Author/s:
Iseli, RK;Lee, EK;Lewis, E;Duncan, G;Maier, AB

Title:
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Date:
2021-03-01

Citation:
Iseli, R. K., Lee, E. K., Lewis, E., Duncan, G. & Maier, A. B. (2021). Foot disease and physical function in older adults: A systematic review and meta-analysis. Australasian Journal on Ageing, 40 (1), pp.35-47. https://doi.org/10.1111/ajag.12892.

Foot disease and physical function in older adults: a systematic review and meta-analysis

Rebecca K Iseli[1,2]; Elton K Lee[1]; Ellen Lewis[3]; Gregory Duncan[4]; Andrea B Maier[1,5]

Affiliations:

[1] Department of Medicine and Aged Care, @AgeMelbourne, The Royal Melbourne Hospital, The University of Melbourne, Parkville, Victoria, Australia

[2] Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Parkville, Australia

[3]Podiatry Department, The Royal Melbourne Hospital, Parkville, Victoria, Australia

[4] Eastern Health Clinical School, Monash University, Box Hill, Victoria, Australia

[5] Department of Human Movement Sciences, @AgeAmsterdam, Amsterdam Movement Sciences, Vrije Universiteit, Van der Boechorststraat, Amsterdam, The Netherlands

Funding: Nil

Conflicts of interest: None to declare

Corresponding author:

Dr Rebecca Iseli

Department of Medicine and Aged Care, @AgeMelbourne, The Royal Melbourne Hospital, The University of Melbourne, Parkville, Victoria, Australia

Email: rebecca.iseli@mh.org.au

ABSTRACT (150 words)

Objectives To systematically assess the literature of the association between foot disease (foot ulceration, infection, critical ischaemia and/or Charcot neuroarthropathy) and physical function in older adults.
Methods Literature search of MEDLINE, Embase and CINAHL. Studies were included if foot disease and physical function were assessed in participants of mean or median age ≥65 years.
Results Of 2,574 abstracts screened, 19 studies (13 longitudinal, 6 cross-sectional) reporting on 5634 participants, 42.9% female, were included. Diabetic foot disease and critical ischaemia were most studied (n = 5017, 40.4% female). In 8 studies with control groups, foot disease was associated with worse physical function. Meta-analysis of 5 studies (n = 1503, 45.1% female) found an association between foot disease and worse physical function (SMD (95% CI): 1.00 (0.40, 1.62), p 0.001).
Conclusion Foot disease is associated with worse physical function in older adults. Future research should include broader study populations and intervention strategies.

Keywords: Accidental falls, Foot diseases, Foot ulcer, Peripheral arterial disease, Physical functional performance

Acknowledgements
We kindly acknowledge Mr Patrick Condron for his assistance with the search of the literature.

Author contributions
Study conception by RKI, GD and ABM. Search strategy developed by RKI and EKL. Screening and data extraction performed by RKI and EKL; conflicts resolved by EL and ABM. RKI performed the data analysis. Manuscript development led by RKI with contribution from all authors.

Funding
None to declare.

Conflicts of Interest

None to declare.

DR. REBECCA K ISELI (Orcid ID : 0000-0003-2403-5104)

Article type : Review Article

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ABSTRACT (150 words)

Objectives To systematically assess the literature examining the association between foot disease (foot ulceration, infection, critical ischaemia and/or Charcot neuroarthropathy) and physical function in older adults.

Methods Literature search of MEDLINE, Embase and CINAHL. Studies were included if foot disease and physical function were assessed in participants of mean or median age ≥65 years.

Results Of 2,574 abstracts screened, 19 studies (13 longitudinal, 6 cross-sectional) reporting on 5634 participants, 43% female, were included. Diabetes-related foot disease and critical ischaemia were most studied (n = 5017, 40% female). In 8 studies with control groups, foot disease was associated with poorer physical function. Meta-analysis of 5 studies (n = 1503, 45% female) found an association between foot disease and poorer physical function (SMD (95% CI): 1.00 (0.40, 1.62), p 0.001).

Conclusion Foot disease is associated with poorer physical function in older adults. Future research should include broader study populations and intervention strategies.

Keywords: Accidental falls, Foot diseases, Foot ulcer, Peripheral arterial disease, Physical functional performance

Impact statement: (45 words)

This systematic review and meta-analysis found an association between foot disease and poorer physical function in older adults. Further studies of foot disease in general populations of older adults and interventional studies aiming to attenuate the impact of foot disease on physical function are warranted.

Introduction

Foot problems, such as pain, deformity, muscle weakness and reduced range of motion, increase in prevalence with advancing age.[1, 2] Foot disease, which is defined as foot ulceration, infection, critical ischaemia and/or Charcot neuroarthropathy[3], is the most severe form of foot problems and prevalent in 5 to 12% of hospital inpatients.[1, 3, 4] Foot problems and foot disease are associated with poorer health outcomes.[5] In community dwelling older adults, foot problems have been associated with a higher risk of falling,[6] reduced independence in activities of daily living (ADLs)[7, 8] and reduced quality of life.[9-12] Podiatry interventions in older adults with foot problems are associated with better physical function[13] and reduced risk of falls.[14]

Most studies of foot disease have been undertaken in specific disease related populations, such as people with diabetes, rather than general populations.[3] People with diabetes-related foot disease have a higher risk of falls, hospitalization and amputation,[15, 16] and podiatry intervention has been shown to attenuate these risks.[17, 18]

It is likely that foot disease would be associated with poorer physical function in older adults. It is important to examine this association, as foot disease may be more readily diagnosed by non-podiatrists than milder foot problems, and there is potential for intervention. The aim of this study, therefore, is to systematically review the current literature to determine the association between foot disease and physical function in older adults.

