care priority was generated when the interquartile range was <1, indicating an agreement of more than 50%. A sub-sample of 11 participants was randomly chosen from 20 participants and interviewed to provide rationales for their ranking of each care priority. Qualitative data were analysed using thematic analysis.

Results: Consensus was reached on 24 short-term care priorities and 12 long-term care priorities. The rationales for endorsing each of the care priorities generated three themes: preparedness; mental health, and psychological and spiritual well-being; and participating in life, with respect and dignity like everyone else.

Conclusion: Our results highlight the significance of improving patient access to education and planning support prior to undergoing limb amputations. In addition, they indicate the importance of optimising post-amputation rehabilitation programmes that will enable people with amputations to participate in meaningful life roles that provide them with purpose, dignity, and self-respect. The knowledge of care priorities revealed in this study may promote effective patient-centred care and strengthen patients' adherence to treatment and improve clinical outcomes.

1. Introduction

Lower limb amputations (LLAs) are the most commonly performed type of amputation surgery worldwide (267). Approximately 455 per 100 000 people undergo LLAs annually (125). The most common reason for LLAs in developed countries is peripheral vascular disease (268). In developing countries, however, common reasons for LLAs are trauma, infection or complications of uncontrolled diabetes (269). Lower limb amputations are associated with adverse psychological, emotional and functional effects that contribute to a poor health-related quality of life (152).

Clinical practice guideline for the rehabilitation of people with LLAs was recently published (270). The purpose of this guideline is to provide clinicians involved in the rehabilitation of people with LLAs with an evidence-based framework for assessment and management. However, this guideline was formulated based on the contributions of health care professionals only, who may not always prioritise the elements of treatment that are important to the patient (259). In addition, the process involved in formulating this guideline risks disregarding the principle of patient-centeredness, which recognises a patient as an integral member of the healthcare team involved in clinical decision-making (271).

The growing evidence indicates that patients may not receive the treatment they need or want as a result of not being involved in clinical decision-making (25). For example, a recent study revealed a mismatch in post-surgical care priorities between patients and health care providers (272). A mismatch between the treatment priorities of the patient and health care professionals is concerning and might result in poor adherence to treatment and rehabilitation outcomes and eventually, disability (273).

In recent years, strategies have been implemented to promote the involvement of patients in healthcare decision-making. The National Institute of Care and Excellence (NICE) guidelines on shared decision-making encourage the involvement of patients in decision-making by recognising them as "experts with unique knowledge of their own health, preference for treatment and outcomes" (274, 275). The benefit of involving patients in decision-making is that health professionals will have a better understanding of what is important to the patient at a specific time-point (276). In addition, it will promote the collaborative design of the treatment plan specific to the needs of the patient.

We conceived this study with the aim of generating patient consensus on care priorities for people who have had LLAs for a year or less and for those who have had LLAs for more than a year.

2. Methods

Ethical approval for this study was granted by the Faculty of Health Sciences Human Research Ethics Committee of the University of Cape Town [ref: 066/2020]. Approval to conduct the study at Groote Schuur Hospital was sought from and granted by the hospital's management

2.1 Study design

A modified three-round patient Delphi study was conducted to generate consensus on treatment priorities for people with LLAs. The Delphi design allows recommendations to be derived from the collective judgements of participants and allows participants to anonymously share their opinions and work towards a mutual agreement on a topic of interest (28, 277). This allows participants to contribute to the discussion equally, preventing participants with strong personalities from controlling the discussion and eventually the outcome (174).

2.2 Research setting

This study was undertaken at Groote Schuur Hospital - a tertiary-level academic hospital based in Cape Town, South Africa.

2.3 Recruitment

We recruited the participants for this study from a pre-existing ethics-approved database held by the acute care surgical unit [Acute care surgery online database- HREC 020/2018; Valid until 30 Sep 2021]. This registry includes patients who have undergone limb amputations and provided consent to be contacted for research purposes. The population of interest were people with LLAs. The sampling frame was adults (18 years or older) who have undergone LLAs at Groote Schuur Hospital between 2018 and 2021, and can speak, read and write in the English, isiXhosa or Afrikaans language. This sample is broadly demographically representative of people living in the greater Cape Town area. In addition, the sample was chosen because of its expertise (experts by experience). The patients have a personal experience of living with LLA and were likely to provide valuable insight into care priorities for people with LLAs. The names and contact details of patients who had undergone limb amputations between January 2018 (when the registry was initiated) and April 2021 were retrieved and entered into an excel spreadsheet in date order from the first surgery performed in 2018 to the last surgery performed in April 2021. The list was then rearranged using a random sequence generator. Patients were contacted telephonically starting with the first allocated number to inform them (in the language they comprehend best) about the study and to invite participation. Those who verbally consented to participate in the study were screened for eligibility against the inclusion/exclusion criteria. We included adults who had undergone surgical or traumatic lower limb amputations between January 2018 and April 2021 at Groote Schuur Hospital, and were able to speak and write in English, isiXhosa or Afrikaans - the most commonly spoken languages in Cape Town.

Patients were excluded if they had auditory or speech impairments in such a way that they were unable to hear even with a use of a hearing aid or speak clearly. In addition, we excluded patients who did not arrive at the hospital on the day of data collection.

2.4 Sample size determination

Currently, there are no recommendations on the appropriate sample size in patient Delphi studies, nor is there a standardised definition for a small or large sample (278). This study used a theoretical saturation sampling technique where data collection was terminated when an additional participant could not provide any new insight into the research question (279). Several studies have shown that thematic saturation is often reached after interviewing 20 participants (280-282). In consideration of this, we initiated data collection with a convenience sample of 20 participants. We considered the sample size sufficient if the 20th participant did not provide any new insight to the research question. In a case where the initial sample size was deemed insufficient, we planned to evaluate the results and invite additional participants until thematic saturation was reached.

2.5 Outcome measures

A 5-point Likert scale [1=Strongly disagree; 2=Disagree; 3=No opinion; 4=Agree; 5=Strongly agree] was used by participants during the second and third rounds of the study to anonymously indicate their level of agreement/disagreement with the importance of each care priority (198).

2.6 Procedure

Data were collected by the research assistant who is fluent in the English, isiXhosa and Afrikaans languages and not involved in the treatment of people with amputations. Data collection took place during the COVID-19 pandemic, therefore, on the day of data collection, each participant was provided with a surgical mask and had their hands sanitised before entering the research venue and physical distancing was ensured within the venue. Participants were reimbursed ZAR100 for transport. Transport was organised via dial-a-ride transport services (http://disabilityinfosa.co.za) for participants who did not have independent means of transportation.

Each participant was further remunerated ZAR100 for their participation in the study. An additional ZAR50 was given to the participants who took part in the qualitative study as this participation entailed additional time.

On arrival, the participants were welcomed into the research venue and seated around a table (at least 1 metre apart) where the research assistant reminded them about the purpose of the study and asked them to complete the informed consent (Appendix 12) and patient demographic questionnaire (Appendix 13). Each participant was then given a sanitised pen and a piece of blank A4-size paper to use throughout the study. During the first round, the research assistant verbally asked the participants to anonymously write (based on their own opinion) a list of care priorities after undergoing LLAs. Participants were asked to provide their opinion on two themes: short-term treatment priorities (one year or less after amputation) and long-term treatment priorities (more than a year after amputation) (Figure 5.1: Questions 1 & 2). This round lasted for approximately 45 minutes. The research assistant reviewed the responses with the participants (in a group) to ensure agreement on their meaning. The reviewed responses from the first round were collected by the research assistant and entered by the researcher (who was in the same venue) into an Excel spreadsheet to design a standardised questionnaire with a list of short- and long-term treatment priorities after LLA surgery. Meanwhile, the participants were given a 30-minutes tea break during which the research assistant served them healthy refreshments. Thereafter, the research assistant provided each participant with a printed copy of the amalgamated questionnaire and verbally asked them to anonymously indicate their level of agreement/disagreement with the importance of each care priority on a 5-point Likert-type scale described above (Figure 5.1: Questions 3 & 4). This round lasted for approximately 45 minutes. The responses from the second round were collected by the research assistant and entered by the researcher into the Excel spreadsheet for analysis. Meanwhile, the participants were given a 30-minute tea-break during which the research assistant again served healthy refreshments. Care priorities endorsed (i.e., rated 4 or 5 on 0 – 5 Likert scale) by more than

50% of the participants were carried into the final round. The rest of the items were excluded. In the final round, the research assistant provided participants with a printed summary of group-level responses from the second round and verbally asked them to reconsider their ranking of each care priority if necessary (Figure 5.1: Question 5).

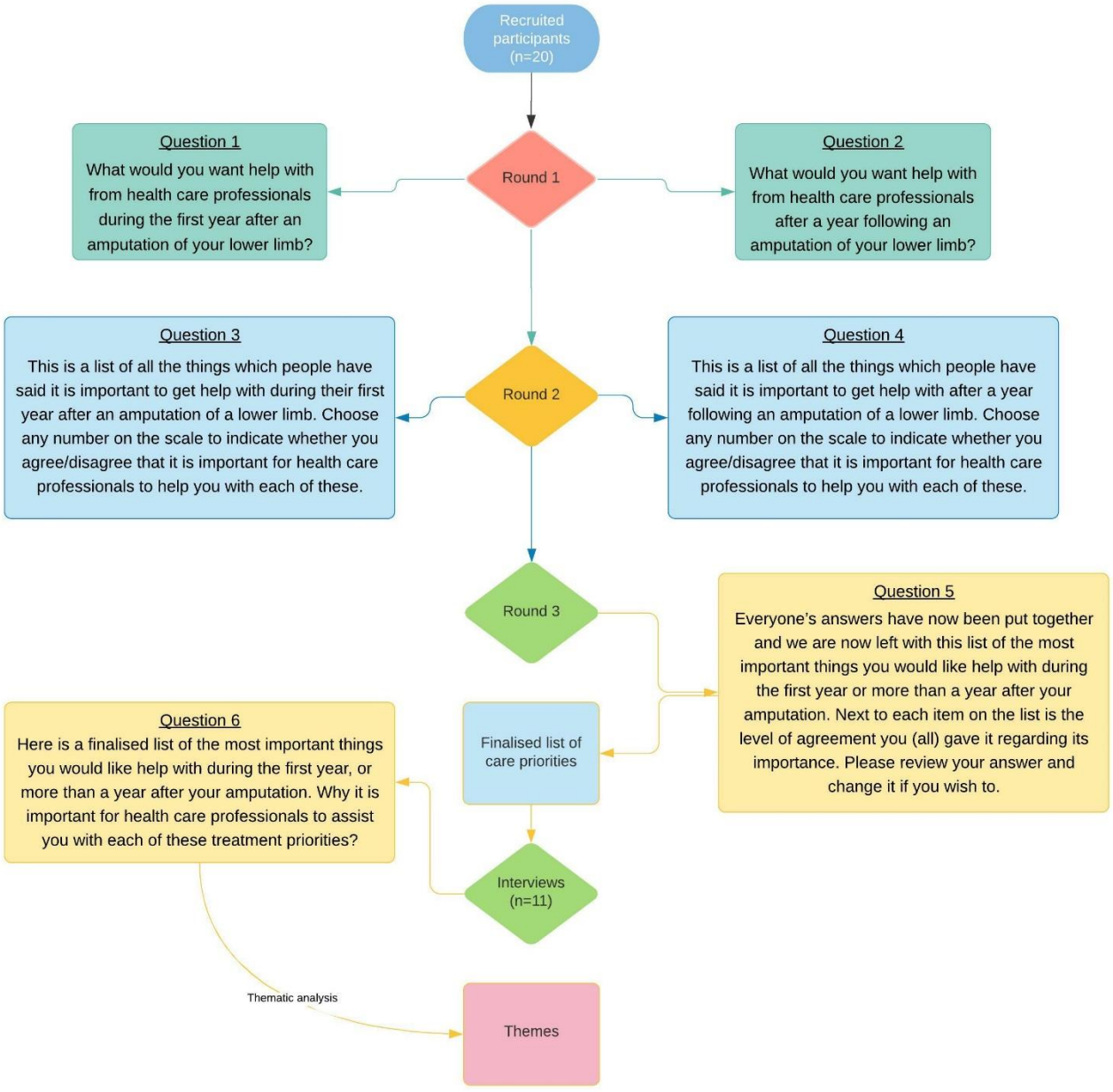


Figure 5.1: The flow-chart illustrating the procedure for data collection.

