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SYSTEMATIC REVIEW

Differences in Symptom Presentation in Women and Men with Confirmed Lower Limb Peripheral Artery Disease: A Systematic Review and Meta-Analysis

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WHAT THIS PAPER ADDS

Some studies have described differences in clinical presentation by sex in patients with lower extremity peripheral artery disease (PAD). To date, there has been no systematic review that has collected and pooled this information to confirm what is described by some authors. This systematic review provides evidence and corroborates sex differences in symptom presentation in patients with PAD. The meta-analysis suggests that women with PAD present less often with intermittent claudication and more often with rest pain than men.

Objective: To evaluate the differences in symptoms between men and women that present with lower limb peripheral artery disease (PAD).

Data Sources: Systematic review and meta-analysis using PubMed, EMBASE, and the Cochrane Library.

Review Methods: A systematic search of the literature to identify studies that examined PAD and its symptoms using PubMed, EMBASE, and the Cochrane Library, which were screened in duplicate by two reviewers. Information on study design, source of data, population characteristics, and outcomes of interest was extracted and used the Newcastle—Ottawa Scale and Cochrane risk of bias tool. Quality of evidence was rated using the GRADE methodology. Estimates of relative effects were pooled to generate pooled odds ratios (OR) and their 95% confidence interval (CI) using a random effects model.

Results: Thirteen cross sectional studies, six cohorts, one case control, and one randomised clinical trial, reporting on 1 929 966 patients with confirmed PAD (established by clinical history, clinical examination, and/or ankle brachial index, or further tests) were included. Women presented less often with intermittent claudication than men (25.9% *vs.* 30.2%) OR 0.78 (95% CI 0.72 — 0.84, very low quality of evidence), while rest pain and atypical leg symptoms were more prevalent in women (12.8% *vs.* 9.2%) OR 1.40 (95% CI 1.22 — 1.60, very low quality of evidence) and (22.8% *vs.* 19.8%) OR 1.18 (95% CI 0.96 — 1.45, very low quality of evidence), respectively.

Conclusion: Women with PAD more often present with rest pain, while their prevalence of intermittent claudication is lower. They also tend to present more often with atypical leg symptoms. This study underlines that PAD symptom presentation differs between the sexes. Therefore, clinicians and researchers should not consider men and women as a single population and report their data separately.

Keywords: Atypical leg symptoms, Intermittent claudication, Peripheral arterial disease, Rest pain, Review, Sex
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INTRODUCTION

Peripheral artery disease (PAD) is a progressive atherosclerotic disorder characterised by stenosis or occlusion of large and medium sized arteries, different to those supplying the heart and the brain. Based on the latest Global, regional, and national prevalence and risk factors for

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peripheral artery disease, published in 2015, 236.62 million people around the world were diagnosed with PAD.[1]

PAD is often diagnosed using the ankle brachial index (ABI), and most of the studies define PAD as an ABI < 0.9. Patients with PAD are at long term risk of death and amputation, and although there is a reduction, the risk of death or amputation remains considerable after revascularisation.[2,3] The long term mortality risk of patients with PAD is similar to that of patients diagnosed with acute myocardial infarction or stroke.[4]

PAD has traditionally been identified as a predominantly male disease; however, recent population studies on PAD have shown that women are affected at least as often as men.[5] For instance, Schramm *et al.* and Teodorescu *et al.* reported a similar prevalence of PAD among women and men,[6,7] which is consistent with studies showeding that the prevalence of PAD in young women (under 50 years) seems to be higher than in men, but for individuals aged 70 — 79 years, there is an equivalent prevalence of PAD among both sexes of approximately 11.5%.[8,9]

Lower extremity PAD can be either asymptomatic or symptomatic. Symptoms may vary from intermittent claudication (IC), rest pain, or tissue loss, to atypical leg symptoms, or a combination of these symptoms.[10] Around 50% of patients diagnosed with PAD are asymptomatic or have atypical leg symptoms. Typical IC, described as pain or weakness while walking that is relieved by rest, occurs in about 10% of all patients with confirmed PAD.[8]

Some studies have suggested that, compared with men, women with PAD have a greater tendency to be asymptomatic or have atypical leg symptoms.[10] These characteristics could delay the diagnosis of PAD, and consequently, might increase the prevalence of more severe diseases, including chronic limb threatening ischaemia (CLTI) at the time of diagnosis.[10] There is evidence that performance status, treatment options, and outcomes of endovascular interventions differ between women and men with PAD.[10–13] However, a comprehensive review of the differences in the symptomatology between women and men with confirmed lower limb PAD is not available. The aim was to evaluate symptom presentation in patients with confirmed PAD and to compare the prevalence of symptoms between women and men. Finally, an attempt was made to identify factors that may be related to the sex symptom association.

MATERIALS AND METHODS

A review protocol describing the inclusion criteria, outcomes of interest, and the data analyses methods was previously specified and registered in PROSPERO (CRD42021242226). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[14] was used to ensure transparent reporting of review methods.

Selection criteria

Observational studies (cross sectional, cohorts, and case control) and randomised clinical trials reporting sex differences, symptom prevalence (Fontaine stage IIa. IIb. III, and Rutherford stage 1 — 4) and characteristics, and differences in treatment by sex in patients with confirmed PAD were considered for inclusion. Confirmed PAD was defined as lower limb PAD established by clinical history, clinical examination, and/ABI, or further studies.[15]

Only studies that reported symptomatic PAD were included. A study was eligible if (1) it included patients aged 18 years or older; (2) the patients had a diagnosis of PAD established either by questionnaires, ABI at rest, treadmill, or duplex; and (3) reported the symptom prevalence and presented the outcome (i.e., symptom prevalence in terms of IC; rest pain, Rutherford 4 or Fontaine stage III; and atypical leg symptoms, or lower extremity symptom that was not consistent with classic IC) separately for women and men.