Methods

The protocol of the systematic review was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

guidelines[19] and registered with the PROSPERO International prospective register of systematic reviews (CRD42020169885). MEDLINE (from 1946), EMBASE (from 1974), and CINAHL (from 1937) databases were systematically searched for studies published until February 23, 2020. The search strategy was developed with the assistance of a senior research librarian, and included synonyms of foot disease, physical function and older adult. Further studies were identified by searching the reference lists of included articles. The complete search strategy for each database is included in Appendix I. Inclusion criteria were: randomised controlled trials or observational studies (cross-sectional or longitudinal); diagnosis of foot disease, defined as foot ulceration, infection, critical ischemia (toe pressure <30mmHg or Ankle Brachial Index <0.5) or Charcot neuroarthropathy; participants with and without foot disease were assessed using a measure of physical function; article published in English; mean or median age ≥65 years. Any measure of physical function, or measure related to physical function, was accepted: falls were included, given the strong association between poorer physical function and higher risk of falls.[20] Studies without primary data, such as conference abstracts and reviews, were excluded.

Articles were managed with Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia; available at www.covidence.org). Titles and abstracts were independently reviewed by two reviewers (RKI, EKL). Disagreements were resolved by discussion with a third reviewer (EL). Full texts of included articles were independently assessed and data extraction performed by two reviewers (RKI, EKL). The quality and risk of bias of individual studies was assessed by two independent reviewers (RKI, EKL) using the Newcastle-Ottawa Scale (NOS).[21] The NOS provides an assessment of the methodological quality of case control and cohort studies with a maximum score of 9 points.[21] Studies with a NOS score between 0 and 3 points was defined as low quality, 4 to 6 points as moderate quality and 7 to 9 points as high quality.[22] Publication bias was examined with a funnel plot.[23]

Meta-analysis was performed using Comprehensive Meta-Analysis software (version 2.0; Biostat Inc., Engle-wood, NJ), with a random effects model to account for

heterogeneity.[24] Studies reporting physical function measures were compared using Standardised Mean Difference (SMD) where the published data was sufficient to calculate SMD. For studies reporting multiple physical function measures, the mean of the SMD was used in the meta-analysis. The SMD may be interpreted as representing a small, medium or large effect size based on the cut off points of 0.2, 0.5 and 0.8 respectively. [25] Heterogeneity was expressed using the I^2 statistic (low <25%; moderate <50%; high >50%).[26] Reporting bias was assessed using a funnel plot.[27] P values below 0.05 were considered significant.

Results

Of 2,574 articles eligible for title and abstract screening, 88 were eligible for full text screening and 19 articles were included in the systematic review. Figure 1 shows the selection process of included articles.

Table 1 shows the descriptive characteristics of the included articles. The studies included a total of 5634 participants and the proportion of female participants ranged from 0 to 81% (mean 43%). The study populations were community dwelling (2202 participants, 9 studies);[28-36] hospitalised (2068 participants, 8 studies);[37-44] institutionalised (702 participants, 1 study);[45] and, mixed population (662 participants, 1 study).[46] Six studies were cross-sectional[29-31, 33-35] and 13 longitudinal.[28, 32, 36-46] Eight of the 19 studies featured a control group:[28-31, 33-36] cross-sectional studies were more likely to include a control group (6 of 8 studies) than longitudinal studies (2 of 13 studies). Eight studies were undertaken in participants with diabetes-related foot disease: 6 of these studies included only participants with diabetes[28, 30, 31, 37, 38, 40] and 2 studies also included participants without diabetes.[29, 39] Eight studies were undertaken in participants with critical limb ischaemia (CLI): 7 of these studies were revascularisation studies, comparing physical function before and after intervention;[32, 41-46] the other study compared outpatients with peripheral arterial disease of varying severity with controls.[33] The studies of foot disease due to CLI included a significant proportion of participants with diabetes (range 25 - 70%). Two studies were undertaken in outpatients with Rheumatoid Arthritis without diabetes[34, 35] and one study was conducted in a general cohort of older adults presenting to an Emergency Department, of which 21% were people with diabetes.[36]

Physical function

A wide range of physical function measures were reported (Table 1), including functional status (9 studies);[29, 34, 35, 37, 39-41, 45, 46] ambulatory function (6 studies);[32, 33, 38, 42-44] physical activity (4 studies);[28, 30, 32, 33] residential status (3 studies);[42-44] frailty (2 studies);[29, 46] and Health Related Quality of Life (HRQL)(2 studies).[31, 46] One study reported falls.[36]

Table 2 summarises the association between foot disease and physical function. All eight studies that included a control group reported significantly poorer physical function in participants with foot disease. These differences were reported for: functional status (Stanford Health Assessment Questionnaire (HAQ) and Foot Impact Scale (FIS) scores); [29, 34, 35] physical activity (daily step count,[28] daily activity unit scores,[33] Summary Performance Score[33]); self-reported activity (more sitting time; lower likelihood of undertaking vigorous exercise);[30] frailty (Edmonton Frail Scale);[29] HRQL (Short-Form 36 Health Survey scores);[31] and, falls.[36]