Thereafter, final consensus was reached on short- and long-term care priorities endorsed by more than 50% of the participants. The finalised list of care priorities was clustered into biomedical, psychological and physiological care priorities. A sub-sample of 11 participants (from those who completed the study) was selected using a computerised random number generator to take part in the qualitative study.

2.7 Procedure for the interviews

The interviews were conducted individually, with each participant attending a private, one-on-one session with the research assistant. The research assistant provided the participant with a questionnaire listing the identified short- and long-term treatment priorities from the Delphi. The participant was asked to explain why they think it is important for health care professionals to assist them with each of the short- and long-term treatment priorities on the finalised list (Figure 1: Question 6). Each interview lasted approximately 30 minutes. The interviews were audio recorded. The audio recordings were curated in preparation for data analysis.

2.8 Analysis

Data were analysed by calculating the interquartile ranges from the responses provided for each care priority during the second and third rounds of the Delphi. Consensus on each care priority was indicated by an agreement of more than 50% (202). The level of consensus on each care priority was presented as weak (≥50% – 60%), moderate (>60% – 70%) or strong (>70%). These cut-off points are recommended in the methodological criteria for defining consensus in Delphi studies (203). Qualitative data were analysed using exploratory thematic analysis as described by Braun and Clarke (283). The reflexive and subjective nature of qualitative data suggests that its analysis is influenced, to some degree, by researchers' biases, views, and opinions (284). In consideration of this, two reviewers independently transcribed audio data into text. Reviewer one is an African male physiotherapist with a special interest in chronic pain and patient centred rehabilitation, and reviewer two is an African female social worker with a special interest in social development and

public participation in policy design and implementation. Transcribed data were read several times to identify similar phrases and ideas, which were then assigned a code by each independent reviewer. The reviewers then compared their results and grouped codes with similar meaning to develop main themes. Subthemes were generated where extensive data were available on a particular theme, following which meaning was derived to address a research question. We ranked the importance of the themes based on the number of care priorities identified within each theme.

3. Results

The study included 20 participants [Male (n=16); Female (n=4)] with a median [IQR] age of 65.5 [50 – 71] (Table 5.1). All the participants had lower limb amputations, with most having amputations above the knee (55%). The participants had undergone amputation surgery a median of 10 months [11.5 – 31] prior to the study. The indications for amputations were complications due to uncontrolled diabetes, peripheral vascular diseases, infection, and trauma. The participants had attended school up to a median of grade 10 [8 – 12]. All the participants were unemployed, and they presented with comorbidities including diabetes, hypertension, hypercholesterolaemia.

Table 5.1: A summary of the demographic characteristics of the participants (n=20).

Variable	Measure
Sample size [n (%)]	
All the participants	20 (100)
Male	16 (80)
Female	4 (20)
Age [median (IQR)]	
All the participants	65.5 (50 – 71)
Male	65.5 (50 – 71)
Female	58.5 (49.5 – 66.5)

Indication for amputation [n (%)]	
Infection	7 (35)
Peripheral vascular disease	6 (30)
Diabetic complications	4 (20)
Trauma	3 (15)
Level of amputation [n (%)]	
Above knee amputation	11 (55)
Below knee amputation	9 (45)
Months since amputation [median (IQR)]	
All the participants	16 (11.5 – 31)
Comorbidities [n (%)][9]	
Diabetes	12 (60)
Hypertension	10 (50)
Hypercholesterolaemia	9 (45)
Peripheral vascular disease	6 (30)
Highest grade of education [median (IQR)]	
All the participants	10 [8 – 12]
Employment status [n (%)]	
Unemployed	20 (100)

3.1 Care priorities

The short- and long-term care priorities for the participants with lower limb amputations in this study are presented in Table 5.2 and Table 5.3, respectively. Twenty-five short-term care priorities and 13 long-term care priorities were proposed at the beginning of the study. Consensus was

[9] The proportion of patients with comorbidities does not add up to 100% because some patients had more than one comorbidity.

reached on 24 short-term care priorities and 12 long-term care priorities. From these, strong consensus was reached on 22 short-term and 11 long-term care priorities in the biological, practical, psychological and spiritual domains.

Table 5.2: Short-term care priorities for people with lower limb amputations (n=20).

Proposed care priorities	Percentage (%) of participants who endorsed each treatment in round 2.	Percentage of participants who endorsed each treatment in round 3.	Consensus reached? (Yes/No)	Level of consensus[10]
Biomedical				
Phantom limb pain management	62	71.4	Yes	Strong
Residual limb pain management	95.2	100	Yes	Strong
Low back pain management	85.7	81	Yes	Strong
Residual limb tremors	57.1	57.1	Yes	Strong
Physical rehabilitation	95.2	100	Yes	Strong
Getting and using a prosthetic leg	85.7	95.2	Yes	Strong
Getting and using a wheelchair	95.2	85.7	Yes	Strong

10 The level of consensus is presented as weak (≥50% - 60%), moderate (>60% - 70%) or strong (>70%).

Getting and using crutches	62	66.7	Yes	Moderate
Psychological and Spiritual				
Post-amputation depression	95.2	95.2	Yes	Strong
Pre-amputation education	95.2	85.7	Yes	Strong
Post-amputation education	76.2	81	Yes	Strong
Stress management	62	57	Yes	Weak
Sleep management	81	95.2	Yes	Strong
Counselling for family members	76.2	76.2	Yes	Strong
Educating family members on how to support me.	85.7	76.2	Yes	Strong
Spiritual support	71.4	85.7	Yes	Strong
Practical				

Getting a job/return to work	100	100	Yes	Strong
Adjusting the house space	100	100	Yes	Strong
Getting financial support	100	100	Yes	Strong
Getting transportation	95.2	95.2	Yes	Strong
Getting accommodation on the ground floor	85.7	90.5	Yes	Strong
Getting spacious accommodation	85.7	100	Yes	Strong
Getting assistance from a home-based carer.	76.2	71.4	Yes	Strong
Getting legal assistance with housing	47.6	_____	No	_____
Supply of water and food	66.7	76.2	Yes	Strong

Table 5.3: Long-term care priorities for people with lower limb amputations (n=20).

Proposed care priorities	Percentage (%) of participants who endorsed each care priority in round 2[11].	Percentage of participants who endorsed each care priority in round 3.	Consensus reached? (Yes/No)	Level of consensus[12]
Biomedical				
Getting and using a prosthetic leg	95.2	95.2	Yes	Strong
Improving the ability to walk	100	100	Yes	Strong
Psychological				
Post-amputation depression	95.2	95.2	Yes	Strong
Stress management	76.2	85.7	Yes	Strong
Getting ongoing patient counselling	85.7	85.7	Yes	Strong

11 Endorsed = rated a care priority as important on a 0 – 5 Likert scale.

12 The level of consensus is presented as weak (≥50% - 60%), moderate (>60% - 70%) or strong (>70%).

Getting family counselling	71.4	66.7	Yes	Moderate
Practical				
Getting financial support	100	100	Yes	Strong
Getting transportation	85.7	85.7	Yes	Strong
Functional independence	100	100	Yes	Strong
Getting spacious housing	81	85.7	Yes	Strong
Quitting smoking	33.3	47.6	No	_____
Getting accommodation on the ground floor	95.2	95.2	Yes	Strong
Getting a supply of food and water	100	100	Yes	Strong

4. Rationales for endorsing care priorities.

The participants interviewed in the study endorsed the care priorities according to the clinical pathway stages involved in the management of people with limb amputations. The general consensus among the participants was that pre-amputation, they wanted education support to help them manage their expectations and prepare for life after amputation. In the early stage after amputation, they wanted help with dealing with the psychological trauma of having lost a limb. In the long-term, however, the participants prioritised the need for living a functional and normal life, with respect and dignity like everyone else.

4.1 Theme 1: Preparedness

This theme was generated based on the analysis illustrated in Supplementary File 1. The participants indicated that being prepared for life after amputation is important, and that this could be achieved by undergoing pre-amputation patient education and family counselling. This theme was expanded into one subtheme: access to information.

The participants indicated that undergoing pre-amputation education would help them prepare (by putting support measures in place) for the demands and expectation of life after amputation. For example, one participant said, "*Health professionals know what's going to happen. I haven't got that foresight. If they give it to me, I'd know what to expect and how to handle things outside (the hospital). They would prepare me for that*". In addition, the participants indicated that pre-amputation education is necessary to help them deal (emotionally) with the loss of a limb. One participant mentioned, "*I wasn't prepared for what I went through. I wasn't prepared to see my leg gone… When I saw my leg, I had a stroke. It could have helped to be more prepared*".

The participants also expressed that undergoing family counselling would help the family identify potential needs of the person with an amputation and prepare ways they could accommodate them. For example, one participant said, "*It is important to let the family know what's going to happen, and how they can support me after (amputation)*".

4.1.1 Subtheme 1: Access to information

The participants indicated that getting access to information and planning of support is essential. Some of the ways suggested for this to be achieved was by increasing the awareness of PLP pre-operatively and providing pre- and post-amputation education for thorough preparation for life after limb loss.

One participant expressed that getting help with PLP management would help create awareness that PLP is real pain and people can get help, *"I never knew what PLP is, and I used to take strong medication to take the pain away and it didn't work. Treatment should make people aware that PLP is real, and it can go away easily"*.

The participants also indicated that undergoing pre-amputation education is important, as this would help them manage their expectations about life after amputation. In the same way, the participants indicated that post-amputation education would help them evaluate (together with the healthcare professional) whether they are coping with life after amputation and make adjustments where necessary.

4.2 Theme 2: Mental health, and psychological and spiritual well-being.

This theme was generated based on the analysis illustrated in Supplementary File 2. The participants indicated that mental health, and psychological and spiritual well-being is essential for people with amputations. The participants alluded to the significance of getting help with mental health, and psychological and spiritual well-being because of the influence these have on recovery in the long-term.

The participants expressed that being provided with financial and spiritual support, post-amputation education, medical treatment for PLP and post-amputation depression, and being re-integrated into the work environment would all contribute to improving mental health, and psychological and spiritual well-being.

A priority was reintegration into the work environment. The participants indicated that being integrated into the work environment is essential because working provides one with peace of mind by breaking the patterns of ruminating about the amputated limb. In this regard, one participant said, "*Working gives you a peace of mind. (When working) you don't have time to think about the amputated leg…*". In addition, the participants indicated that working helps combat the feeling of helplessness that could result in depression. One participant expressed, "*I have been supporting my family since I was 16, and what I have been doing all these years I can't do anymore. It is depressing*".

The participants indicated that another key component for improving mental and psychological well-being is getting financial support (grant), primarily from the government. The participants expressed that getting financial support would help them address the burden of their financially related stress. For example, one participant said, "*It will help me to manage my stress because I will be able to buy some food and pay some bills. It will take a bit of the burden off my shoulders*".

The participants also mentioned that getting spiritual support is essential because this would help them foster a positive mindset, acquire strength and fortitude, reconcile with God to understand reasons for inflicting such a punishment on them, and to be on good terms with God to avoid further punishment. One participant was quoted saying, *"It is important to get some answers. Why is God punishing me? I am doing everything right. Why is he doing this to me".* Another participant stated, *"When you are alive in spirit you know that you have God on your side at least, even though he took your legs".*

The participants expressed that getting medical treatment for PLP is essential for reducing the feeling of helplessness caused by having unbearable pain that is not considered normal in society. For instance, one participant said, "*When you cannot handle the pain, you can be depressed and have suicidal thoughts in the end*". Likewise, the participants indicated that undergoing post-amputation counselling is essential because it would help identify patients who are at high risk of falling into depression and help them better deal with the painful loss of a limb and livelihood. Further, the participants indicated that addressing post-amputation depression using this approach is necessary to help them cope with the new realities of life after amputation, restore their zeal for living, improve relations with other people, and curb suicidal thoughts. In this regard, one participant said "*Getting help will help to reduce my suicidal thoughts. The main thing is depression can kill you, because I was on a brink on killing myself after the amputation".*

4.3 Theme 3: Participating in life, with respect and dignity like everyone else.

The participants expressed that living a functional and normal life, with respect and dignity is important in the long-term. This theme is comprised of four subthemes: mobility, facilitating free movement, reducing barriers to access, and dignity and purpose.