Studies were excluded if they were review articles or case reports. For articles that used the same database, the article with most data available about symptoms by sex was chosen.

Search strategy

The search terms used were relevant keywords and MeSH terms relating to PAD, including “peripheral arterial disease”, “peripheral artery disease”, “arterial occlusive disease”, and “peripheral vascular disease”; it combined with words related to sex, such as “sex”, “gender”, “sex specific”, “gender specific”, “women and men” and “female and male”, and with words related to symptoms, including “intermittent claudication”, “symptom”, “claudication”, “claudication intermittent”, “rest pain”, and “pain”. The Boolean Operators “AND” or “OR” were applied to facilitate the search. The data sources used were MEDLINE (via PubMed), EMBASE (via Embase.com), and the Cochrane Library (via Cochrane review and CENTRAL). The search strategy was conducted on 15 February 2021. The search period was restricted to publications between January 2000 and February 2021. Additionally, the search was restricted to papers written in English. The detailed search strategy can be found in Supplementary Table S1.

Eligibility assessment, based on title/abstract and full text was performed independently by two reviewers (C.P., R.V.) using the Rayyan web tool. A third author acted as an arbitrator if there was disagreement between the reviewers (M.B.).

Data extraction and quality assessment

A data extraction sheet was developed using Excel. It was tested and adjusted accordingly. The information extracted from the studies was divided into four categories: (1) general information (year of publication, country, author, and title); (2) characteristics of the study (type of study, sample size, risk of bias, and inclusion criteria); (3) characteristics of the participants (mean age, percentage of women and men, smoking status, and prevalence of hypertension, diabetes and coronary heart disease or myocardial infarction); and (4) outcome data (prevalence of IC, rest pain, atypical leg symptoms). The first review author (C.P.) extracted the data from included studies, and the second author (R.V.) checked the data for correctness.

The risk of bias of the included studies was assessed by two independent authors (C.P., R.V.). The quality of observational studies was appraised using the Newcastle–Ottawa Scale (NOS) for cohort and case control studies and adjusted for cross sectional studies; the Cochrane Risk of Bias Collaboration's tool was used for assessing the risk of bias in randomised trials.[16,17]

The GRADE approach was used to assess the quality of evidence as high, moderate, low, or very low based on risk of bias, inconsistency, indirectness, and imprecision.[55] Reasons to upgrade the quality of evidence, including large effect magnitude, dose response, or limited residual confounding, were not considered applicable to the body of evidence.

Outcomes and statistical analyses

The primary outcomes were the prevalence of IC, rest pain, and atypical leg symptoms. The combined results were expressed as odds ratios (ORs) for women *vs.* men (control group).

Statistical analyses were performed using the Cochrane Collaboration's software for preparing and maintaining Cochrane reviews, RevMan 5.4. Dichotomous outcomes such as IC, rest pain, and atypical leg symptoms (yes/no) were calculated, and the relationships between women and men were reported as ORs with 95% confidence interval (CI). Statistical significance was defined as a two sided $\alpha < .05$. Given that clinical heterogeneity was suspected in patients and symptom characteristics across the included studies, a random effect model was applied for all outcomes.

Previous evidence showed that smoking, diabetes, and hypertension are risk factors associated with PAD. These characteristics could potentially explain the heterogeneity. Therefore, subgroups were defined based on mean proportion of smokers ($\leq$ 50%, $\geq$ 50%), hypertension (the cut off point for subjects with hypertension was higher [$\leq$ 70%, $\geq$ 70%] because in only two studies that reported hypertension, was the prevalence $<$ 50%), and diabetes ($\leq$ 50%, $\geq$ 50%) in the overall population. In addition, a subgroup analysis was performed according to the year of publication (2000 – 2005, 2006 – 2010, 2011 – 2021), with the rationale that the reporting and contribution of women in subsequent studies may have changed over time. These subgroup analyses were performed for all outcomes. To explore differences in studies reporting IC, a subgroup analysis was conducted based on the stage of IC.

Finally, sensitivity analyses were conducted to assess the contribution of each study to the pooled estimate for each outcome. Individual studies with the largest population were excluded one at a time and the pooled OR estimates for the remaining studies were calculated. Thus, for IC, the studies by Lo *et al.*, Peters *et al.*, and Behrendt *et al.* were excluded one at the time. For rest pain, Peter *et al.* and Haine *et al.* were excluded, and for atypical leg symptoms, McDermott *et al.* was excluded.