Studies without a control group included participants with diabetes-related foot disease and CLI having hospitalisation or surgical intervention for their foot disease. Participants with diabetes-related foot disease had high rates of functional impairment measured by Barthel Index (BI)[37, 40] and Functional Independence Measure (FIM).[39] Participants with foot disease due to CLI reported high rates of functional impairment and reduced ambulatory capacity, with limited improvement in these domains after intervention.[32, 41-44, 46]

Other outcomes reported

Table 2 shows other outcomes reported by the included studies: amputation rate was reported by 2 studies;[37, 38] institutionalisation rates were reported by 4 studies[39, 42-44] and mortality was reported by 10 studies:[32, 37-44, 46] none of these studies included a control group. Institutionalisation rates ranged from 11% in a study of patients undergoing major amputation for foot disease[39] to 28% in a study of nonagenarians undergoing treatment for CLI related foot disease.[43] Mortality ranged from 0% in a small study of 3-4 months follow up[32] to 97% at 5 years in the afore-mentioned nonagenarian study.[43]

Quality assessment

Table 3 presents the risk of bias quality assessment for included studies based on the Newcastle-Ottawa Scale (see Supplementary Appendix II). Two studies were of high quality,[33, 46] 16 studies were of moderate quality[28-32, 34-42, 44, 45] and 1 study was of low quality.[43]

Meta-analysis

Of the 8 studies reporting physical function measures for both foot disease and control groups, 5 studies (n=1503) were included in the meta-analysis.[28-30, 33, 35] The meta-analysis (shown in figure 2) found significantly poorer physical function in patients with foot disease: SMD (95% CI): 1.00 (0.40, 1.62), p 0.001. There was high heterogeneity (I^2=96%). There was asymmetry in the funnel plot, suggesting presence of reporting bias.[23, 27]

Discussion

This systematic review found an association between foot disease and poorer physical function. Foot problems (incorporating foot pain and deformity) have been associated with poorer physical function in older adults, as measured by ADL independence,[7, 8] quality of life[9] and falls.[2] Given that foot disease represents more severe foot pathology than foot problems, a greater association with poorer physical function may be anticipated. An association between foot disease and lower physical activity has also been shown in studies of younger cohorts with diabetes-related foot ulceration[47], as well as high disability burden[48] and risk of lower limb amputation.[49]

Most studies were undertaken in specific disease related populations with diabetes-related foot disease or critical ischaemia; however, prevalence studies suggest that foot disease is also common in populations without diabetes and hospitalised older adults.[3, 4] An Australian survey in general hospital inpatients (mean age 62 years) reported prevalence of foot disease of 10%, only 46% of whom were people with diabetes.[1] Similarly, in a retrospective study of patients admitted to a US hospital with foot ulceration only 54% had diabetes-related foot disease.[50]

The studies of foot disease populations without control groups reported poor physical function as well as high institutionalisation and mortality rates among participants.[32,

[37-46] Institutionalisation rates were comparable to reported rates for older patients with other common admission diagnoses, such as hip fracture,[51] stroke or functional decline requiring hospital admission.[52] Mortality rates in foot disease populations were higher than reported rates for these other common admission diagnoses.[51, 52]

The association between foot disease and poorer physical function does not necessarily imply causation, particularly given most of the studies with a control group were cross-sectional.[29-31, 33-35] There are a number of reasons, however, that physical function may be poorer in the presence of foot disease. Foot pain, which is usually a symptom of foot disease,[53] has been associated with higher risk of falls, impaired balance, gait abnormalities and reduced independence in ADLs.[6, 54] Critical ischaemia, one form of foot disease, is associated with reduced balance and physical activity.[33]

The findings of this review highlight the importance of diagnosing foot disease, as well as the need for further studies of foot disease in general populations of older adults. Given that podiatry intervention has been shown to reduce the risk of falls for older adults with foot problems[14] and to reduce amputation and hospitalisation rates in people with diabetes,[17, 18] interventional studies aiming to improve physical function in older adults with foot disease may be warranted.

Strengths and limitations

To the best of our knowledge, this is the first systematic review investigating the association between foot disease and physical function in older adults. There was evidence of reporting bias based on the funnel plot, which is a limitation of this study: reasons for this include the possibility of unpublished negative studies and restricting articles to those published in English. Heterogeneity in the meta-analysis was high due to differences in study populations and range of outcome measures. This was addressed using a random effects analysis but must be considered in interpreting the results. A broad definition of physical function measures was used for this meta-analysis, including falls. Although falls are strongly associated with poorer physical function, other factors may also increase the risk of falling.[20] Comparing physical function outcomes using SMD, and use of the mean SMD for studies with multiple outcome measures, allowed comparison between studies using different measures

to provide a pooled estimate of effect; however, this technique may have led to under- or over-estimate of the association[25] and is another limitation of this review.

Conclusion

Foot disease is associated with poorer physical function in older adults. Most studies to date have included specific disease-related cohorts of patients and reported a range of physical function measures. Future research should include broader study populations with control groups without foot disease.