This theme was generated based on the analysis illustrated in Supplementary File 3. The participants indicated that being able to perform basic and instrumental ADL and participate in meaningful social activities after amputation is important, and that this could be achieved by being provided with a prosthetic leg and wheelchair, and getting help with PLP management, physical rehabilitation, and home-based assistance.

The participants expressed that assistance provided by a home-based carer during the early phase after amputation would help them perform challenging ADL. One participant said, "*In the beginning it is important to have someone assist you with things like, how to take a shower, and show you a new way of doing things*".

The participants mentioned that undergoing physical rehabilitation would help them adjust to new physical demands after amputation. In this regard, one participant said, "*It helps you on how to handle your disability. For example, if you get a prosthesis, you wouldn't know how to use it unless you get (physical) therapy first to help you get used to it*".

The participants also indicated that having access to and using assistive devices such as a wheelchair and prosthetic leg are key for improving functional independence. The participants expressed that using a prosthetic leg enables active involvement in instrumental ADL such as walking. Further, the participant indicated that using a wheelchair would allow for the complete use of the upper limbs when mobilising. For instance, one participant mentioned, "*It helps you to be able to function properly. In my case, I got a wheelchair at home because if I want to do something, my hands are free. I can cook. I can clean. But I can't do these if I am on crutches*".

4.3.1 Subtheme 1: Mobility

This subtheme was generated based on the analysis illustrated in Supplementary File 2. The participants mentioned that improving the mobility of people with LLAs is essential to allow participation, and that this could be achieved by providing them with crutches, transportation, a wheelchair, a prosthetic leg, and accommodation on ground-floor level.

The participants mentioned that being provided with crutches would enable them to mobilise in areas where it is often challenging to use other larger assistive devices such as a wheelchair. For example, one participant mentioned, "*There are places you could go with the crutches and not the wheelchair. For instance, if I've got to go up the staircase I can't go up with the wheelchair and vice versa, I can come down (only) with the crutches and not the wheelchair*".

The participants also mentioned that being provided with a wheelchair would enable them to mobilise over longer distances. Further, they indicated that having a prosthetic leg would help them mobilise normally from one point to another without the use of typical assistive devices such as crutches and a wheelchair.

4.3.2 Subtheme 2: Facilitating free movement

The participants mentioned that free movement from one point to another, without hindrance is key to improved overall mobility of people with LLAs, and that this could be achieved by adjusting the space in the house according to the needs of the person with an amputation.

The participants indicated that it is important to adjust the space to remove obstacles that could cause falls and injuries. They indicated that this would allow free movement into spaces that are usually challenging to mobilise into when using assistive devices. For example, one participant said, "*Adjusting the space allows free movement. I have a neighbour who also had her leg amputated. It was really difficult for her to move around with a wheelchair because of narrow spaces*". This indicates the essential role of free movement in enhancing access.

4.3.3 Subtheme 3: Reducing barriers to access

The participants indicated that having equal access into homes and facilities is essential, and that this could be achieved by providing them with accommodation on ground floor level and transportation tailored to the needs of people with lower limb amputations.

The participants indicated having their accommodation on a ground level is necessary to allow for facilitated access into and out of the house. For instance, one participant said, "*It is convenient to live on a ground floor. It is easy to get in the house and out if you are on the ground floor*".

In addition, the participants indicated that the availability of transportation tailored for people with LLAs will allow them equal access to medical facilities. In this regard, one participant said, "*There isn't effective transportation for people with amputations in my area. One day, I had to take a taxi and got off the main road. I had to walk uphill, and it took me an hour and half to get here. There is no transport coming this way and it took a lot out of me. For the appointments, a collection and drop-off (of patients) could make getting here easier*". This indicates that free movement and reduced barriers to access are important in facilitating improved functional independence and participation that is necessary for living a dignified and purposeful life.

4.3.4 Subtheme 4: Dignity and purpose

This subtheme was generated based on the analysis illustrated in Supplementary File 5. The participants indicated that living a life filled with dignity and purpose after amputation is important, and that this could be achieved by being provided with remunerative work, financial support, clean water and food, physical rehabilitation, and a prosthetic leg.

The participants mentioned that being integrated into a work environment would give them a sense of purpose and progress. For instance, one participant said, "*When you are employed, you go to bed looking forward to the next day. Your life goes on normally, and you are also useful to your family*".

The participants indicated that having remunerative work would restore their dignity and assure them a meaningful life role in their family. In addition, they mentioned that working will help them maintain the current quality of life to a standard similar with that prior to limb amputation. In this regard, one participant said, "*Working is important. Even if people with amputations get a grant, it is minimum compared to what they might have earned. It is difficult to sustain your family who are used to that amount with this (lesser) amount now*".

The participants, particularly the elderly who cannot return to work, indicated that receiving financial support would restore their dignity as they would be able to pay for their essential needs. In this regard, one participant said, "*Getting financial support will be helpful. I have people I must pay to push me around in a wheelchair, and to lift me up and down the stairs. Money helps me to achieve* these things". Lastly, the participants indicated that their livelihood could be ensured by getting a regular supply of clean water and food because these are essential for maintaining good health, nutrition, and sanitation.

4. Discussion

This is the first study on patient-generated care priorities for people with LLAs. In this study, consensus was reached on 24 short-term care priorities [biomedical (n=8); psychological (n=8); practical (n=8)] and 12 long-term care priorities [biomedical (n=2); psychological (n=4); practical (n=6)]. The analysis of qualitative data on the rationales for endorsing the care priorities generated three themes: (1) preparedness; (2) mental health, and psychological and spiritual well-being; and (3) participating in life, with respect and dignity like everyone else.

The participants supported "Mental health, and psychological and spiritual well-being" as the most important theme generated from this study. This was not surprising as mental health problems are a leading cause of disability worldwide (285). The onset of PLP, and a lack of financial and spiritual support were identified as some of the factors contributing to a deterioration in mental health, and psychological and spiritual well-being in people with LLAs in this study. Considering that LLAs often result in loss of function and participation in remunerative work, the amalgamation of these factors is likely to contribute to a heightened experience of complex feelings and emotions including despair, helplessness, and depression (286). A recent qualitative study investigating the effects of amputations on mental health found that having a LLA is associated with grief, decreased self-esteem and distorted body-image, withdrawal from meaningful engagement in family and social roles, and loss of enthusiasm about the future (287). In light of this, we found it surprising that four available clinical practice guidelines for individuals with amputations did not identify post-amputation depression, and the need for financial and spiritual support as important care priorities in people with amputations, despite the growing evidence indicating their role in the recovery of people with LLAs (262, 288-290). These results highlight the need to involve mental health practitioners (e.g. psychologist, psychiatrist and counsellor) in the interdisciplinary perioperative management of people with amputations.

The collaborative effort made by healthcare professionals and relevant stakeholders addressing contributors for, and effects of, poor mental health, could play a significant role in improving the quality of life of people with LLAs.

Preparation through access to information and planning of support prior to amputation is an essential tool for improved post-surgical outcomes (291). However, the effective practice of patient-education is not always possible due to several barriers including language diversity and increased clinical workload or lack of time (292). The healthcare system in South Africa is overburdened and under-resourced (293). Therefore, in people scheduled for limb amputations, priority is often targeted towards the surgical procedure, and comprehensive pre-amputation patient education is often overlooked (294). In addition, the wide variety of cultural groups makes it challenging for healthcare professionals from other backgrounds to communicate in the languages local people comprehend best. As a result, strategies aimed at effectively preparing patients for life after amputation appear to be lacking. The uncertainty regarding life after amputation could exacerbate mental health problems and physical disability (294). For example, in a previous South African study, people with LLAs expressed their uncertainties about life after amputation, specifically regarding recovery, functional independence and participation in meaningful life roles (295). Similarly, the participants in this study highlighted the significance of having access to information and planning support to enable them to return to meaningful life roles.

A study examining the role of pre-operative psychological preparedness on post-amputation adjustment found that psychological preparedness resulted in a less complicated postoperative adjustment and grieving experience (291). In consideration of these findings and the results of this study, we recommend that a standardised educational tool be designed and incorporated into the standardised management protocol for people scheduled for elective amputations. An immediate post-amputation education programme would be pertinent for those undergoing emergency amputations (296).

Furthermore, implementing pain-education programmes targeting patients at community level may further contribute to the improvement of patient-centred care, and perhaps, alleviate the burden of people with amputations continuing with medical care.

The need to participate and live a functional and normal life, with respect and dignity like everyone else was consistent across all the participants in this study. This was chiefly a priority more than a year after amputation when physical and psychological adaptation to living with an amputation has been achieved (297). A recent study by Batten and colleagues revealed mobilising with a prosthesis as a key predictor for functional independence in people with LLAs (298). Their findings support those of another study which showed improved functional independence and reduced need for home adaptation following prosthetic training in mobility and ADL (299). Furthermore, using a prosthesis may enhance the users' body-image, which is essential for improving the sense of wholeness, as indicated by the participants in this study (300). The participants in this study expressed the need for a prosthetic leg. However, their expectations may not be a realistic considering they had a median age of 65.5 (50 – 71) years, presented with comorbidities, and that most had transfemoral amputations, which are relatively physically demanding compared to transtibial amputations (301). Further, for a patient to be eligible for a prosthesis, they would have to be able to perform tasks including but not limited to hopping over an obstacle 10 cm high, hopping for 16 meters, standing on the intact leg with eyes closed, and picking an object from the ground without support (302). The patient profile in this study suggests that most would not meet the strict criteria for prescribing a prosthesis, which favours the relatively young and healthy patients with LLA (302). It is worth mentioning that a prosthesis remains an expensive aid, which most people in developing countries cannot afford (303). This, therefore, raises a concern on issues of free movement and equal access for people with LLAs (304).

The need for free movement and equal access speaks to the core challenge encountered by many people with LLAs in South Africa. Many live in informal settlements where houses are typically small

and the environment terrain is uneven, hindering free mobility, particularly when using a wheelchair (295). In addition, some people live in apartment buildings where the only access is via stairs. In consideration of these challenges, it is imperative that rehabilitation professionals provide eligible patients with comprehensive prosthetic training, and to partner with healthcare funders to subsidise and improve the process of acquiring a prosthesis after successful training. Further, it is essential for government and private entities to improve and adapt the current infrastructure to facilitate equal access for people with amputations to essential services such as hospitals, shopping centres and places of occupation.

Retaining people with amputations in the remunerative work environment is often overlooked by healthcare professionals, primarily because the immediate priority after amputation is promoting tissue healing, optimising pain management, and improving function (305). In the long-term, however, the participants in this study indicated it is essential to be integrated into the remunerative work environment, mainly to generate wages necessary for living a life of dignity and purpose. Our findings are consistent with those reported elsewhere (295, 306-308). While returning to work is necessary for people with amputations, the high unemployment rate in developing countries means that they are often replaced with more competitive candidates prior to their recovery (306). In addition, institutional barriers such as a lack of infrastructure adaptation, and poor adjusting of the heavy workload and/or work role add to the challenges faced by amputees, who are often desperate to return to work (309). Schoppen et al (309) showed that addressing these challenges led to a 100% success rate in maintaining employment after amputation. Therefore, it is imperative for healthcare professionals such as occupational therapists involved in vocational rehabilitation to liaise with employers on effectively implementing the strategies necessary for the successful return of people with LLAs to work.