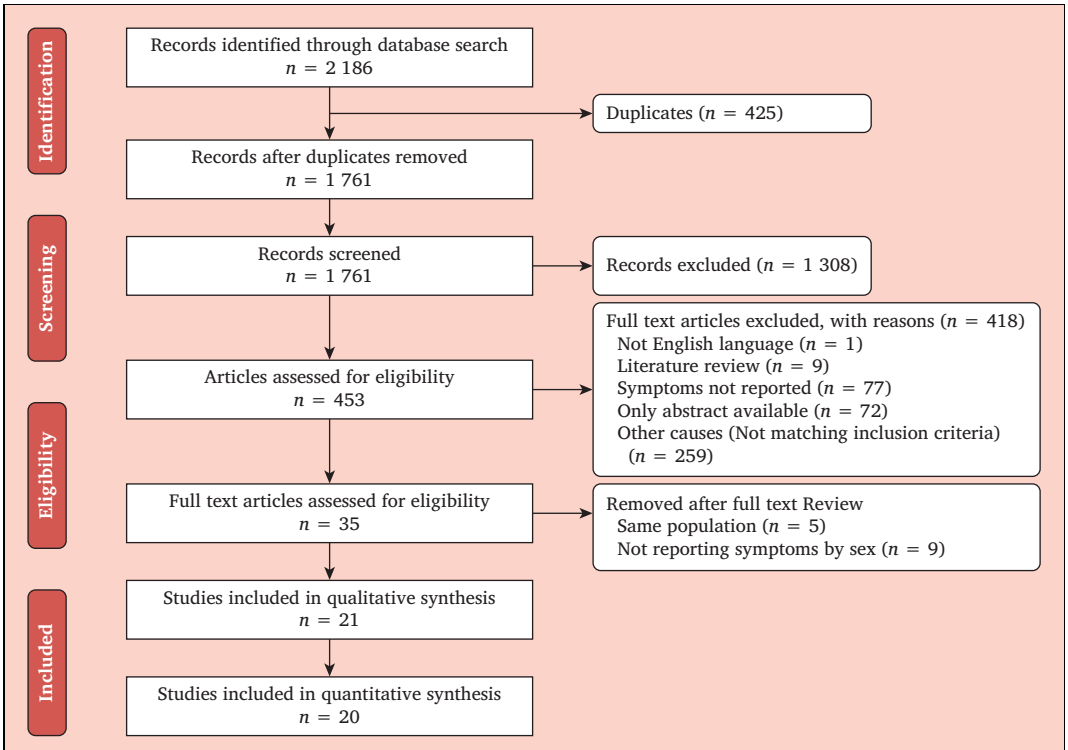

Figure 1. Preferred reporting items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram of the literature search strategy to identify studies on symptom differences by sex in patients with peripheral artery disease.

RESULTS

Literature search results

A total of 2 186 studies were identified in the different databases, of which 425 were excluded as being duplicate publications. After reviewing titles and abstracts, 453 studies were assessed for eligibility; and finally, 35 articles were selected for full text review. Figure 1 presents a flow diagram for the PRISMA process used to identify the included studies.

During the full text review, 14 studies were discarded: five because they studied the same population,[18–22] and nine because they did not stratify the symptoms by sex but by either PAD status, race, or a different factor.[23–31] Supplementary Table S2 gives the characteristics of the studies excluded.

Study and population characteristics

A total of 13 cross sectional,[32–44] six cohort,[45–50] one case control study,[51] and one randomised clinical trial[52] met the inclusion criteria and were selected for detailed analysis. Together these studies report on 1 950 169 patients (1 929 966 with confirmed PAD). The studies were

Table 1. Characteristics of the 21 included studies on symptom differences by sex in patients with peripheral artery disease (PAD)

Author	Publication year	Country	Study design	Inclusion criteria	NOS/Cochrane risk of bias	Sample size − *n*	Confirmed PAD − *n*
McDermott *et al.*[32]	2003	United States	Cross sectional	Patients with ABI < 0.90	7	460	460
Dang *et al.*[36]	2013	China	Cross sectional	Elderly with DM2	7	323	323
Smolderen *et al.*[42]	2009	The Netherlands	Cross sectional	Patients with ABI < 0.90	7	628	628
Collins *et al.*[35]	2006	United States	Cross sectional	People > 50 y	7	403	67
Brevetti *et al.*[34]	2008	Italy	Cross sectional	Patients with ABI < 0.90	8	231	231
Behrendt *et al.*[33]	2019	Germany	Cross sectional	PET of PAD	8	23 715	23 715
Kumakura *et al.*[39]	2011	Japan	Cross sectional	Patients with ABI < 0.90	6	730	730
Gardner[37]	2002	United States	Cross sectional	Patients with Fontaine stage II	8	560	560
Murabito *et al.*[40]	2002	United States	Cross sectional	People > 40 years old	8	3 313	118
Vliegenthart *et al.*[44]	2002	The Netherlands	Cross sectional	People > 55 years old	8	3 975	557
Krishnan *et al.*[38]	2017	India	Cross sectional	People ≥ 20 and ≤ 79 y	9	1 148	299
Sigvant *et al.*[41]	2007	Sweden	Cross sectional	People ≥ 60 and ≤ 90 y	9	5 080	914
Tekin *et al.*[43]	2011	Turkey	Cross sectional	Patients at a geriatric centre	6	507	30
Jelani *et al.*[47]	2020	Several countries	Cohort	Patients ABI < 0.90	7	1 243	1 243
Choi *et al.*[46]	2019	Korea	Cohort	Patients treated with EVT	7	3 073	3 073
Sartipy *et al.*[50]	2019	Sweden	Cohort	Patients ABI < 0.90	9	5 080	957
Lo *et al.*[48]	2014	United States	Cohort	Patients with PAD + revascularisation	8	1 797 885	1 797 885
Al-Zoubi *et al.*[45]	2019	Saudi Arabia	Cohort	Patients with DM2 + symptomatic PAD	6	364	364
Peters *et al.*[49]	2020	Germany	Cohort	Patients ≥ 40 y + symptomatic PAD	8	83 867	83 867
Brevetti *et al.*[51]	2004	Italy	Case-control	People ≥ 40 and ≤ 80 y	8	3 699	60
Haine *et al.*[52]	2020	International	RCT	Patients ≥ 50 y with PAD	Low risk	13 885	13 885

NOS = Newcastle–Ottawa score; ABI = Ankle brachial Index; DM2 = diabetes mellitus type 2; PET = percutaneous endovascular treatment; EVT = endovascular treatment for symptomatic PAD; RCT = randomised clinical trial.

published between 2002 and 2020, with sample sizes ranging from 231 subjects in the smallest study to 1 797 885 in the largest study. Of the 21 included studies, 14 aimed to study sex differences in PAD patients, of which two focused primarily on sex differences in symptoms.[32,33,35–37,39,41,45–50,52] The other studies included, although not focusing on sex differences, did report separate data for women and men with respect to symptoms as a secondary objective. Table 1 shows the studies general characteristics.