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TABLES

Table 1: Study characteristics of included articles

First author, Year (Ref)	Study design	N	Population	Age, years	Female, %	Follow up, months	Physical Function	Physical Function measure(s)
Populations with diabetes:								
Armstrong, 2004 [28]	L, O, P	100	Outpatients with risk factors for foot disease (excluded PAD)	68.5 (10)	5	8.4 (2.8)	Daily activity Activity clusters	Step count CV of activity
Boas, 2018 [29]	C	150	Outpatients with & without FU; controls without diabetes	Range 67.7-71.5	56	N/A	Frailty Functional disability	EFS HAQ
Chu, 2016 [37]	L, O, P	245	Toe amputation for DFU	69.3 (9.4)	41	60	ADL	BI
Hartmann, 2017 [38]	L, O, R	245	Hospitalised for DFS	71	16	6	Mobility at discharge	Non-validated measure: mobile vs immobile
Hershkovitz, 2013 [39]	L, O, P	117	Lower limb amputation (61% DFS) admitted to rehabilitation	74.7 (8.1)	39	12	Prosthesis use Functional status by prosthesis group	Prosthesis yes/no FIM

Johnson, 2019 [30]	C	240	Community based, past history of FU or no FU (no active FU)	68.7 (10.5)	42	N/A	Self-reported physical activity	lPAQ-SF
Seker, 2016 [40]	L, O, R	87	TTA or TFA for DFU	TTA 69.3 TFA 70.7	36	79.1	Functional status by amputee group	BI, AMP
Valensi, 2005 [31]	C	335	With and without DFU	DFU 65.5 (11.2) no-DFU 62.3 (12.7)	38	N/A	HRQL	SF-36 Diabetic Foot Ulcer Scale
Populations with critical lower limb ischaemia:								
Duggan, 1994 [41]	L, O, R	38	Limb salvage surgery (70% with diabetes)	72.1	45	18.6	Functional status	RAND-36
Gardner, 2001 [32]	L, O	20	Lower limb re-vascularisation (70% with diabetes)	68	0	3	Before and after revascularisation: Ambulatory function Physical activity Self-reported physical activity	 20MWT 6min walk test, Steps/day, PAD-PAR, LTPA, WIQ

Iida, 2017 [46]	L, O, P	662	With or without revascularisation (R+ vs R-) (62% with diabetes)	77 (10) R+ 82 (9) R-	41 R+ 59 R-	12	ADL Frailty HRQL	Modified KATZ index Life-Space Assessment 5m gait velocity Grip strength EQ-5D EuroQol VAS
McDermott, 2002 [33]	C	740	Outpatients with PAD and controls (28% with diabetes)	70.9 (8.4)	44	N/A	Ambulatory function Physical activity	6-min walk test Summary performance score Activity units/day
Pomposelli, 1998 [42]	L, O, R	262	Undergoing LEAR (67% with diabetes)	83.6	55	12	Residential status Ambulatory function	Non-validated measures
Saarinen, 2015 [43]	L, O, R	233	CLI (n=170) or acute limb ischemia (n=63) having vascular intervention	92 (median)	81	NR	Residential status Ambulatory function	Non-validated measures

			(25% with diabetes)					
Taylor, 2006 [44]	L, O, R	841	Vascular intervention (54% with diabetes)	68.1 (12.1)	43	27.5 (21.6)	Residential status Ambulatory function	Non-validated measures
Vogel, 2014 [45]	L, O, R	702	Nursing home residents having revascularisation (63% with diabetes)	NR	57	6	ADL	Minimum Data Set ADL-Long form score
Populations with Rheumatoid arthritis (RA):								
Firth, 2008 [34]	C	81	Outpatients with FU (n=15) or no FU (n=66) (0% with diabetes)	65 (13) FU+	27 FU+	N/A	Functional disability	Foot impact scale HAQ
Firth, 2014 [35]	C	273	Outpatients with FU (n=83) or no FU (n= 190) (0% with diabetes)	71 FU+ 62 FU-	79	N/A	Functional disability	Foot impact scale HAQ
General population older adults:								
Carpenter, 2009 [36]	L, O, P	263	Community dwelling, presenting to	76	63	6	Falls	Self-reported fall

	Emergency (21% with diabetes)

Abbreviations: ( ) – standard deviation; [ ] – interquartile range; ADL – Activities of Daily Living; AMP - Amputee Mobility Predictor; BI - Barthel Index; C – cross-sectional; CLI – Critical Limb Ischaemia; CV – Coefficient of variation; DFS – Diabetic Foot Syndrome; DFU – Diabetic Foot Ulcer; EFS - Edmonton Frail Scale; EQ-5D – EuroQol 5 Dimension; EuroQol VAS – EuroQol Visual Analogue Scale; FIM – Functional Independence Measure; FU – foot ulcer; HAQ - Stanford Health Assessment Questionnaire; HRQL – Health Related Quality of Life; IPAQ-SF – International Physical Activity Questionnaire Short Form; L – longitudinal; LEAR - Lower Extremity Arterial Reconstruction; LTPA - Minnesota Leisure Time Physical Activity; NR – not reported; O – observational; P – prospective; PAD-PAR - Peripheral Arterial Disease Physical Activity Recall; PAD – Peripheral Arterial Disease; R – retrospective; RAND-36 – RAND-36 Item Health Assessment Survey Version 1.0; SF-36 – Short-Form 36 Health Survey; TFA – trans-femoral amputation; TTA – trans-tibial amputation; WIQ - Walking Impairment Questionnaire; 20MWT – 20 meter walk test