4.1 Limitations

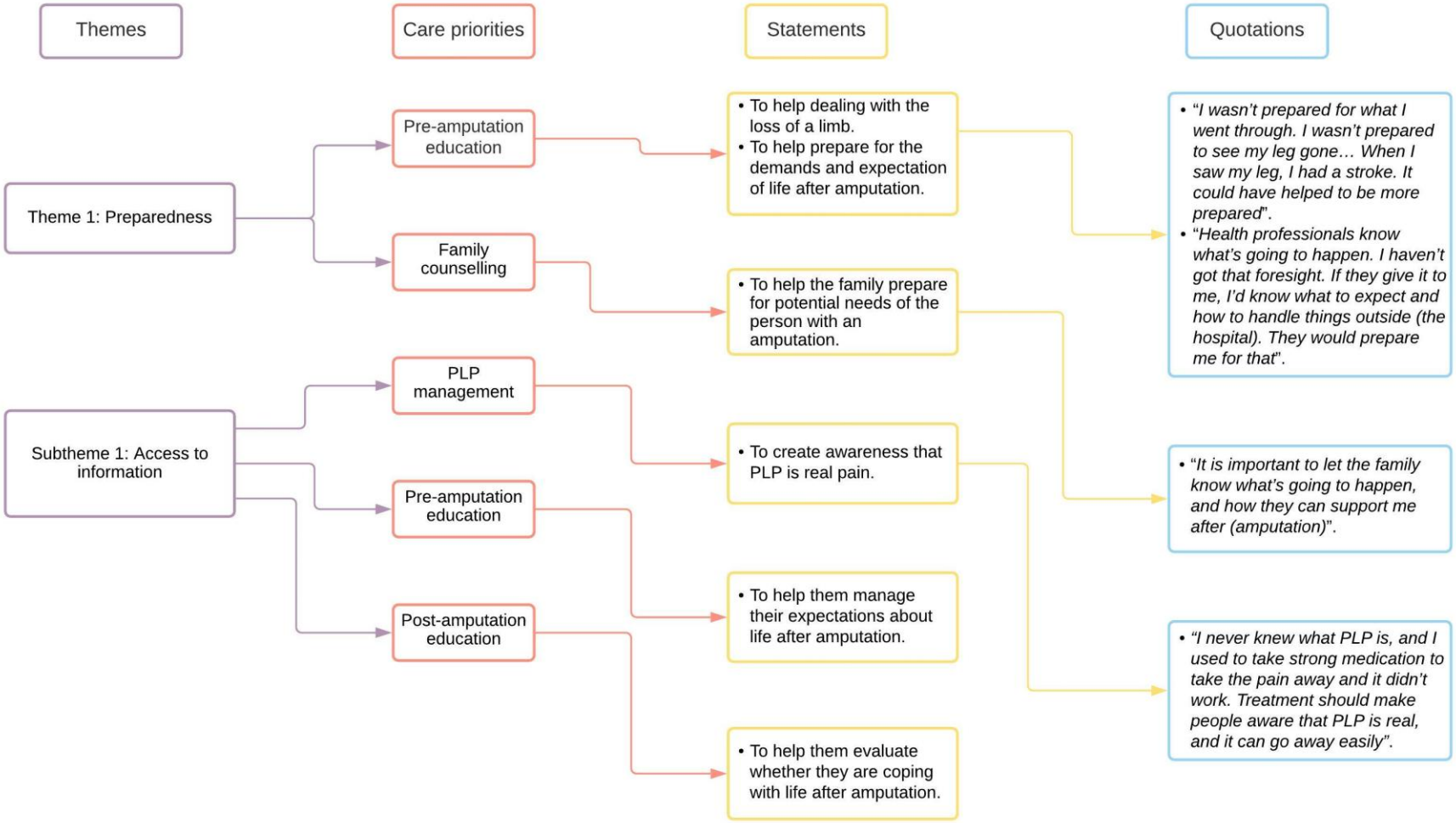
The results of this study were derived from a sample of people with LLAs. Therefore, the results may not be generalisable to people with upper limb amputations. The rating of care priorities in this study could have been improved by clarifying the meaning of each care priority so that the participants hold the same understanding. We had intended to recruit additional participants until thematic saturation was reached during the first round of the Delphi. However, we could not recruit additional participants because of strict Covid protocols. One important consideration is that the interpretation of qualitative data is influenced, to some extent, by the researchers' biases, views and opinions. We limited the potential effect of these by having two reviewers analyse data independently and reach consensus on the results. Nonetheless, the results of this study should be interpreted with a clear understanding of the cultural context from which they were derived.

5. Conclusion

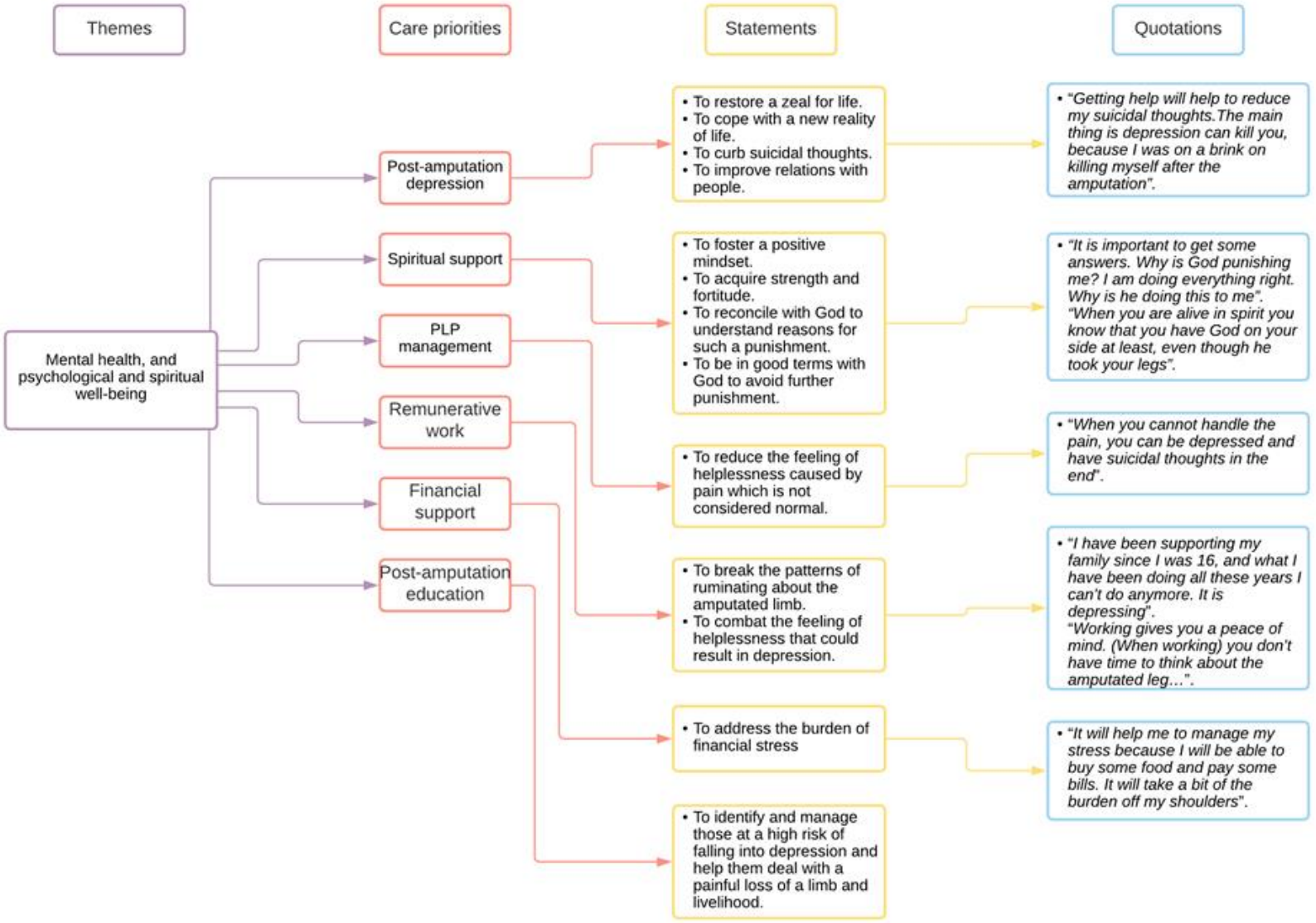
This study reveals some discrepancy between patient- and expert-derived care priorities for people with LLAs. Our findings indicate that people with LLAs prioritise access to information and planning of support pre-operatively; and mental health, and psychological and spiritual well-being during the first year after amputation. In the long-term, however, the priority was living a functional and normal life, with respect and dignity like everyone else. The findings of this study indicate that effective management of people with LLAs should not only be focused on improving biomedical outcomes but should also address psychosocial factors that contribute towards improving their dignity, purpose, and participation in meaningful life roles. Further, they highlight the critical role of mental health professionals and the need for vocational training for people with LLAs. The involvement of patients in decision-making may promote efficient health-service delivery and strengthen patients' adherence to treatment and improve clinical outcomes.

6. Supplementary files

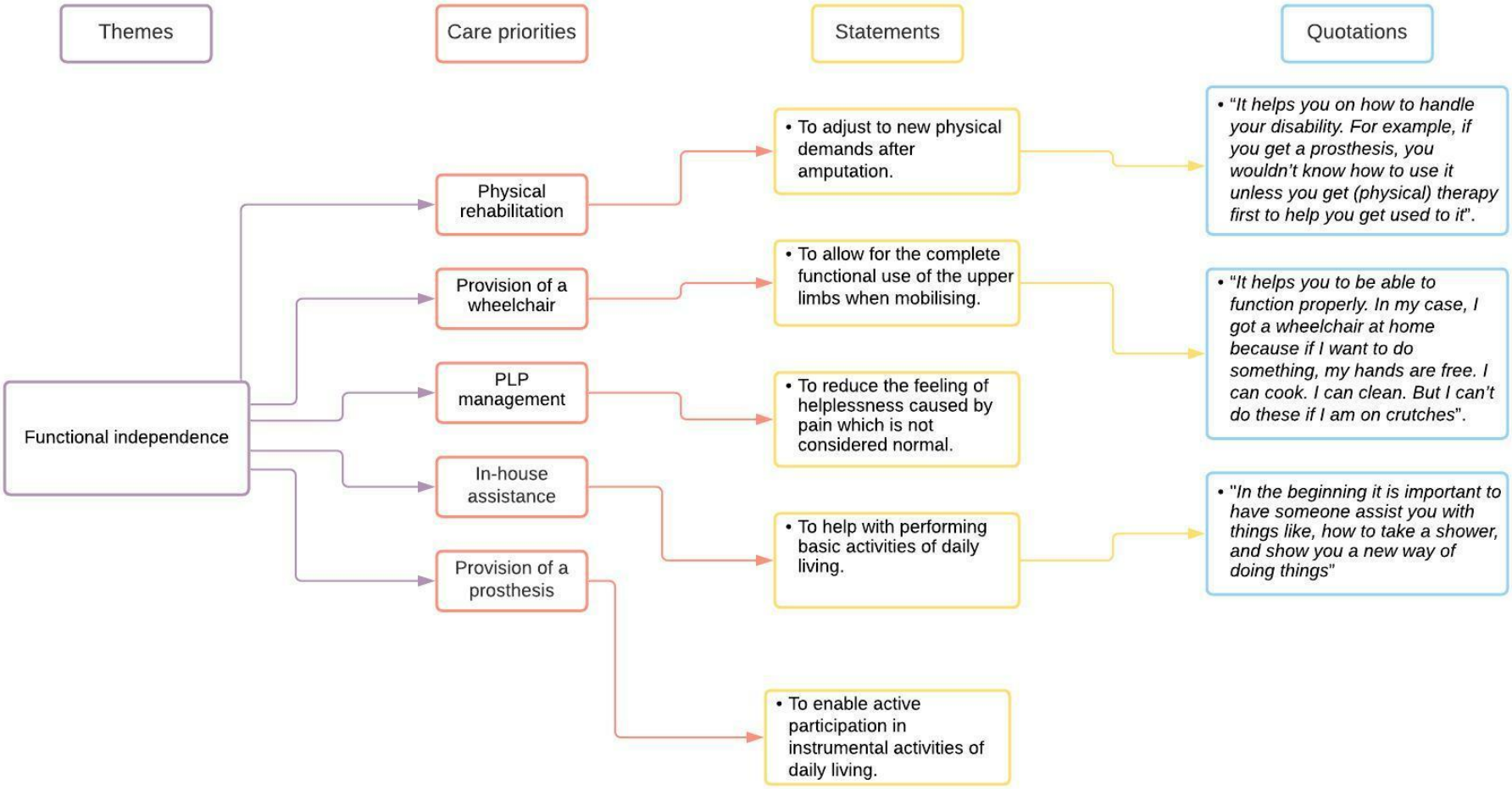
Supplementary file 5.1: Access to education and planning of support



