



# Universiteit Utrecht

*Graduate School of Life Sciences  
Epidemiology*

## MASTER THESIS

***Differences between women and men with peripheral artery disease. A look at symptoms and primary health care contacts***

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## *Abstract*

Women with peripheral arterial disease (PAD) are often under-diagnosed, present with more advanced disease and, at older ages, and have a worse outcome than men.

This study investigates possible differences in symptom presentation between women and men with PAD. In addition, it aims to determine whether there are differences between women and men in the frequency and reasons for contacting a general practitioner (GP) six months before diagnosis of PAD.

We conducted a systematic review and meta-analysis and a retrospective study comparing two cohorts to achieve these objectives. The first study compiled the existing information on symptomatology and evidenced that women have a lower prevalence of typical intermittent claudication and are more likely to have rest pain and atypical leg symptoms. This review highlights the importance of reporting data separately for women and men. The second study established no differences in the number of consultations between women and men before PAD. Thus, the under-diagnosis in women cannot be explained by differences at the GP level.

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## Contents

<b>CHAPTER 1</b> .....	<b>6</b>
1.0 Introduction.....	6
1.1 Systematic Reviews an overview.....	7
1.2 Zero inflated negative binomial regression: An introduction to the model.....	7
1.3 References.....	8
<b>CHAPTER 2</b> .....	<b>9</b>
<i>Differences in symptoms between women and men with confirmed lower limb peripheral artery disease. A systematic review and meta-analysis</i> .....	9
2.1 Introduction.....	9
2.2 Methods.....	10
2.2.1 Selection criteria.....	10
2.2.2 Search strategy.....	10
2.2.3 Data extraction and quality assessment.....	11
2.2.4 Statistical analysis.....	11
2.3 Results.....	12
2.3.1 Literature search.....	12
2.3.2 Study and population characteristics.....	13
2.3.3 Quality of the included studies.....	14
2.3.4 Intermittent claudication.....	14
2.3.5 Rest pain.....	16
2.3.6 Atypical leg symptoms.....	17
2.3.7 Sensitivity analyses.....	18
2.4 Discussion.....	18
2.5 Conclusion.....	20
2.6 References.....	20
2.7 Supplementary material.....	25
<b>CHAPTER 3</b> .....	<b>27</b>
<i>Differences between women and men in primary health care contact preceding diagnosis of peripheral artery disease</i> .....	27
3.1 Introduction.....	27
3.2 Methods.....	28
3.2.1 Data source.....	28
3.2.2 Population.....	28
3.2.3 Data extraction.....	28
3.2.4 Variables of interest.....	29
3.2.5 Statistical analyses.....	29
3.3 Results.....	29
3.3.1 Evaluation of the model.....	30
3.3.2 Health care contacts.....	31
3.3.3 Zero health care contact.....	32
3.4 Discussion.....	33
3.4.1 Strength and limitations.....	34
3.5 Conclusion.....	34
3.6 References.....	34
3.7 Supplementary material.....	36

## CHAPTER 1

### *1.0 Introduction*

Thinking about the differences in health status between women and men is a complex issue because the problem extends beyond biological differences. The social and environmental components, which are sometimes difficult to determine, play an essential and decisive role. Evidence shows that even though women live longer than men, they experience poorer health and face more healthcare challenges than men.<sup>1</sup> This pattern is observed in cardiovascular disease. The prevalence of cardiovascular disease is higher in men.<sup>2</sup> However, women are more prone to suffer disease misclassification, underdiagnosis and undertreatment. Factors that contribute to worse prognosis and higher mortality rates in women compared with their counterparts.<sup>3</sup>

In cardiovascular disease, the reasons for the inequality between women and men are rather broad. For instance, it is recognised that women develop coronary heart disease (CHD) later than men, and evidence suggests the role of hormones in delaying the manifestation of atherosclerotic disease in women.<sup>4</sup> Nevertheless, age and hormones are not the sole factors explaining the discrepancies between women and men. Women are also more exposed to poverty, have insufficient access to health services and education, suffer more often domestic violence, and have lower salaries than men- factors that increase the stress and increase the cardiovascular risks.<sup>4</sup> In addition, historically, there has been an underrepresentation of women in clinical trials,<sup>5</sup> which makes less available gender-specific data.

Peripheral arterial disease (PAD) is defined by the American Heart Association (AHA) as “a narrowing of the peripheral arteries that carry blood from the heart to other parts of the body”. PAD is no exception and is a clear example of gender disparities. It had been considered a predominantly male disease; however, there is strong evidence that women have the disease with the same frequency as men and, in most cases, have worse outcomes and prognoses.<sup>6</sup> Although the inclusion of women in different PAD studies has improved in recent years, there are still some knowledge gaps. This thesis aims to establish the differences in symptomatology and primary health care contact between women and men with PAD. Here is intended to determine whether women and men with lower limb PAD are clinically identical or whether there are differences in symptomatology that could explain the underdiagnosis and worse prognosis in women. Additionally, our goal is to determine differences in the number of primary health care contacts before a PAD diagnosis. To achieve these aims, we carried out a systematic review and meta-analysis, and a retrospective study comparing two cohorts.

### *1.1 Systematic Reviews an overview*

Evidence synthesis is critical in medicine and, above all, in clinical practice to guide decisions. However, the number of articles published each week and the evidence derived from them exceeds the ability of clinicians and policymakers to extract and process all these information. To help clinician to take decision is important to gather and synthetizes the existing evidence to provide summarize information to a research question.