Overall, women represented 43.9% of the total population with confirmed PAD. Thirteen studies[32–34,36,37,39,45–50,52] reported age by sex, but only 11[32,34,36,37,39,45–47,49,50,52] reported mean and standard deviation. Women were slightly older with a mean difference 2.25 years (95% CI 0.13 − 4.37, $p = .03$, $I^2 = 100\%$). Of the studies that reported smoking status, women tended to smoke less often than men (16.9% *vs.* 23.7%) OR 0.52 (95% CI 0.40 − 0.68, $p < .001$, $I^2 = 96\%$). Prevalence of coronary heart disease (35.5% *vs.* 43.9%) OR 0.67 (95% CI 0.61 − 0.74, $p <$

Table 2. Characteristics of the population from the 21 included studies on symptom differences by sex in patients with peripheral artery disease (PAD)

Author	Confirmed PAD − *n*	Female − %	Age − y	Hypertension	Diabetes	CHD	Smoking
			MD (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
McDermott *et al.*[32]	460	40.7	1.70 (0.14–3.26)	NR	0.72 (0.48–1.08)	0.54 (0.35–0.84)	0.93 (0.59–1.46)
Dang *et al.*[36]	323	23.5	5.95 (3.62–8.28)	NR	2.51 (1.48–4.25)	NR	NR
Smolderen *et al.*[42]	628	33.1	NR	NR	NR	NR	NR
Collins *et al.*[35]	67	49.3	NR	1.88 (0.49–7.15)	1.21 (0.46–3.16)	NR	0.78 (0.27–2.24)
Brevetti *et al.*[34]	231	29.4	2.70 (−0.05 − 4.45)	1.42 (0.61–3.32)	2.78 (1.53–5.04)	0.71 (0.40–1.27)	0.75 (0.41–1.37)
Behrendt *et al.*[33]	23 715	39.7	NR	NR	0.67 (0.61–0.72)	NR	NR
Kumakura *et al.*[39]	730	20.3	2.70 (0.75–4.65)	1.42 (0.98–2.08)	1.52 (1.05–2.21)	0.78 (0.53–1.13)	0.07 (0.05–0.11)
Gardner *et al.*[37]	560	12.9	−2.00 (−2.25 − −1.75)	1.45 (0.85–2.47)	0.92 (0.53–1.58)	NR	0.96 (0.58–1.58)
Murabito *et al.*[40]	118	49.2	NR	1.38 (0.64–2.96)	0.58 (0.26–1.31)	0.22 (0.08–0.64)	0.62 (0.30–1.29)
Vliegenthart *et al.*[44]	557	64.3	NR	NR	NR	NR	0.39 (0.27–0.57)
Krishnan *et al.*[38]	299	62.2	NR	NR	NR	NR	NR
Sigvant *et al.*[41]	914	58.4	NR	NR	NR	NR	NR
Tekin *et al.*[43]	30	43.3	NR	NR	NR	NR	NR
Jelani *et al.*[47]	1 243	38.0	0.70 (−0.40 − 1.80)	1.91 (1.40–2.60)	1.18 (0.93–1.51)	0.73 (0.57–0.92)	1.04 (0.82–1.32)
Choi *et al.*[46]	3 073	18.0	2.00 (1.05–2.95)	1.40 (1.12–1.75)	1.37 (1.13–1.66)	1.08 (0.81–1.45)	0.18 (0.13–0.24)
Sartipy *et al.*[50]	957	59.6	0.50 (−0.53 − 1.53)	1.06 (0.82–1.37)	0.61 (0.44–0.86)	0.45 (0.32–0.62)	0.29 (0.22–0.39)
Lo *et al.*[48]	1 797 885	44.0	NR	1.28 (1.28–1.29)	0.90 (0.89–0.90)	0.71 (0.70–0.71)	NR
Al-Zoubi *et al.*[45]	364	22.5	5.00 (2.40–7.60)	1.05 (0.63–1.75)	–	0.77 (0.46–1.29)	1.22 (0.73–2.03)
Peters *et al.*[49]	83 867	45.8	4.50 (4.63–4.64)	1.17 (1.12–1.21)	0.64 (0.62–0.66)	0.60 (0.59–0.62)	0.75 (0.72–0.78)
Brevetti *et al.*[51]	60	53.7	NR	NR	NR	NR	NR
Haine *et al.*[52]	13 885	28.0	1.70 (1.38–2.02)	1.27 (1.16–1.40)	1.12 (1.04–1.21)	0.66 (0.61–0.72)	0.71 (0.66–0.77)
Total	1 929 966	43.9	2.25 (0.13–4.37)	1.27 (1.19–1.35)	1.00 (0.85–1.16)	0.67 (0.61–0.74)	0.52 (0.40–0.68)
p value			<.001	<.001	<.001	<.001	<.001
I^2 − %			100	72	98	92	96
Quality of evidence (GRADE)			⊕○○○ Very low*	⊕○○○ Very low*	⊕○○○ Very low*	⊕○○○ Very low*	⊕○○○ Very low*

The total at the bottom gives the pooled data across studies. MD = mean difference; CI = confidence interval; OR = odds ratio; NR = not reported; CHD = coronary heart disease.

* The quality of this evidence was downgraded due to serious inconsistency (high I^2 statistic test), and serious indirectness.

.001, I^2 = 92%) and diabetes were also lower in women (44.3% *vs.* 47.2%); however, the latter was not significant: OR 1.00 (95% CI 0.85 — 1.16, p = .96, I^2 = 98%). On the other hand, hypertension was reported more often in women (57.3% *vs.* 51.3%): OR 1.27 (95% CI 1.19 — 1.35, p < .001, I^2 = 72%). The quality of the evidence was considered very low, downgraded due to inconsistency and indirectness. A complete description of the baseline characteristics can be found in Table 2.

Quality of the included studies

Quality among the observational studies was assessed using the Newcastle—Ottawa score. There was significant heterogeneity in sample size, setting, and inclusion criteria. The only randomised study had a low risk of bias (see also Table 1).