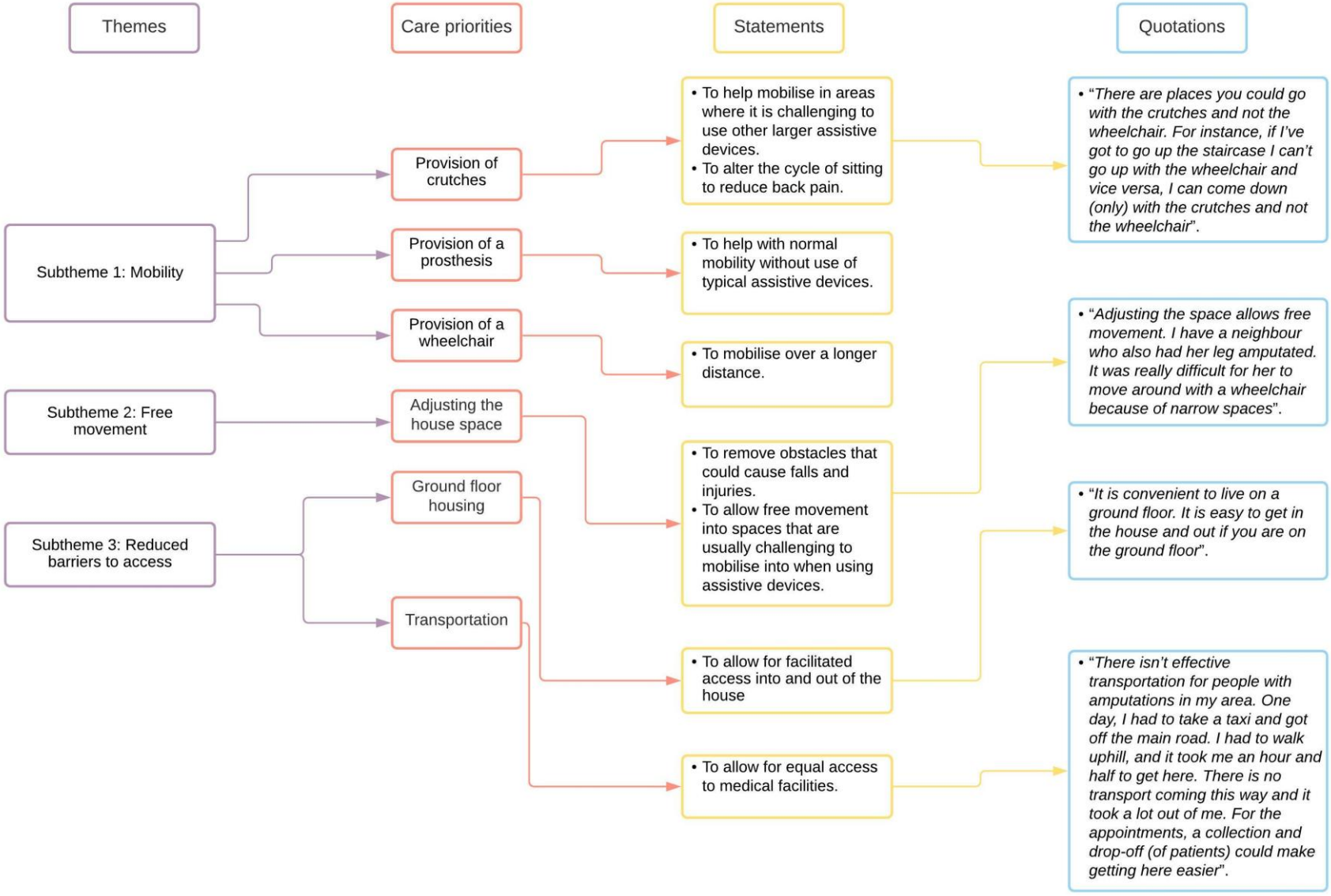
Supplementary file 5.2: Mental health, and psychological and spiritual wellbeing.



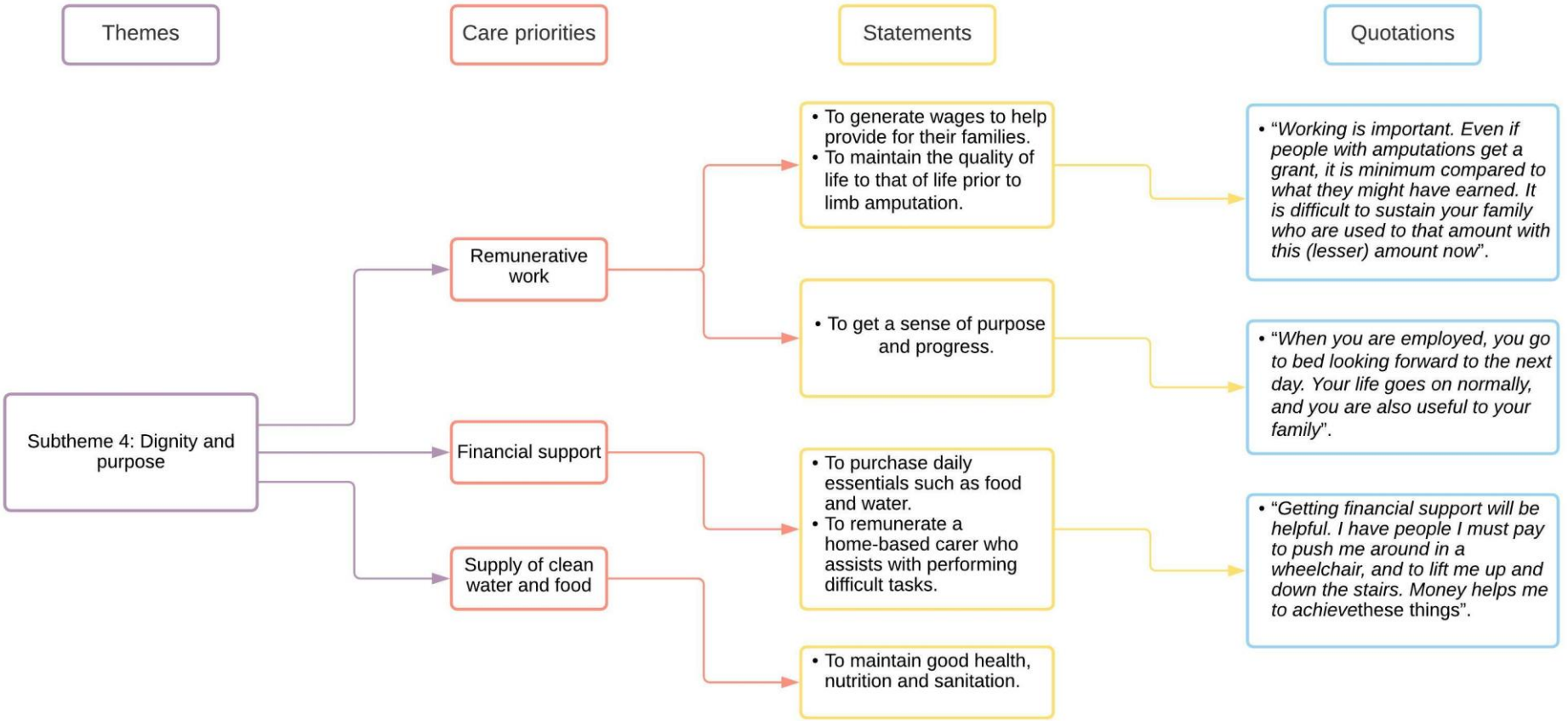
Supplementary file 5.3: Living a functional and normal life, with respect and dignity like everyone else.



Supplementary file 5.4: Mobility, free movement, and reduced barriers to access.



Supplementary file 5.5: Dignity and purpose.



Chapter 6: Conclusion and recommendations

The aim of the concluding chapter of this dissertation is to summarise the key research findings and draw conclusions on the objectives underpinning each study included in this body of work. In addition, this concluding chapter aims to make recommendations for further research and implementation.

6.1 Overview of key findings

Prior to our study, no study had been conducted to determine a robust estimate of the global prevalence of PLP. Therefore, we aimed to address the gap in the literature by conducting a systematic-review and meta-analysis including 37 studies (39 data sets) with a total of 12738 participants from various global regions. The pooling of all studies using the random-effects model revealed a prevalence estimate of 64% [95%CI: 60.0 – 68.1]. This high prevalence estimate, in conjunction with the narrow confidence interval suggests that six out of 10 people with amputations globally are experiencing PLP.

We were also interested in determining if the prevalence of PLP differs significantly amongst people with amputations living in developed countries versus those living in developing countries. The subgroup analyses stratified by the developmental status of the countries in which the studies were conducted revealed an estimated pooled prevalence of 67% [95% CI: 62.0 –71.6] in developed countries and 54% [95% CI: 44.8–63.1] in developing countries, with a significantly lower prevalence rate in developing countries [U = 57, p = 0.03]. While the aim of this research was not to determine the reasons for such a significant difference, we hypothesised that the lower prevalence estimates in developing countries may be attributed to, among other reasons, a low number of studies conducted in developing countries. This was mostly notable when we could not find any study determining the prevalence of PLP in an African population.

Our exploratory analysis of the risk factors for PLP revealed several risk factors that were consistently positively associated with PLP. These risk factors included having a lower limb amputation, residual limb pain, non-painful phantom sensations, persistent pre-amputation pain, proximal site of amputation, and diabetic cause of amputation were grouped into pre-operative, peri-operative, and post-operative domains. From amongst these important risk factors, persistent pre-amputation pain and residual limb pain play a crucial role in the initiation and maintenance of pain, respectively. Further, these predictors for PLP are modifiable and could be used as targets for treatment in the prevention or management of PLP.

In consideration of the paucity of research investigating the prevalence of and risk factors for PLP in African populations, we conducted a cross-sectional study aiming to determine the PLP prevalence and risk factors for PLP in people who have undergone limb amputations at GSH. The study included 106 participants [male (n=66); female (n=40)] with lower limb amputations and a median [IQR] age of 59 [53 – 67]. Data were analysed using 129 amputation cases because 23 participants had double amputations. The overall prevalence of PLP during the week preceding data collection was 51% [95% CI: 41.8 – 59.7]. This prevalence estimate is in keeping with the results of the meta-analysis of PLP prevalence studies conducted in developing countries (Chapter 2). Likewise, pre-amputation pain was identified as a predictor for PLP, thus confirming its significant role in the onset of PLP in people with amputations. The high burden of PLP raises the need for strengthening strategies for creating awareness on PLP and associated complications, and for developing guidelines for effective patient-centred management.

The current NICE guidelines for the management of PLP may not be appropriate because pharmacological treatments included in these guidelines are no more effective than placebo. In fact, there is level 1 evidence that recommended pharmacological treatments are ineffective: memantine (30mg/day for 4 days), gabapentin (2.4g/day for 6 weeks) and amitriptyline (10 - 125mg/day for 6 weeks) showed no benefit over placebo (23). The weak evidence for pharmacological treatments

and the inability to conduct meta-analyses for non-pharmacological interventions (due to use of varying treatment protocols and study methodologies) meant that consensus on the best management of PLP had to be generated using an alternative approach. Therefore, we conducted a Delphi study aiming to reach expert consensus and make recommendations on effective treatments for PLP in people with limb amputations. Twenty experts who completed the study were anaesthesiologists (n=3), physiatrists (n=3), psychologists (n=2), neurologists (n=2), physiotherapists (n=8), nurse (n=1) and occupational therapist (n=1). Fifteen of these, described themselves as clinician-researchers, three described themselves as full-time researchers and two described themselves as full-time clinicians. Consensus was reached on seven treatments [non-pharmacological (n=6); pharmacological (n=1)] that were considered effective for managing PLP, and on two treatments [citalopram (60%) and PRFS of the dorsal root ganglion (70%)] that were considered ineffective because of a lack of scientific evidence supporting their efficacy in people with PLP. Graded Motor Imagery, mirror therapy and amitriptyline were endorsed by most experts because of the available supporting scientific evidence and their reported efficacy in clinical practice. Cognitive Behavioural Therapy, virtual reality training and use of a functional prosthesis were endorsed by most experts because of their reported efficacy in clinical practice, even though there is essentially no scientific evidence supporting the use of these treatments for PLP. The findings of this study indicate the important role for non-pharmacological interventions in the effective management of PLP. In addition, they raise a need for research to develop evidence for treatments that were endorsed for their efficacy in clinical practice. Further, the various treatments endorsed in this study indicate the importance of managing PLP using an interdisciplinary approach addressing the biopsychosocial determinants of pain.