Table 2: Reported study outcomes of included articles

First author, Year (Ref)	**Physical Function**	**Physical function measure**	**Outcome**	**Other outcomes reported**
Populations with diabetes:				
Armstrong,			8% developed FU	

2004 [28]	Physical activity	Step count, steps/day (SD)	Lower daily activity and higher CV of activity in FU group 809.0 (612.2) FU+; 1394.5 (868.5) controls; p = 0.03	
	Activity clusters	CV of activity, % (SD)	96 (50) FU+; 45 (15) controls; p = 0.02	
Boas, 2018 [29]			DFU group more frail and greater functional disability	
	Frailty	EFS severity, n (%)	15 (30%) D+FU+; 1 (2%) D+FU-, 0 (0%) D-FU-; p <0.001	
	Functional disability	HAQ, mean (SD)	2.4 (0.6) D+FU+; 0.5 (0.9) D+FU-; 0.2 (0.5) D-FU-; p < 0.001	
Chu, 2016 [37]	ADL		32% moderate/severe ADL impairment; higher re-amputation incidence if moderate/severe ADL impairment	Re-amputation 49%
		BI, dichotomised, n (%)	BI >60 (good/mild dysfunction) 126 (68%) BI <60 (moderate/severe dysfunction) 59 (32%)	Mortality 38%
Hartmann, 2017 [38]	Mobility at discharge		Mobility decreased with age; didn't improve with revascularisation	Amputation 3% Mortality 9%
		Mobile, %, by age group	80% <65 years; 71% 65-74 years; 58% 75 years; 53% 84 years	
Hershkovitz, 2013 [39]	Prosthesis use	Prosthesis suitable, n (%)	Higher FIM scores in prosthesis group 27 (23%)	Mortality 46% Institutionalisation 11%
	Functional status	FIM, mean (SD)	Admission 73.6 (14.3) Discharge 90.8 (13.7) Prosthesis + Admission 50.4 (17.4) Discharge 55.7 (22.4) Prosthesis –	
Johnson, 2019 [30]	Self-	Walking time, min/wk	13% had a history of FU Correlation (R) with history of FU -0.0, NS	

	reported physical activity	Moderate exercise, min/wk	Correlation (R) with history of FU -0.0, NS	
		Vigorous exercise, min/wk	Correlation (R) with history of FU -0.1, NS	
		Sitting time, min/wk	Correlation (R) with history of FU 0.2, $p < 0.05$	
		Moderate exercise, Yes/No	Phi coefficient with history of FU 0.1, NS	
		Vigorous exercise, Yes/No	Phi coefficient with history of FU -0.1, $p < 0.05$	
		PA guidelines met, Yes/No	Phi coefficient with history of FU -0.1, NS	
Seker, 2016 [40]	Functional status	BI, mean	TTA 82.5; TFA 80.2, NS	Mortality 66%
		AMP, mean	TTA 32.3/29.5 prosthesis+/-; TFA 26.9/22.7 prosthesis+/-, $p <0.05$	
Valensi, 2005 [31]	HRQL	SF-36	Poorer HRQL in DFU group in all SF-36 domains, $p<0.001$ Age, type of diabetes, DFU severity (Wagner grade) and number of FU significant and independent predictors of HRQL impairment	
Populations with critical lower limb ischaemia:				
Duggan, 1994 [41]	Functional status	RAND-36, preoperative compared to postoperative	Deterioration in general health and mobility after surgery, lower scores post operatively in all domains except pain	Mortality 39%

Gardner, 2001 [32]			Measured physical activity did not change; significant improvement in self-reported ambulatory and physical activity	Mortality 0%
			Before and after revascularisation:	
	Ambulatory function	20MWT, m/s, mean (SD)	0.9 (0.1), 1.0 (0.1), p = 0.92	
		6min walk, m, mean (SD)	85 (9), 101 (11), p = 0.74	
	Physical activity	Steps/day, mean (SD)	2921 (1030), 2643 (1155), p = 0.88	
		WIQ distance; speed; stairs (%)	7 (2%), 26 (7%); 9 (4%), 25 (7%); 12 (5%), 29 (8%); all p < 0.001	
	Self-reported physical activity	PAD-PAR, MET-h/day, mean (SD)	41 (5), 105 (7), p < 0.001	
		LTPA, Kcal/day, mean (SD)	58 (8), 136 (22), p < 0.001	
Iida, 2017 [46]			Non-revascularised group older, frailer	Mortality 34%
			HRQL significantly improved in revascularized group, ADL did not	
			Revascularised (R+) vs non-revascularised (R-) at baseline; R+ at 1 year	
			2.8 (2.4) vs 1.4 (2.0), p < 0.001; 2.3 (2.4)	
	ADL	Modified KATZ index, mean (SD)	19 (22), 10 (17), p < 0.001; 18 (25)	
		Life-Space Assessment, mean (SD)	13.9, 9.0, p < 0.001; NR	
	Frailty	5m gait, velocity >10sec,		