Symptom prevalence

For IC, 20 studies involving 1 929 429 patients were included. The study by Gardner *et al.*[37] was excluded from the quantitative analysis because one of its inclusion criteria was that all the included participants were classified as Fontaine stage II (i.e., (a) a positive Rose questionnaire for IC, (b) IC elicited during a graded treadmill test, and (c) an ABI at rest < 0.90). As the entire population of this study had IC, their inclusion would have biased the results.

The included studies showed that among the symptomatic patients, women had a lower prevalence of IC (25.9%) than men (30.2%) with OR 0.78 (95% CI 0.72 — 0.84, p < .001). Significant heterogeneity between studies was identified (I^2 = 86%) (Fig. 2). These results were consistent in subgroup analyses by smoking and diabetes prevalence (Fig. 3). The quality of evidence was considered very low, downgraded due to inconsistency and indirectness (Supplementary Table S3).

In studies with more than 70% of the population having hypertension, IC was also observed less frequently in women, OR 0.79 (95% CI 0.72 — 0.85, p < .001, I^2 = 89%). The subgroup analysis by year of publication was consistent with women having less IC in all three periods, but with an increase in the later years with OR 0.41 (95% CI 0.20 — 0.83, p = .010, I^2 = 71%) in the studies from 2000 to 2005 to OR 0.82 (95% CI 0.76 — 0.89, p < .001, I^2 = 90%) in the studies from 2011 onwards. All these subgroup analyses were considered as very low quality of evidence due to inconsistency and indirectness (Supplementary Fig. S1).

Finally, four studies[36,46,47,52] described the grades of IC among women and men. Mild claudication was reported less often in women OR 0.74 (95% CI 0.61 — 0.91, p = .003, I^2 = 0%), and considered very low quality of evidence due to imprecision and indirectness. The subgroup analyses for moderate and severe claudication were not statistically significant, and the quality of evidence was considered very low due to inconsistency and indirectness (Supplementary Fig. S1).

Nine of 20 studies reported on rest pain.[32–34,36,39,42,46,49,52] In these studies, women more frequently reported to have rest pain than men (12.8% *vs.* 9.2%) OR 1.40 (95% CI 1.22 — 1.60, p < .001, I^2 = 72%) (Fig. 4A). The quality of evidence was considered very low, downgraded due to inconsistency and indirectness.

Separate subgroup analyses were performed by grouping the studies according to the proportion of subjects with

Study	Women Events	Women Total	Men Events	Men Total	Odds ratio for intermittent claudication M–H, Random, 95% CI	Odds ratio M–H, Random, 95% CI	Weight
Gardner *et al.*[37]	72	72	488	488		Not estimable	
Brevetti *et al.*[51]	20	32	27	28		0.06 [0.01, 0.51]	0.1%
Murabito *et al.*[40]	8	58	25	60		0.22 [0.09, 0.55]	0.7%
Brevetti *et al.*[34]	53	68	146	163		0.41 [0.19, 0.88]	0.9%
Al–Zoubi *et al.*[45]	19	82	107	282		0.49 [0.28, 0.87]	1.6%
Kumakura *et al.*[39]	86	148	418	582		0.54 [0.37, 0.79]	3.3%
Vliegenthart *et al.*[44]	22	358	21	199		0.55 [0.30, 1.04]	1.4%
Choi *et al.*[46]	308	550	1 731	2 523		0.58 [0.48, 0.70]	8.3%
Sigvant *et al.*[41]	163	534	163	380		0.58 [0.44, 0.77]	5.3%
Smolderen *et al.*[42]	34	208	104	420		0.59 [0.39, 0.91]	2.6%
Sartipy *et al.*[50]	166	587	154	393		0.61 [0.47, 0.80]	5.4%
Dang *et al.*[36]	37	76	141	247		0.71 [0.43, 1.19]	1.9%
Jelani *et al.*[47]	461	470	762	773		0.74 [0.30, 1.80]	0.7%
McDermott *et al.*[32]	54	187	96	273		0.75 [0.50, 1.12]	2.9%
Tekin *et al.*[43]	6	13	9	17		0.76 [0.18, 3.24]	0.3%
Lo *et al.*[48]	189 224	791 069	281 808	1 006 816		0.81 [0.80, 0.81]	17.0%
Peters *et al.*[49]	20 051	38 431	25 274	45 436		0.87 [0.85, 0.89]	16.7%
Behrendt *et al.*[33]	5 591	9 415	8 643	14 300		0.96 [0.91, 1.01]	15.8%
Krishnan *et al.*[38]	21	186	13	113		0.98 [0.47, 2.04]	1.0%
Haine *et al.*[52]	2 993	3 888	7 645	9 997		1.03 [0.94, 1.12]	13.9%
Collins *et al.*[35]	3	33	2	34		1.60 [0.25, 10.25]	0.2%
Total (95% CI)		**846 465**		**1 083 524**		**0.78 [0.72, 0.84]**	**100.0%**
Total events	219 392		327 777				

Heterogeneity: Tau^2 = 0.01; Chi^2 = 140.28, df = 19 (p <.001); I^2 = 86%
Test for overall effect: Z = 6.58 (p <.001)
Test for subgroup differences: Not applicable

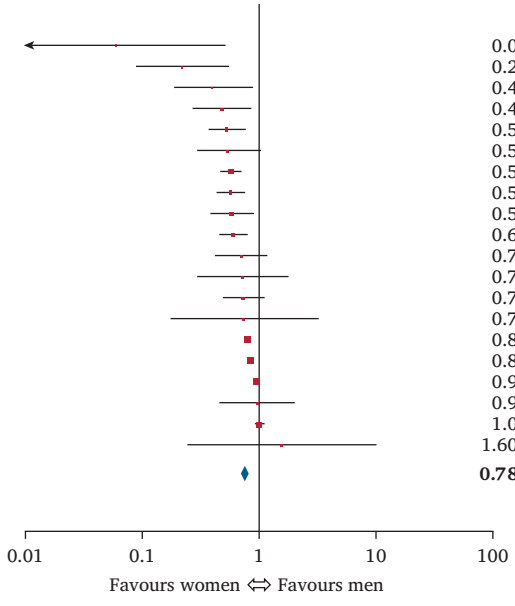

Figure 2. Forest plot of 20 studies reporting intermittent claudication (IC) differences by sex in patients with peripheral artery disease. OR = odds ratio; M-H = Mantel-Haenszel; CI = confidence interval.