The current treatment guidelines for the management of people with LLAs were formulated with the contribution of health care professionals only, who may not always prioritise the elements of care that are important to the patient at a specific time-point.

The growing evidence indicates that patients may not receive the treatment they need or want as a result of not being involved in clinical decision-making. To address a mismatch in patient-healthcare provider care priorities, we conducted a final study with the aim of generating patient consensus on care priorities for people with LLAs during the first year and treatment priorities after the first year. In addition, we aimed to gather rationales for endorsing each of the proposed care priorities. In this study, we included 20 participants [Male (n=16); Female (n=4)] with a median [IQR] age of 65.5 [50 – 71]. All the participants had lower limb amputations and had undergone amputation a median of 16 [11.5 – 31] months at the time of recruitment. The indications for amputations were complications due to uncontrolled diabetes, peripheral vascular diseases, infection, and trauma. According to our knowledge, this is the first study on patient-generated care priorities for people with LLAs. In this study, consensus was reached on 24 short-term care priorities (first year) [biomedical (n=8); psychological (n=8); practical (n=8)] and 12 long-term care priorities [biomedical (n=2); psychological (n=4); practical (n=6)]. The analysis of qualitative data on the rationales for endorsing the care priorities generated three themes: (1) preparedness, (2) mental health, and psychological and spiritual well-being, and (3) participating in life, with respect and dignity like everyone else. The consensus among the participants was that pre-amputation they wanted education support to help them manage their expectations and prepare for life after amputation. In the early stage after amputation, they wanted help with dealing with the psychological trauma of having lost a limb. In the long-term, however, the participants prioritised the need for living a functional and normal life, with respect and dignity like everyone else.

The four related studies enhance our understanding of the burden of PLP, expert recommendations on the best management of PLP, and patient-generated short- and long-term care priorities for people with LLAs.

6.2 Recommendations

The four interconnected studies address the gap in the study of the global prevalence of PLP and add to the limited evidence on the best management of PLP and patient-generated care priorities for people with LLAs. However, several aspects beyond the scope of this work require investigation. Further investigation should be focused on strengthening the body of work on people with amputations and those with PLP within the African context. This is necessary to advance the quality of healthcare provided to African patients with amputations. In addition, it will enable healthcare professionals generate evidence-informed recommendations for clinical implementation and further research in the diverse African populations.

6.2.1 Recommendations for further research

The specific recommendations for future research include:

1. Conducting large prospective longitudinal cohort studies investigating the prevalence, predictors and effects (e.g., interference with function) of PLP in African people with amputations, who are continuing with medical care and those who have been discharged from continuing medical care post-amputation.
2. Conducting prospective longitudinal cohort studies investigating the mechanisms and factors predisposing people with surgical and traumatic amputations to developing high-impact PLP compared with people who have congenital amputations.
3. Conducting randomised control trials examining the effects of mirror therapy versus covered mirror therapy (sham) on pre-amputation pain and post-amputation outcomes including PLP, physical function, and depression.
4. Conducting a case-control studies investigating the neural mechanisms by which somatosensory feedback from a prosthetic leg reduces PLP in people with LLAs.

5. Conducting Delphi studies with a qualitative component aimed at designing and testing a pre-amputation education program aimed at providing planning support for people scheduled for elective amputation surgeries.
6. Conducting an expert Delphi study designing and validating an assessment tool for PLP, its characteristics and effects.
7. Conducting an expert Delphi study to develop a standardised definition of PLP.
8. Building upon the existing promising literature by conducting rigorous randomised control trials investigating the effectiveness of GMI versus sham GMI treatment for reducing chronic PLP and disability in a large and heterogenous sample of people with amputations.
9. Conducting case-series studies investigating the long-term effects of virtual reality training in PLP management and exploring its utility as a potential alternative for mirror therapy.
10. Conducting randomised control trials investigating the effects of CBT on PLP severity, disability and quality of life and cohort studies exploring the mechanisms by which CBT works to alleviate pain.

6.2.1 Recommendations for implementation.

Recommendations for implementation include:

1. Implementation of evidence- and population-based education programmes focusing on the chronic diseases of lifestyle, including diabetes, and strategies for prevention and self-management. Improvement in health-literacy among people with diabetes is associated with a decreased risk of deteriorating health status, increased chances of hospitalisation and complications that may indicate a surgical amputation of a limb.
2. Motivating for immediate physical rehabilitation after a limb amputation and provision of a prosthesis to eligible candidates. A delayed use of a prosthesis after amputation is associated with physical deconditioning and disability. Therefore, it is imperative to enforce health systems that allow for a provision of an interim prosthesis immediately after successful training until

there are no drastic changes in the volume of the stump. Using a prosthesis after amputation has been shown to improve the embodiment of a prosthesis which facilitates mobility and function and would let patients have a dignified life like everyone else.

3. Incorporating home-based sensory discrimination training as a supplement to already existing therapies such as GMI and mirror therapy. Sensory discrimination training is proposed to normalise cortical reorganisation by addressing a mismatch between the brain's sensory output and sensory feedback from the amputated limb (249). This mechanism of action is similar to that by which GMI reduces PLP. Therefore, incorporating sensory-discrimination training into a home-programme of people undergoing GMI or mirror therapy may result in augmented treatment effects.
4. Prioritising the involvement of mental health practitioners (e.g. psychologist, psychiatrist and counsellor) in the interdisciplinary management of people with amputations. The collaborative effort made by healthcare professionals and relevant stakeholders addressing contributors for and effects of poor mental health, could play a significant role in improving the quality of life of people with LLAs.
5. Empowering healthcare professionals involved in vocational rehabilitation to liaise with employers on effectively implementing strategies necessary for the successful return of people with LLAs to work.

6.3 Conclusion

The aim of this research was to gain an insight into the global prevalence of PLP in people with amputations, particularly amongst those living in South Africa, and to reach consensus on the best treatments for PLP and patient-generated care priorities for people with LLAs. These respective aims were realised by analysing data using a variety of study designs such as systematic review and meta-analysis, cross-sectional, expert Delphi, and patient Delphi designs.

Six out of 10 people with amputations suffer from PLP. Healthcare professionals ought to raise awareness about the high statistics and implement evidence-based strategies for alleviating PLP by targeting the relevant underlying mechanisms and modifiable risk factors. The current evidence suggests that non-pharmacological and non-interventional treatments have an important role in the management of PLP. In addition, it suggests that PLP is best managed using multimodal analgesia addressing biopsychosocial contributors for PLP.

Though the evidence points us to the effective approach of addressing pain in people with amputations, it is essential to promote patient-centred care by involving patients in clinical decision-making. Our findings on patient-generated care priorities indicate that people with LLAs prioritise being prepared by having access to information and planning of support pre-operatively, and getting help with their mental health, and psychological and spiritual well-being during the early post-operative phase, and in the long term they prioritise living a functional and normal life with dignity. Involving patients in decision making addresses the discrepancy between the treatment goals of the patient and the care provider. People with amputations endure a traumatic experience of losing a limb and face additional struggles in adjusting to a new reality of life thereafter. Developing post-surgical complications including PLP and being disabled without having a functional, normal, and dignified life contribute further to a poor health-related quality of life. People with amputation deserve better holistic care. Therefore, healthcare professionals can improve on this care by being patient-centred, partnering with patients in clinical decision making, using multimodal pharmacological and non-pharmacological pain approaches, and working with interdisciplinary teams to restore function and meaningful life roles. Consequently, this may strengthen patients' adherence to treatment, improve clinical outcomes and promote efficient health-service delivery. Overall, this body of work contributes to our knowledge of the burden of PLP and strategies for intervention in clinical practice. This research has also provided direction for future work that will contribute towards the strengthening of healthcare services for people with amputations in Africa.

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8. Appendices

Appendix 1: Human Research Ethic Committee letter of approval (HREC Ref: 066/2020).

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

30 June 2020

HREC REF: 066/2020

A/Prof R Parker
Division of Anaesthesia & Perioperative Medicine
D-23 NGHS
Email: romy.parker@uct.ac.za
Student: Katleho.limakatso@uct.ac.za

Dear A/Prof Parker

PROJECT TITLE: PHANTOM LIMB PAIN: A CROSS-SECTIONAL SURVEY OF PREVALENCE AND RISK FACTORS IN AMPUTEES (PHD DEGREE - MR KATLEHO LIMAKATSO)

Thank you for your response letter dated 10 June 2020, addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020.

Approval is granted for one year until the 30 June 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: - Mr Katleho Limakatso will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

HREC 066/2020sa

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix 2: Human Research Ethics Committee letter of approval (HREC Ref: 355/2019.

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
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11 June 2019

HREC REF: 355/2019

A/Prof R Parker
Division of Anaesthesia & Perioperative Medicine
D23
NGSH

Dear A/Prof Parker

PROJECT TITLE: TREATMENT RECOMMENDATIONS FOR PHANTOM LIMB PAIN IN PEOPLE WITH AMPUTATIONS: AN EXPERT CONSENSUS DELPHI STUDY (PHD CANDIDATE - MR K LIMAKATSO)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 June 2020.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student: Mr Kathleho Limakatso will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix 3: Human Research Ethics Committee letter of approval (HREC Ref: 771/2020).

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

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13 January 2021

HREC REF: 771/2020

Prof R Parker
Division of Anaesthesia & Perioperative Medicine
Ward D23, NGSH
Email: Romy.parker@uct.ac.za
Student: Katleho.limakatso@uct.ac.za

Dear Prof Parker

PROJECT TITLE: CARE PRIORITIES FOR PATIENTS WITH LOWER LIMB AMPUTATIONS: A PATIENT DELPHI STUDY (PHD CANDIDATE: MR K LIMAKATSO)

Thank you for your response letter, addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study, subject to the following: -

1. The data sheet needs to show the additional data that has been identified from the literature that affects needs for amputee patients.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 January 2022.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Mr Katheio Limakatso will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix 4: Systematic review protocol.

Limakatso et al. Systematic Reviews (2019) 8:17
https://doi.org/10.1186/s13643-018-0938-8

Systematic Reviews

PROTOCOL Open Access

The prevalence of phantom limb pain and associated risk factors in people with amputations: a systematic review protocol

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Abstract

Background: The prevalence of phantom limb pain (PLP) in people with amputations is unclear because of the conflicting reports across the literature. It is proposed that the conflicting reports on the prevalence of PLP are a consequence of variations in the time period during which the studies were undertaken, countries in which the studies were conducted and recruitment processes implemented during collection of epidemiological data. In consideration of these factors, we aim to gather and critically appraise relevant literature to determine the prevalence estimate of and risk factors for PLP in people with amputations.

Methods: We will use a customised search strategy containing relevant words and terms to search the following databases: MEDLINE/PubMed (via EBSCOhost), PsycINFO (via EBSCOhost), PsycArticles, Cumulative Index to Nursing and Allied Health Literature (CINAHL) (via EBSCOhost), Africa-Wide Information (via EBSCOhost), Health Source: Nursing/Academic Edition (via EBSCOhost) SCOPUS, Web of Science and Academic Search Premier (via EBSCOhost). The risk of bias assessment will be conducted using a risk of bias assessment tool for prevalence studies, and data will be extracted using a piloted customised data extraction sheet. Data extracted from individual studies will be entered into Review Manager 5 and assessed for clinical and statistical heterogeneity. Studies will be pooled for meta-analysis using the random-effects model to determine a summary estimate of the prevalence of PLP across included studies. A statistically significant level will be set at $p < 0.05$.