		%	31.7, 47; NR	
		Grip strength ≤15/≤10		
		M/F, %	0.4 (0.3), 0.3 (0.3); 0.4 (0.3)	
	HRQL	EQ-5D, mean (SD)	43 (22), 39 (24), p 0.18; 55 (25)	
		EuroQol VAS, mean (SD)		
McDermott,			Participants with CLI had worse physical function than controls	
2002 [33]	Ambulatory	Stops on 6-min walk	OR (95%CI) 11.7 (4.9-27.7), p < 0.001	
	function	6-min walk, feet	Regression co-efficient (95%CI) -523 (-592 to -454), p < 0.001	
		4m walk velocity, m/s	Regression co-efficient (95%CI) -0.21 (-0.27 to -0.15), p < 0.001	
	Physical	Activity units/day	Regression co-efficient (95%CI) -515 (-657 to -373), p < 0.001	
	activity	Summary performance	Regression co-efficient (95%CI) -1.7 (-2.14 to -1.26), p < 0.001	
	Lower	score		
	extremity	Tandem stance hold 10s	OR (95% CI) 0.37 (0.18 to 0.76), p 0.007	
	function			
Pomposelli,		Non-validated measure	Ambulatory function score worsened post-operatively	Mortality 56%
1998 [42]			Pre-operative vs post-operative	Institutionalisation
	Residential	Score 1-4, mean	1.8, 1.9, p < 0.05	10%
	status			
	Ambulatory	Score 1-4, mean	1.6, 1.7, p < 0.05	
	function			
Saarinen,		Non-validated measure	Worse residential status and ambulatory function	Mortality 97%
2015 [43]			postoperatively; Pre-operative vs post-operative:	Institutionalisation
	Residential	Living in home-like	83, 72	28%

	status	circumstances, %		
	Ambulatory function	Ambulatory (with/without aid), %	91, 82	
Taylor, 2006 [44]	Ambulatory function and living status	Non-validated measure	Premorbid impaired ambulation and dementia predictors of poor function	Mortality 58% Institutionalisation 19%
		Change in ambulatory status, %	29	
		Independence maintained, %	81	
Vogel, 2014 [45]	Functional status	Minimum Data Set ADL-Long form score, change in score at 6 months by baseline ADL group	Most patients had ADL limitations prior to hospitalisation; these deteriorated during hospitalisation by 3 points and at 6 months had improved by 5-8 points Mean ADL function improved 1.6 points per month after hospital discharge	
Populations with Rheumatoid arthritis (RA):				
Firth, 2008 [34]	Functional disability		Mann-Whitney U scores comparing groups:	
		Foot impact scale	Higher score FU group, U = 302.5, p = 0.01	
		HAQ	Greater reduction self-care capacity FU group. U = 351.5, p = 0.05	
Firth, 2014 [35]	Functional disability		Worse functional status in FU group FU vs control group	
		Foot impact scale, mean (SD), OR (95% CI)	34.5 (10.9), 27.4 (13.8), 1.1 (1.0 – 1.1)	

	HAQ, mean (SD), OR (95% CI)	1.9 (0.9), 1.5 (0.9), 1.7 (1.3 – 2.3)
General population older adults:		
Carpenter, 2009 [36]	Falls	Reported fall during follow up period	8% had a FU; FU associated with increased risk of falling Cox regression analysis HR 3.71 (95%CI 1.73-7.95)

Abbreviations: ADL – Activities of Daily Living; AMP - Amputee Mobility Predictor; BI - Barthel Index; CLI – Critical Limb Ischaemia; CV - Coefficient of variation ; D – Diabetic; DFS – Diabetic Foot Syndrome; DFU – Diabetic Foot Ulcer; EFS - Edmonton Frail Scale; EQ-5D – EuroQol 5 Dimension; EuroQol VAS – EuroQol Visual Analogue Scale; FIM – Functional Independence Measure; FU – foot ulcer; HAQ - Stanford Health Assessment Questionnaire; HRQL – Health Related Quality of Life; IPAQ-SF – International Physical Activity Questionnaire Short Form; LEAR - Lower Extremity Arterial Reconstruction; LTPA - Minnesota Leisure Time Physical Activity; m – metres; Min – minutes; NR – not reported; NS – not significant; PA – Physical activity; PAD-PAR - Peripheral Arterial Disease Physical Activity Recall; PVD – Peripheral Vascular Disease; RAND-36 – RAND-36 Item Health Assessment Survey Version 1.0; s – seconds; SF-36 – Short-Form 36 Health Survey; TFA – trans-femoral amputation; TTA – trans-tibial amputation; wk – week; WIQ - Walking Impairment Questionnaire; 20MWT – 20 meter walk test

Table 3: Risk of bias quality assessment (Newcastle-Ottawa Scale)

First author, year	**Selection**				**Comparability**	**Outcome**			**Score**	**Quality**
	Representative-ness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not present at start	Adjustment for confounders	Assessment of outcome	Adequacy of duration of follow-up	Adequacy of completeness of follow-up		
Armstrong,	-	+	+	+	-	+	+	+	6	Moderate