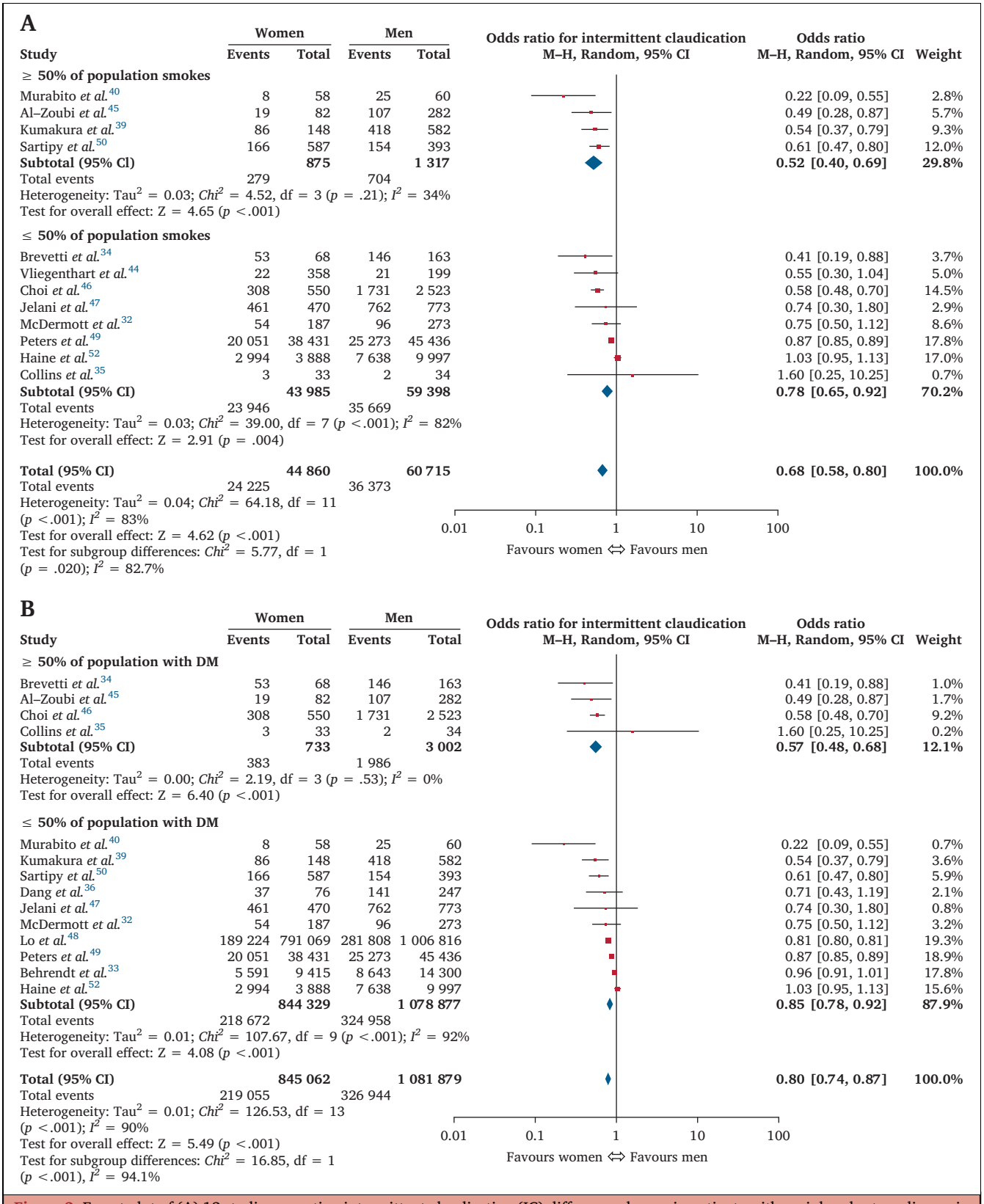

Figure 3. Forest plot of (A) 12 studies reporting intermittent claudication (IC) differences by sex in patients with peripheral artery disease in populations with ≥ 50% or ≤ 50% of smokers, and (B) 14 studies reporting IC in populations with ≥ 50% or ≤ 50% of people with diabetes mellitus (DM). OR = odds ratio; M-H = Mantel–Haenszel; CI = confidence interval.

diabetes and hypertension in their population. Rest pain in women was more prevalent in studies with a lower prevalence of diabetes (≤ 50%), OR 1.32 (95% CI 1.15 — 1.53, $p < .001$, $I^2 = 77\%$) with very low quality of evidence, and in those with < 70% of hypertension in their population, OR 1.43 (95% CI 1.19 — 1.72, $p < .001$, $I^2 = 18\%$) with very low quality of evidence because of imprecision and indirectness. The subgroup analysis on smoking was not possible because, in the studies reporting rest pain, less than 50% of the population included were smokers. Therefore, a subgroup analysis with a cut off of 25% smoking prevalence was performed. Rest pain was primarily found in women among studies with smoking prevalence ≤ 25% OR 1.57 (95% CI 1.19 — 2.07, $p = .001$, $I^2 = 67\%$), with very low quality of evidence due to inconsistency, imprecision, and indirectness.