Discussion: As far as we know, a systematic review and meta-analysis on the prevalence of, and risk factors for PLP in people with amputations has not been conducted. Given the varying reports in the literature, it is necessary to determine an estimate of the prevalence of PLP to generate an informed conclusion on this subject. The results of this review will be published in an internationally accredited journal and used to inform researchers, clinicians, policy-makers and the public about the burden of, and risk factors for PLP. This will be done with a further aim to improve the quality of pain management in society.

Systematic review registration: PROSPERO CRD42018094821

Keywords: Prevalence, Risk factors, Phantom limb pain, Amputations

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Background

Phantom limb pain (PLP) is defined as pain felt in the missing portion of the amputated limb following amputation [1]. Phantom limb pain commonly occurs in people with limb amputations due to trauma or surgery. However, some cases of PLP have been reported in congenital amputees [2, 3]. It has been proposed that risk factors such as persisting pre-operative pain, stump pain and time period since amputation contribute to the onset of PLP [4]. Phantom limb pain remains a serious public health problem because it is common and often undertreated [5]. As a result, persisting PLP may contribute further to depression and problems with prosthesis use, sleep and participation in activities of daily function [1, 6, 7].

The prevalence of PLP among people with amputation is unclear, perhaps because of conflicting reports across the literature. While some studies report a high prevalence of 85% [8, 9], one study has reported a markedly lower prevalence of 33% [10]. The conflicting reports in the literature regarding the prevalence of PLP is perplexing. It has been proposed that such discrepancy is likely caused by a variation in the time period during which the studies were undertaken, the countries in which the studies were conducted and the recruitment processes implemented during collection of epidemiological data [11].

Early studies, conducted during a period when PLP was commonly characterised as a psychiatric disorder, reported low prevalence rates [12]. Perhaps low rates could be accounted for by the patients' fear of reporting their pain to avoid the stigma associated to PLP. Low prevalence rates are also recorded in studies conducted in developing countries where the stigma associated with chronic pain conditions is still common [13]. Finally, many prevalence studies of PLP were conducted in clinical settings using patients continuing with medical care, introducing a recruitment bias [10, 14–17]. Thus, patients without access to clinical care may be unaccounted for in these statistics.

Prevalence studies are key to informing researchers, clinicians, policy-makers and the public about the burden of disease in society [18]. However, a wide variation in the reported prevalence of PLP does not provide a definitive prevalence estimate, and therefore hinders the development or implementation of effective interventions for preventing or treating PLP. Further, up to date, there is no systematic review that has synthesised data on the risk factors for PLP. To address this gap in the literature, a systematic review and meta-analysis will be conducted by gathering and critically appraising relevant literature regarding the prevalence of, and risk factors for PLP in people with amputations. The results of this review will enable us to generate an evidence-informed conclusion on the prevalence estimate of PLP, as well as associated risk factors in people with amputations. Further, they will be used to motivate for the development and implementation of pragmatic interventions that may prevent or reduce PLP in people with amputation. The current evidence suggests that rehabilitation approaches rather than pharmacological approaches are most effective for treating PLP [19]. Therefore, the results of this review may also highlight the need for enough access not only to medication but also to physiotherapists and occupational therapists for the treatment of PLP.

Objective

The purpose of this review will be to determine the prevalence estimate of and risk factors for PLP in people with amputations. In addition, this review will determine if there is an association between the prevalence of PLP and the development status (developed vs developing) of countries in which the studies were conducted.

Methods

This protocol was developed in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-Analysis Protocol (PRISMA-P) guidelines [20], and has been registered on PROSPERO—an international prospective register of systematic reviews with health-related outcome [21]. The PRISMA-P guidelines fulfilled by this protocol are presented in Additional file 1.

Criteria for selecting studies for this review

Inclusion criteria

- Study design and participants: published and unpublished prevalence case-control, cross-sectional and cohort studies on PLP in surgical, traumatic and congenital amputees aged ≥ 18 years.
- Outcome: prevalence of PLP and/or risk factors for PLP.
- Study setting: clinical and community-based studies conducted worldwide.
- Language of publication: studies published in the English language.
- Years: 1980–2018

Exclusion criteria

- Intervention (only) studies.

Search strategy for identification of studies

Electronic searches

One investigator (KL) and a senior medical librarian will use a customised search strategy (Appendix) containing appropriate words and terms to search the following databases: MEDLINE/PubMed (via EBSCOhost), PsycINFO (via EBSCOhost), PsycArticles, Cumulative Index to Nursing and Allied Health Literature (CINAHL) (via

EBSCOhost), Africa-Wide Information (via EBSCOhost), Health Source: Nursing/Academic Edition (via EBSCOhost) SCOPUS, Web of Science and Academic Search Premier (via EBSCOhost). Studies identified from this electronic search will be saved on EndNote X8 programme, which will also be used to remove duplicates [22].

Search of other sources

We will search the reference list of all eligible studies to identify additional studies with the potential for inclusion in this review. To identify grey literature, we will search OpenGrey www.opengrey.eu, and contact experts on ResearchGate www.researchgate.net to seek unpublished, and ongoing studies that may be eligible for inclusion.

Data collection and analysis

Study screening

Following the removal of duplicates, retained studies will be transferred to the Covidence systematic review software available at www.covidence.org. This software will be used as an online collaboration platform for reviewers during the entire screening process. Two reviewers (KL and GJB) will independently screen study titles and abstracts for eligibility. Two reviewers (KL and GJB) will independently assess full-text articles retained from the initial screening for eligibility using the inclusion and exclusion criteria. The entire review process will be illustrated using a PRISMA flowchart detailing included studies and excluded studies, with reasons for their exclusion.

Data extraction and management

Two reviewers (KL and GJB) will independently extract data using a piloted customised data extraction sheet. The following data will be extracted: authors, year of publication, study setting, country of study, sample size, participants' age and gender, site of amputation, PLP prevalence and risk factors, and author conflict of interest statement. Completed data extraction forms will be stored on a password-protected online storage platform which will be accessible only to the reviewers. Any disagreements between reviewers will be resolved by discussion. A third reviewer (RP) will be consulted if a consensus cannot be reached.

Risk of bias assessment

Two reviewers (KL and GJB) will independently conduct a risk of bias assessment using a risk of bias assessment tool for prevalence studies developed by Hoy et al. [23]. The results of this assessment will be classified as either low, moderate or high risk. Any disagreements between reviewers will be resolved by discussion. A third reviewer (VJM) will be consulted if a consensus cannot be reached.

Data analysis

Data extracted from individual studies will be entered into Review Manager 5 [24] for analysis. Clinical heterogeneity will be determined based on similarities or differences in participant and outcome characteristics, recruitment procedures and study setting [25]. Statistical heterogeneity will be assessed using the I^2 statistic, and the results will be presented as low (< 25%), moderate (25–50%) and high (> 50%) [26]. Subject to consideration of heterogeneity and risk of bias, studies will be pooled for meta-analysis using the random-effects model to determine a summary estimate of PLP prevalence across included studies. A statistically significant level will be set at $p < 0.05$. A narrative data analysis will be conducted where there is insufficient data to conduct a meta-analysis. A funnel plot will be generated to assess for possible publication bias [27]. In addition, the Egger's regression test will be used to assess for the asymmetry of the funnel plot. A significant result ($p < 0.05$) will indicate a possible publication bias [27]. Risk factors for PLP will be identified from included studies and synthesised descriptively. Cohen's Kappa will be used to determine inter-rater agreement during screening, data extraction and risk of bias assessment as either minimal (0–0.39), weak (0.40–0.59), substantial (0.60–0.79) or strong (0.80–0.90) [28].

Subgroup analysis

A subgroup analysis on the prevalence of PLP will be conducted based on the development status of the countries in which the studies were conducted. Each country will be allocated to either group (developing vs developed) using the World Economic Situation and Prospects (WESP) classification system [29]. Vascular complications are the common cause of amputations in developed countries and traumatic accidents are the common cause of amputations in developing countries [30–32]. Regardless of the differences in the reasons for amputations, recent evidence shows that there is a similar number of limb amputations conducted in developing and developed countries [33, 34]. However, it is unclear whether there is a difference in the reported prevalence of PLP between developing and developed countries. The purpose of this subgroup analysis is to determine if this is the case.

Grading the certainty of evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology will be used to determine the certainty of evidence regarding the prevalence of PLP. The quality of evidence will be graded as high if further research is unlikely to change the effect estimates, moderate if further research is likely to have a considerable impact on the effect estimates and low if further research is likely to be capable of changing the effect estimates [35].

Dealing with missing data

We will contact the authors of included studies to request missing data as necessary. If additional data cannot be obtained, each study with incomplete data will not be analysed.

Discussion

As far as we know, a systematic review and meta-analysis on the prevalence of and risk factors for PLP in people with amputations has not been conducted. Given the conflicting reports in the literature concerning the prevalence of PLP, it is necessary to determine the estimate of the prevalence of PLP to generate an informed conclusion on this subject. The results of this review will be published in a peer-reviewed journal and used to inform researchers, clinicians, policy-makers and the public about the burden of PLP in society. Further, they will be used to motivate for the development and implementation of pragmatic interventions that could prevent or reduce PLP in people with amputation. By clarifying risk factors for PLP, this study will provide empirical evidence that may enable clinicians to identify priorities for diagnosing, treating and preventing PLP.

Appendix

Search strategy [PubMed]

1. Amputation [MeSH] OR Amputation, Traumatic [MeSH] OR Amputation Stumps [MeSH] OR Amputee OR amputees OR amputation OR limb deficiency OR limb loss.
2. Phantom Limb [MeSH] OR Phantom limb OR phantom pain OR phantom sensations OR phantom sensation OR residual limb pain
3. Epidemiology [MeSH] OR Epidemiology [Subheading] OR Prevalence [MeSH] OR Risk Factors [MeSH]
4. associated OR association OR burden OR case-control OR cohort OR correlation OR correlates OR cross-sectional OR determinant OR epidemiology OR epidemiological OR epidemiologic OR frequency OR incidence OR interview OR likelihood ratio OR observational OR occur OR occurrence OR odds ratios OR predict OR predictor OR prediction OR present OR presentation OR prevalence OR prevalent OR probability OR prognosis OR prognostic OR proportion OR prospective OR questionnaire OR questionnaires OR rate OR retrospective OR risk OR risks OR self-report OR statistic OR surveillance OR survey OR surveys
5. 1 AND 2 AND 3 AND 4

Additional file

Additional file 1: PRISMA-P Checklist. (DOCX 30 kb)

Abbreviations

CINAHL: Cumulative Index to Nursing and Allied Health Literature; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; PLP: Phantom limb pain; PRISMA-P: Preferred Reporting Items of Systematic Reviews and Meta-Analysis Protocol

Acknowledgements

The authors would like to acknowledge the assistance of Mrs. Mary Shelton (Health Sciences reference librarian, University of Cape Town) in development of the search strategy.

Funding

The first author is funded by the Start-up Emerging Researcher Award (SERA) and the Research Development Grant (RDG) provided by the University of Cape Town. VJM is funded by an Innovation postdoctoral fellowship from the National Research Foundation of South Africa.

Availability of data and materials

Data identified through a literature search will be made available upon reasonable request.

Authors' contributions

KL, RP and VJM conceptualised the study; KL wrote the manuscript, and all authors edited and approved the manuscript.

Authors' information

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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Received: 8 November 2018 Accepted: 26 December 2018
Published online: 10 January 2019

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Appendix 5: Acute care surgery online database - HREC 020/2018.

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
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Website: www.health.uct.ac.za/fhs/research/humanethics/forms

14 September 2018

HREC REF NO: R020/2018

Dr S Rayamajhi
Acute Care Surgery
J45, OMB

Dear Dr Rayamajhi

PROJECT TITLE: *ACUTE CARE SURGERY ONLINE CLINICAL TOOL /DATABASE*

Thank you for submitting your database to the Faculty of Health Sciences Human Research Ethics Committee.

The HREC has **approved** the registration of your database.

Please Note: All research, including that undertaken for a master's or doctoral degree, using registered databases, registries and repositories, requires submission as a new study. It requires an application form (FHS013) and a protocol which has undergone departmental review. The study will receive its own HREC REF number which will be linked to the main database or repository.

The registration of this registry is valid until **30 September 2021.**

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS

Appendix 6: Patient information sheet.