2004										
Boas, 2018	-	+	+	-	+	+	-	+	5	Moderate
Carpenter, 2009	+	+	+	+	-	+	+	-	6	Moderate
Chu, 2016	-	-	+	+	-	+	+	+	5	Moderate
Duggan, 1994	-	-	+	-	-	+	+	+	4	Moderate
Firth, 2008	-	+	+	-	-	+	-	+	4	Moderate
Firth, 2014	-	+	+	-	-	+	-	+	4	Moderate
Gardner, 2001	-	-	+	+	-	+	-	+	4	Moderate
Hartmann, 2017	-	-	+	+	-	-	+	+	4	Moderate
Hershkovitz, 2013	-	-	+	-	-	+	+	-	3	Moderate
Iida, 2017	-	-	+	+	++	+	+	+	7	High
Johnson, 2019	-	+	+	-	-	+	-	+	4	Moderate
McDermott, 2002	+	+	+	-	++	+	-	+	7	High
Pomposelli, 1998	-	-	+	+	-	-	+	+	4	Moderate
Saarinen, 2015	-	-	+	+	-	-	-	+	3	Low
Seker, 2016	-	-	+	-	-	+	+	+	4	Moderate
Taylor, 2006	-	-	+	+	-	-	+	+	4	Moderate

Valensi, 2005	-	+	+	-	+	+	-	+	5	Moderate
Vogel, 2014	-	-	+	+	-	+	+	+	5	Moderate

Figure 1: PRISMA flow diagram

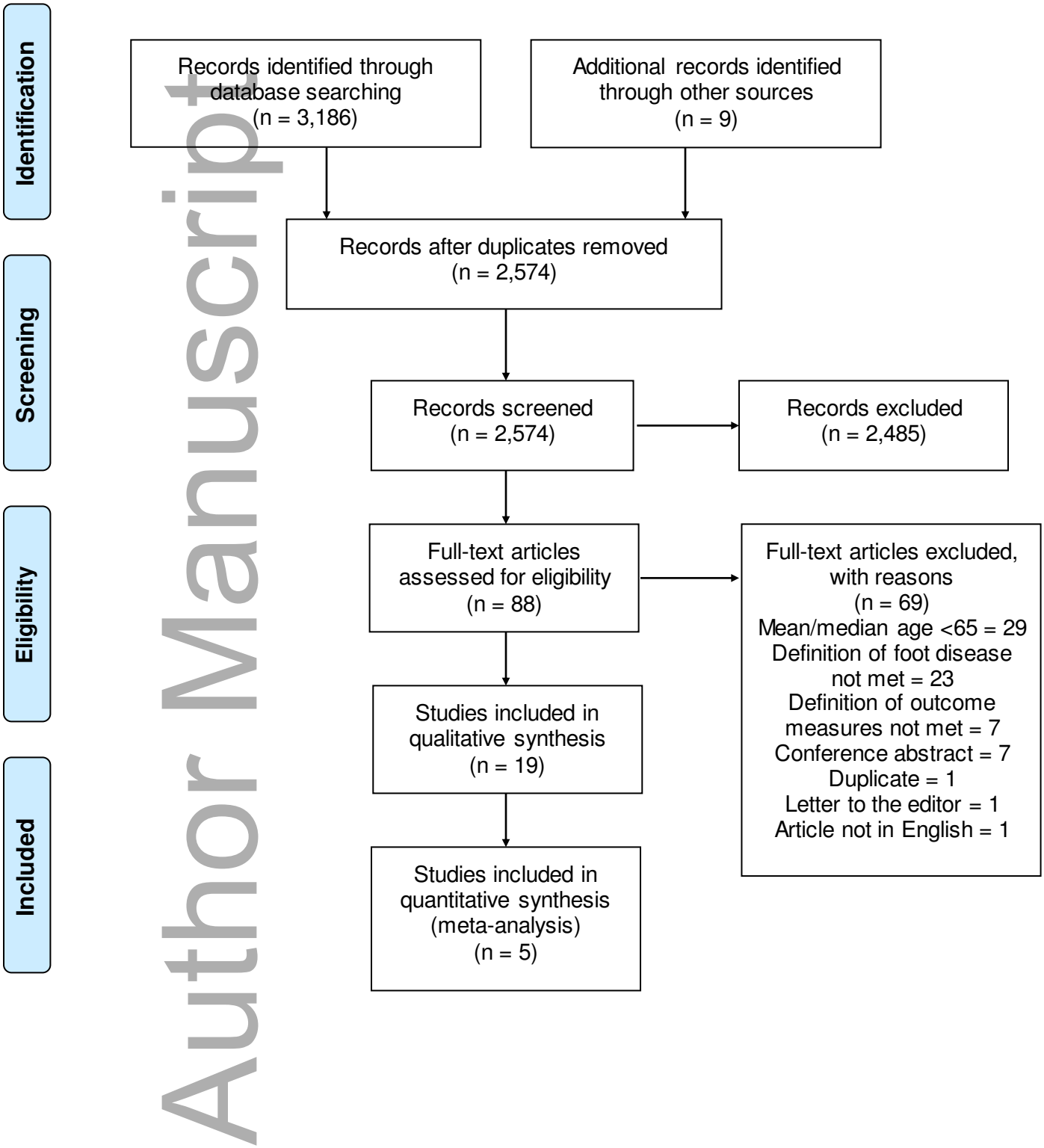
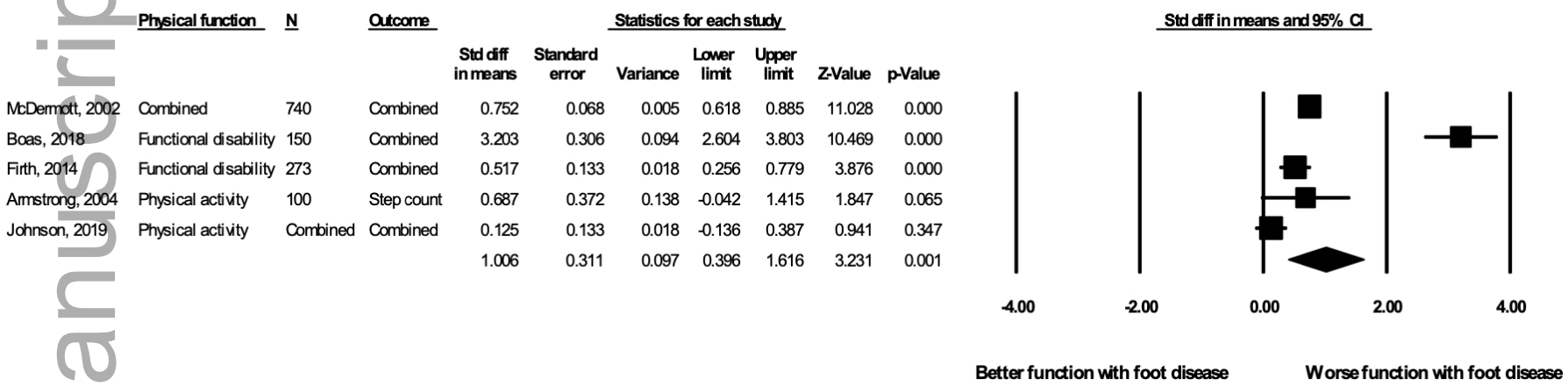