Finally, four studies reported atypical leg symptoms.[32,35,42,47] Women more often had atypical leg symptoms (22.8% *vs.* 19.8%) OR 1.18 (95% CI 0.96 — 1.45), and the heterogeneity was low $I^2 = 36\%$. The quality of evidence was considered very low, downgraded due to inconsistency, indirectness, and imprecision (Fig. 4B).

Sensitivity analyses

For the outcome, IC symptoms, exclusion of the study by Lo *et al.*[48] resulted in a reduction of IC for women OR 0.72 (95% CI 0.65 — 0.81, $p < .001$, $I^2 = 81\%$). This procedure was repeated and the study with the second largest population, Peters *et al.*,[49] was excluded, resulting in very similar findings; women reported less IC with an OR 0.71 (95% CI 0.64 — 0.79, $p < .001$, $I^2 = 85\%$). Finally, the study by Behrendt *et al.* was removed from the analysis,[33] and these results were also quite similar. This sensitivity analysis was also performed for the outcomes of rest pain and atypical leg symptoms. The quality of evidence in these subgroup analyses was very low due to indirectness and inconsistency.

Because the quality assessment of some of the studies was moderate (NOS = 6), sensitivity analyses were performed, including observational studies with a NOS score of seven or higher and randomised clinical trials with a low risk of bias. The results were consistent with the previous findings. Women reported less IC OR 0.79 (95% CI 0.73 — 0.85), but conversely rest pain OR 1.37 (95% CI 1.20 — 1.58) and atypical leg symptoms OR 1.18 (95% CI 0.96 — 1.45) were more common in women. The quality of this evidence was very low. For IC and rest pain, due to inconsistency and indirectness, and for atypical leg symptoms due to inconsistency, indirectness, and imprecision (Table 3).

DISCUSSION

The reviewed data and meta-analysis of the included studies shows that women with PAD present less often with IC and more often with rest pain compared with men. These

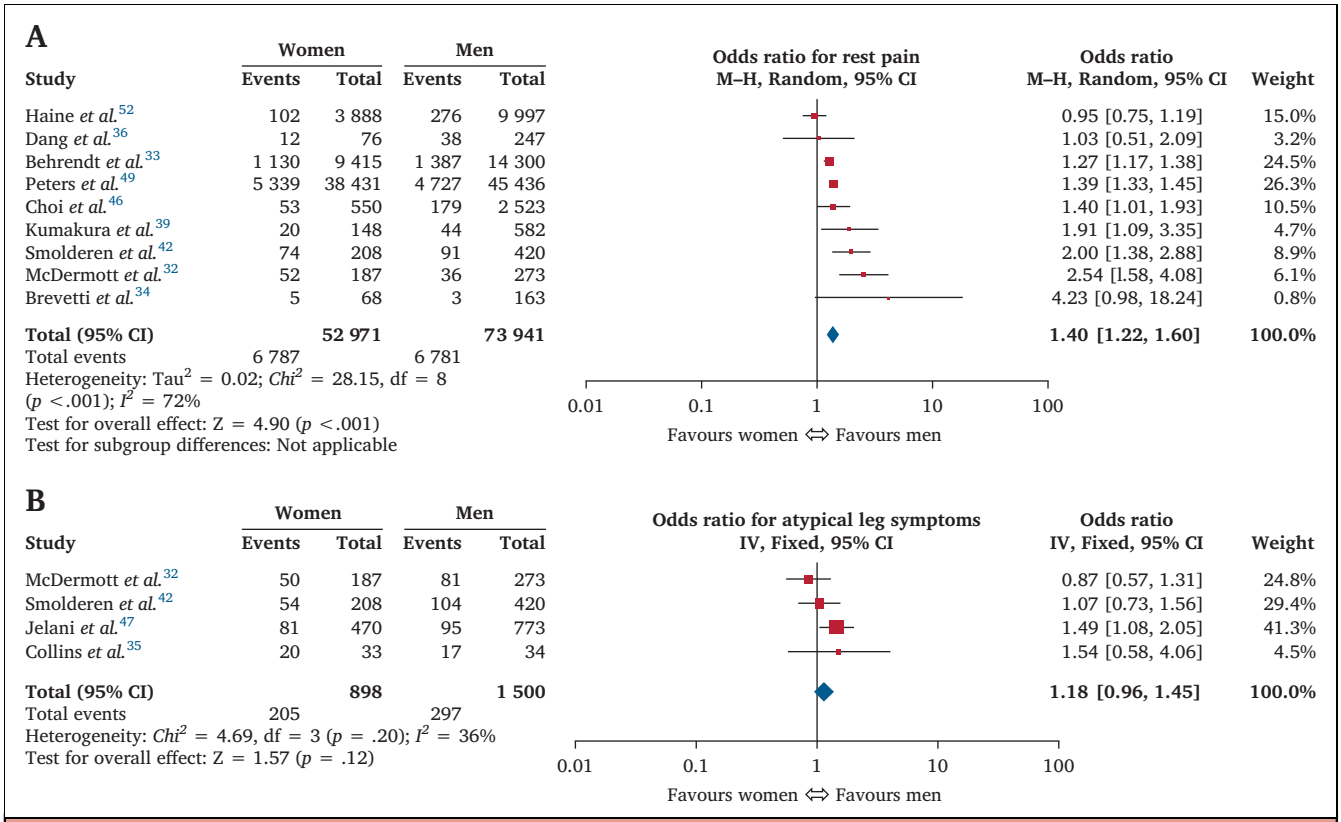

Figure 4. Forest plot of (A) nine studies reporting rest pain and (B) four studies reporting atypical leg symptoms by sex in patients with peripheral artery disease. OR = odds ratio; M-H= Mantel-Haenszel; CI = confidence interval.