Dear Sir/Madam

I am a qualified physiotherapist and PhD student at the University of Cape Town. I am working with your hospital to get information on the number of people who feel pain in the limb that is no longer there after amputation.

I am phoning you because your name was listed in the hospital records. The records state that you had a limb amputation. I am phoning you to invite you to participate in this study. The main reason for this study is to get information on the number of people who feel phantom limb pain after amputation. I also want to find the factors that can cause one to experience this pain after amputations.

First, I will ask you questions to check whether you qualify to take part in the study. If you qualify, I will then ask you short questions about your age, sex, and education level. I will also ask you a few simple questions about phantom limb pain. The telephone interview should take no longer than 30 minutes.

This is a low risk involved in taking part in this study. Remembering the trauma of having had the surgery might affect you emotionally. We will refer you to your nearest relevant clinic for treatment should you feel emotionally unwell. In this study, you might learn a few things about PLP. You will also be given a referral to the nearest relevant clinic if you require assistance with your pain. No payments or benefits will be given to you for taking part in this study. Once we complete the study, we will be able to share our results with you if you are interested in them.

Taking part in the study will not interrupt your normal care at all. Taking part is completely up to you and nothing bad will happen to you if you choose not to take part. If you do choose to take part, you can stop at any time during the interview. You may also choose not to answer some questions if you

do not want to answer them. Your personal information will not be shared with anyone without your permission. The results of this study will be stored safely. Your name will not be used in publications. Should you choose to participate, please feel free to contact the Human Research Ethics Committee on (021) 406 6338 in case you have any questions about your rights and welfare as a participant on the study; the primary supervisor, A/Prof Romy Parker, can be contacted on 021 650-1608 to answer any other questions you may have.

CONSENT FORM:

TITLE OF STUDY: THE PREVALENCE AND RISK FACTORS FOR PHANTOM LIMB PAIN IN PEOPLE WITH AMPUTATIONS.

I understand the outline of this study. I do not feel forced to partake in this study and am doing so willingly. I know that I can withdraw from the study anytime and there will not be any penalty for my action.

Signed: (write name and surname)

On behalf of the participant: _____ Date and Place:

Researcher: _____ Date and Place:

Appendix 7: Sample size calculation.

Home » Mathematics Statistics and Analysis Calculators » Sample Size Calculator

Sample Size Calculator

You can use this free sample size calculator to determine the sample size of a given survey per the sample proportion, margin of error, and required confidence level.

You can calculate the sample size in five simple steps:

1. Choose the required confidence level from the dropdown menu
2. Input the margin of error
3. Input the proportion of the total population (%)
4. If required, specify the population size
5. Click on the "Calculate" button to generate the results.

Online Sample Size Calculator

Confidence Level **(α)**: 95%

Margin of Error **(e)**: 5.3 %

Population Proportion **(p)**: 64 %

Population Size **(N)** (optional)

Calculate

Reset

Results

Your recommended sample size is: **316**

The sample size (n) is calculated according to the formula: $n = z^2 * p * (1 - p) / e^2$

Where: z = 1.96 for a confidence level (α) of 95%, p = proportion (expressed as a decimal), e = margin of error.

z = 1.96, p = 0.64, e = 0.053

$n = 1.96^2 * 0.64 * (1 - 0.64) / 0.053^2$

n = 0.8851 / 0.0028 = 315.096

n ≈ 316

The sample size is equal to 316

Appendix 8: The pain severity scale of the Brief Pain Inventory.

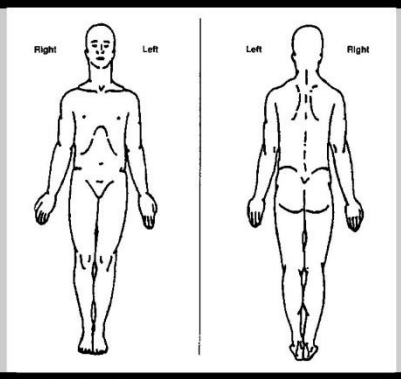
STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Many people who have had amputations report that they can still feel their limb or have pain in the limb which is no longer there. Being able to feel the limb is called phantom limb sensation. Having pain in the limb which is no longer there is called phantom limb pain. In the past week, have you experienced phantom limb pain – pain in your limb which is no longer

1. Yes 2. No



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one nuimber that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Appendix 9: Customised assessment sheet for characteristics and risk factors for PLP.

Many people who have had amputations report that they can still feel their limb or have pain in the limb which is no longer there. Being able to feel the limb is called phantom limb sensation. Having pain in the limb which is no longer there is called phantom limb pain. In the past week, have you experienced phantom limb pain – pain in your limb which is no longer there?

Why was your limb amputated?

Phantom limb pain characteristics.

What words would you use to describe the pain you are experiencing in the limb which is no longer there?

Burning ☐ Sharp ☐ Shooting ☐

Aching ☐ Cramping ☐ Other ☐

Elaborate:_____

Phantom limb pain episodes.

How many times in the past week have you experienced phantom limb pain?

Number of pain episodes:_____

Phantom limb pain duration

How many minutes does each episode usually last?

Duration of episode:_____

Risk factors for phantom limb pain

Pre-operative risk factors

Persistent pre-operative pain:

Did you experience continuous pain in the limb before it was amputated?

Yes ☐ No ☐

Diabetic cause of amputation:

Was your limb amputated because of complications of diabetes?

Yes ☐ No ☐

Traumatic cause of amputation:

Was your limb amputated because of an accident?

Yes ☐ No ☐

Pre-amputation depression:

Were you diagnosed with depression before your limb was amputated?

Yes ☐ No ☐

Lack of pre-amputation counselling/support

Did you receive counselling about your amputation before your limb was amputated?

Yes ☐ No ☐

Perioperative risk factors:

Proximal site of amputation:

Was your limb amputated above the elbow or knee?

Yes ☐ No ☐

Lower limb amputation:

Was the amputation done on your leg?

Yes ☐ No ☐

Bilateral amputation:

Were both your left and right limb amputated?

Yes ☐ No ☐

Post-operative risk factors:

Depression:

Have you been diagnosed with depression since your limb was amputated?

Yes ☐ No ☐

Stump pain:

Do you experience pain in the remaining part of the amputated limb?

Yes ☐ No ☐

Use of Prosthesis:

Do you use a prosthetic limb?

Yes ☐ No ☐

If so, please indicate the type of prosthesis you use: Mechanical ☐ Cosmetic ☐ Myoelectric ☐

Phantom sensations:

Do you feel non-painful sensations in the limb that is no longer there?

Yes ☐ No ☐

Appendix 10: Invitation letter to participate as an expert panellist.

UNIVERSITY OF CAPE TOWN

Department of Anaesthesia and Perioperative Medicine

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21 May 2019

Dear Dr/Prof [insert name]

RE: Invitation for participation in the expert Delphi study for phantom pain management.

I am a registered PhD student in the Departments of Anaesthesia and Perioperative Medicine at the University of Cape Town, South Africa. I am writing to you because you have been identified by our team as an expert in phantom limb pain. Therefore, we would like to invite you to participate in our study as a member of an expert panel. The aim of this study is to develop guidelines and make recommendations on the effective management of PLP in people with amputations.

This study will be conducted using three sequential rounds of anonymous online questionnaires. Each round of the Delphi may take you less than 15 minutes to complete. During the first round, you will be sent an email requesting you to propose treatments for phantom limb pain. Responses from this round will be gathered from panellists and used to design a standardised questionnaire that will be used as the basis for the second round of the Delphi. During the second round, you will be asked to rank the effectiveness of each treatment approach on a 5-point Likert scale [1=Strongly agree; 2=Agree; 3=No opinion; 4=Disagree; 5=Strongly disagree] and provide justification for your rating. The treatments which have been endorsed by 50% or more of the panellists will be carried forward

into the final round. In the final round, you will be sent a questionnaire with a summary of all responses from the second round. Then, you will be asked to review your responses in light of the group's opinion by changing or maintaining your prior rating.

This is a very low risk study. Therefore, you will not be exposed to any harm. Your participation in this study will enable us to formulate guidelines that will enable clinicians to improve the quality and appropriateness of pain management in people with amputations.

Thanks for considering our invitation. Your participation is highly appreciated.

Yours sincerely,

Katleho Limakatso [BSc (Hons),PGDip,MSc,PhD Candidate]

Department of Anaesthesia and Perioperative Medicine,

University of Cape Town,

Anzio Rd,

Observatory 7925,

South Africa.

Katleho.limakatso@uct.ac.za

Appendix 11: Information sheet (telephone script).

Dear Participant

I am a qualified physiotherapist and PhD student at the University of Cape Town. I am working with Groote Schuur Hospital to get information on medical problems that patients would want the most help with after their lower limb amputation.

I am phoning you because your name was listed in the hospital records. The records state that you had a limb amputation in (year of amputation). I am phoning you to invite you to take part in this study. The aim of this study is to find out from patients what the most important problems are that health-care professionals should focus on after limb amputation.

First, I will ask you questions to check if you qualify to take part in the study. If you qualify, I will then invite you to Groote Schuur Hospital (venue, date and time) where we will again tell you about the study process. If you are happy to take part in the study, you will then sign a form showing that you are happy to take part in the study. If you do not wish to take part in the study at that stage, you may pull out of the study and this will not your care. In this study, we will ask you two questions- 1) "What would you want help with from health care professionals during the first year after an amputation of your lower limb?" and 2) "What would you want help with from health care professionals after a year following an amputation of your lower limb?" Your responses and those of other patients will be used to design a form that will list all the things people have mentioned as important. You will then be asked to rank the importance of each response on the form on a scale of 1-5. After this, you might be asked to give reasons for your ranking of each response.

There is a low risk involved in taking part in this study. The study might take 2-3 hours to complete, and you might feel tired. However, you will be given a break after each round, and lunch and snacks will be served free of charge. You will be given R100.00 to help you pay for your transport to and from the hospital. We also realise that time is valuable and spending a day at the hospital is using

your valuable time. To make up for this we will also give you R100.00 for your participation. No other payment or benefit will be given to you for taking part in this study. Once we complete the study, we will be able to share our results with you if you are interested in them.

If you require more information about the study, please feel free to contact the primary supervisor, Prof Romy Parker on 021 650-1608. You can also contact the Human Research Ethics Committee on (021) 406 6338 if you have any questions about your rights and safety as a participant in the study.

Are you interested in taking part in our study? Yes/No

If yes, ask the following questions?

Inclusion criteria

- Do you have an amputation of a lower limb?
- Was your leg amputated between 2017 and 2020?
- Are you 18 years or older?
- Are you able to speak, read and write in the English, isiXhosa or Afrikaans language?
- Do you currently live in Cape Town?

Exclusion criteria

- Do you have hearing and/or talking problems that make it difficult for you to speak properly?
- Do you have eye problems that make it difficult for you to read even when wearing reading glasses?
- Have you been diagnosed with severe mental problems that make it difficult for you to think and remember clearly?

If the patient is eligible for inclusion:

Thank you – you qualify to participate. Do you have a pen and paper? Please come to Groote Schuur (date, time and venue to be confirmed) to complete and sign the agreement form and participate in the study.

If the patient is ineligible for inclusion:

Thank you for taking the time to speak with me. I am afraid you do not qualify to take part in our study. Do you have any questions for me? Thank you for your time

Appendix 12: Consent form.

CONSENT FORM:

STUDY TITLE: CARE PRIORITIES FOR PATIENTS WITH LIMB AMPUTATIONS: A PATIENT-LED DELPHI STUDY

I understand the details of this study. I do not feel forced to take part in this study and am doing so willingly. I know that I can pull out from the study anytime and this will not affect my care.

Signed by:

participant: _____ .

Date:

Investigator: _____ .

Appendix 13: Demographics questionnaire.

Patient Code: _____ Date: _____

Home language: _____

Age: _____

Sex: _____

Time since amputation: _____

Level of amputation: _____

Cause of amputation: _____

Contact details:

Which area do you live in? _____

What is your highest level of education? _____

Are you currently employed? If so, what do you do? _____

Do you use an assistive device? _____

If so, what assistive device you use? _____

Do you have any other medical conditions? If so, please name them:

_____

_____

_____