Figure 2: Meta-analysis of studies reporting physical function in groups with and without foot ulceration, standardised mean difference (random effects model, I^2 = 95.5%)



	Physical function	N	Outcome	Statistics for each study						
				Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
McDermott, 2002	Combined	740	Combined	0.752	0.068	0.005	0.618	0.885	11.028	0.000
Boas, 2018	Functional disability	150	Combined	3.203	0.306	0.094	2.604	3.803	10.469	0.000
Firth, 2014	Functional disability	273	Combined	0.517	0.133	0.018	0.256	0.779	3.876	0.000
Armstrong, 2004	Physical activity	100	Step count	0.687	0.372	0.138	-0.042	1.415	1.847	0.065
Johnson, 2019	Physical activity	Combined	Combined	0.125	0.133	0.018	-0.136	0.387	0.941	0.347
				1.006	0.311	0.097	0.396	1.616	3.231	0.001

Figure 1: PRISMA flow diagram

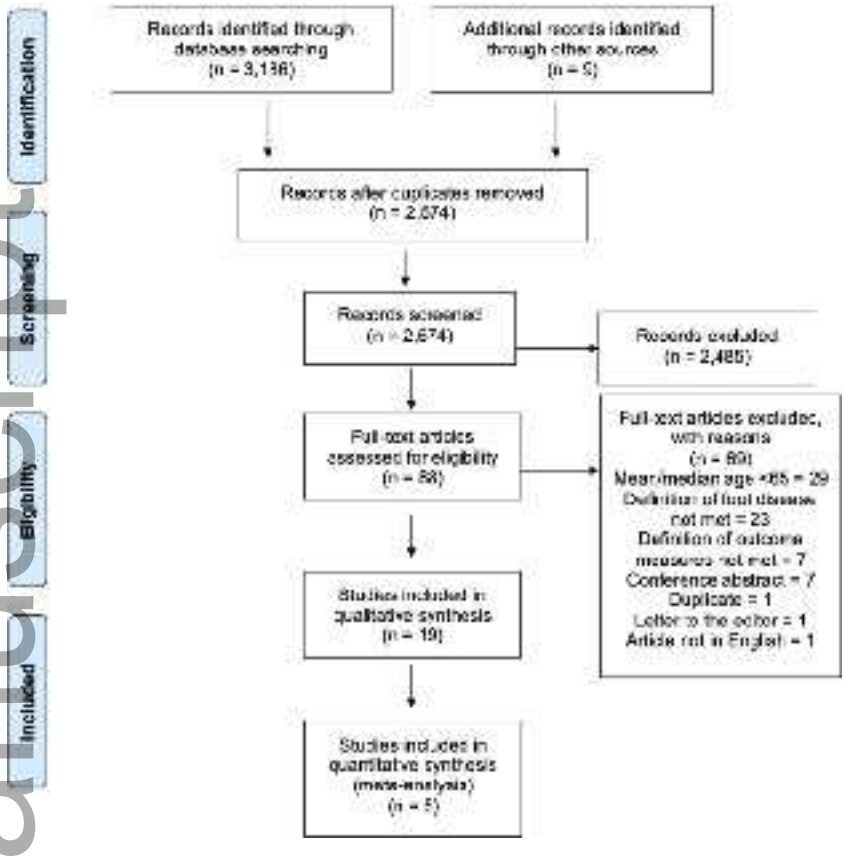


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Figure 2: Meta-analysis of studies reporting physical function in groups with and without foot ulceration, standardised mean differences (random effects model, k = 95.5%)

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