Table 3. Sensitivity analysis of the 21 studies on symptom differences by sex in patients with peripheral artery disease with exclusion of studies with the largest population one a time or with Newcastle–Ottawa score (NOS) < 7 or with moderate or high risk of bias

	Studies − *n*	Patients − *n*	OR (95% CI)	*p*	I^2 − %	Quality of the evidence (GRADE)
Exclusion of studies with the largest population one a time						
Intermittent claudication						
All studies[32–36,38–52]	20	1 929 429	0.78 (0.72–0.84)	<.001	86	⊕○○○ Very low*
Exclusion Lo *et al.*[48]	19	131 544	0.72 (0.65–0.81)	<.001	81	
Exclusion Peters *et al.*[49]	19	1 845 562	0.71 (0.64–0.80)	<.001	84	
Exclusion Behrendt *et al.*[33]	19	1 905 714	0.75 (0.70–0.81)	<.001	83	
Rest pain						
All studies[32–34,36,39,42,46,49,52]	9	126 912	1.40 (1.22–1.60)	<.001	72	⊕○○○ Very low*
Exclusion Peters *et al.*[49]	8	43 045	1.48 (1.18–1.86)	.008	72	
Exclusion Haine *et al.*[52]	8	113 027	1.46 (1.29–1.65)	<.001	62	
Atypical leg symptoms						
All studies[32,35,42,47]	4	2 398	1.18 (0.96–1.45)	.12	36	⊕○○○ Very low†
Exclusion McDermott *et al.*[32]	3	1 938	1.31 (1.03–1.66)	.03	0	
Exclusion of studies with NOS score <7 or with moderate or high risk of bias						
Intermittent claudication						
NOS ≥ 7[32–36,38,40–42,44,46–52]	17	1 928 305	0.79 (0.73–0.85)	<.001	88	⊕○○○ Very low*
Rest pain						
NOS ≥ 7[32–34,36,42,46,49,52]	8	126 182	1.37 (1.20–1.58)	<.001	74	⊕○○○ Very low*
Atypical leg symptoms						
NOS ≥ 7[32,35,42,47]	4	2 398	1.18 (0.96–1.45)	.12	34	⊕○○○ Very low†

OR = odds ratio; CI = confidence interval.

* The quality of this evidence was downgraded due to serious inconsistency (high I^2 statistic test), and serious indirectness (the study outcome is a surrogate for a different outcome).

† The quality of this evidence was downgraded due to serious imprecision (small number of studies with few events), and serious indirectness (the study outcome is a surrogate for a different outcome.

effects are consistent across different subgroups. It is necessary to mention that the study by Lo *et al.*, with more than a million participants, had greater weight compared with the other studies; however, results remained similar after its removal in the sensitivity analyses.

The results are consistent with those described by other literature reviews without meta-analysis which report that women have lower rates of IC and, in contrast, tend to be asymptomatic or have atypical leg symptoms.[5,8,10] However, the reasons for this remain unclear. Some authors suggest that women experience symptoms differently, are less physically active (therefore, do not experience IC),[19] or that they may tend to report their symptoms less often than men.[53]

Some studies have focused on the differences between sexes in PAD, but the existing systematic reviews focused on differences in mortality or long term cardiovascular outcomes.[54] Indeed, studies show that outcomes after endovascular interventions differ between women and men[12,46] and it has also been reported that treatment strategies differ between the sexes.[10,11] However, to date, there was no pooled information on sex related differences in symptomology. This systematic review adds that evidence to the literature by showing that the clinical presentation differs between women and men. Women present more often with atypical leg symptoms and rest pain but less frequently with IC. These results confirm that lower extremity PAD manifests differently among the sexes, which might be one of the contributing factors for the differences in outcome and treatment of PAD between women and men described by some authors. This systematic review corroborates that those women and men with lower extremity PAD should not be considered as a single population and that sex specific data on presentation, diagnosis, drug and interventional therapies, and prognosis should be studied and at least reported separately.

The strengths of this systematic review include the comprehensive search done in different databases that allowed the identification of 2 186 studies, the independence of the authors checking eligibility criteria, assessing the risk of bias, and the extraction of the data. Another strength of the review is the performance of different subgroup analyses and the quality assessment of the evidence using the GRADE approach.

This review also carries some limitations: first, there was substantial heterogeneity between the studies. Probably because, as explained above, some of the included studies did not specifically focus on sex differences in symptom

presentation, but rather on sex differences in risk factors or prevalence of PAD. Second, although a broad search strategy was used, only studies written in English were analysed; therefore, studies with relevant information may have been missed because of the language. Finally, not all the studies reported the outcomes of interest; while 20 studies reported IC, and nine reported rest pain, only four reported atypical leg symptoms. The absence of agreement on the definition of atypical leg symptoms may affect how and whether this symptom was reported. The lack of reporting atypical symptoms limited some of the analyses; for example, subgroup analyses were not possible for this outcome. However, these limitations are unlikely to influence the results significantly since the lower prevalence of IC in women was consistent over several subgroups and in the sensitivity analyses; therefore, it is very likely that the observed effect reflects what is seen in clinical practice.

Conclusion

This systematic review and meta-analysis evaluated the literature on sex differences in symptom presentation in patients with lower limb PAD, which was consistent across several subgroups. Women with PAD present more often with rest pain, while their prevalence of IC is lower. They also tend to present more often with atypical leg symptoms. This study underlines that PAD symptom presentation differs between the sexes. Therefore, clinicians and researchers should not consider men and women as a single population and should study and report their data separately. Future studies are needed to understand the possible reasons for differences in clinical presentation in women and men with PAD, how this influences diagnosis, treatment, and ultimately, and most importantly, outcome.

CONFLICT OF INTEREST STATEMENT AND FUNDING

None.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2021.12.039.

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