A systematic review is a review of a clearly formulated question that uses systematic and reproducible methods to identify, select and critically appraise all relevant research, and to collect and analyse data from the studies that are included in the review.<sup>7</sup>

During the systematic review process, the quality of the studies is assessed and a statistical meta-analysis of the results of the studies is performed based on their quality.<sup>8</sup>

A meta-analysis is a statistical technique for pooling the results of two or more studies that address a similar hypothesis in a similar way. It includes complete statistical reporting of all relevant studies and summarises the results of each study using a quantitative index of effect size. Meta-analyses present the precise estimate of the outcome effect (i.e., treatment) by combining these estimates across studies.<sup>7</sup>

### *1.2 Zero inflated negative binomial regression: An introduction to the model*

Count data (e.g., number of visits to the general practitioner (GP)) are often analysed using a Poisson regression model.<sup>9</sup> Although this model gives a basis to analyse count data, sometimes count data do not meet all the assumptions to follow a poisson distribution and should not be analysed using a Poisson model. Some data, for instance, show over-dispersion, excess of zeroes or both. When data present both over-dispersion and zero excess, a zero-inflated negative binomial model (ZINB) is recommended.<sup>10</sup>

For the ZINB model, the outcome variable's distribution is approximated by mixing two models and two distributions. The first part examines if the behavior ever occurred by using a logistic regression. Logistic regression is commonly used to predict a behavior's occurrence, but with ZINB model the logistic regression predicts non-occurrence (i.e., not GP visits). The second part examines how frequently the behavior occurred, using negative binomial (NB) regression. The resulting ZINB model produce two sets of coefficients, one predicting if the outcome of interest never occurred (logistic) and the other predicting how frequently the outcome occurred (NB). Because mixture models are flexible, the predictors for the two parts of the model can be different.<sup>11</sup>

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## CHAPTER 2

### Differences in symptoms between women and men with confirmed lower limb peripheral artery disease. A systematic review and meta-analysis.

#### 2.1 Introduction

Peripheral artery disease (PAD) is a progressive atherosclerotic disorder characterized by stenosis or occlusion of large and medium-sized arteries, different to those irrigating the heart and the brain.<sup>1</sup> The prevalence of PAD is higher in the lower extremities than in the upper extremity vessels, and it is estimated that there are more than 202 million people diagnosed with lower extremity PAD worldwide.<sup>1</sup>

PAD is often diagnosed using the ankle brachial index (ABI) and its diagnosis is considered at an ABI <0.9. Patients with PAD have a higher risk of long-term death compared to the general population and this risk increases with a decreasing ABI. Furthermore, the long-term mortality risk of patients with PAD is similar to those of patients diagnosed with acute myocardial infarction or stroke.<sup>2</sup>

PAD has traditionally been identified as a predominantly men disease; however, recent population studies in PAD have shown that women are affected at least as often as men.<sup>3</sup> For instance, Collins et al. and Teodorescu et al. reported a similar prevalence of PAD among women and men,<sup>4,5</sup> which is consistent with studies that showed 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%.<sup>1,6</sup>

PAD can be asymptomatic or present with a variety of symptoms, i.e., atypical leg symptoms, intermittent claudication (IC), rest pain or tissue loss.<sup>7</sup> The symptoms observed in PAD relate to the reduced blood flow to the extremities and depend on the metabolic demands of the ischemic tissue during exercise, the degree of collateral circulation, and the size and location of the affected arteries.<sup>8,9</sup> Around 50% of patients diagnosed with PAD are asymptomatic or have atypical leg symptoms. The latter being defined as any lower-extremity symptom that is not consistent with classic IC. Typical IC, described as pain or weakness while walking that is relieved with rest, occurs in about ten per cent among all patients with confirmed PAD.<sup>1</sup>

Some studies have suggested that compared to men, women with PAD have a higher tendency to be asymptomatic or have atypical leg symptoms.<sup>7</sup> These features result in a delayed diagnosis of PAD as well as a higher prevalence of more severe disease, including chronic limb-threatening ischemia at the time of diagnosis (CLTI).<sup>7</sup> There is strong evidence that

performance status, treatment options, and outcomes of endovascular interventions differ between women and men with PAD.<sup>7,8,10,11</sup> However, a comprehensive review of the differences in the symptomatology among women and men with confirmed lower limb PAD is not available. We aimed to evaluate the prevalence of typical and atypical leg symptoms in patients with PAD and to compare this prevalence between women and men. Finally, we attempted to identify factors that may be related to the sex-symptom association.

## 2.2 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)<sup>12</sup> was used to ensure transparent reporting of review methods.

### 2.2.1 Selection criteria

Observational studies (cross-sectional, cohorts, and case-control) and randomised controlled trials investigating sex differences, symptom prevalence and characteristics, and differences in treatment by sex in patients with PAD were considered for inclusion.

A study was eligible if: included patients aged 18 years or older; the diagnosis of symptomatic PAD was established using questionnaires (e.g., Edinburgh Claudication Questionnaire, San Diego Claudication Questionnaire), ABI at rest, treadmill, or Duplex; and reported symptom prevalence and presented the outcomes (i.e., symptom prevalence in terms of IC, rest pain, and atypical leg symptoms) separately for women and men.

We included studies with patients diagnosed with symptomatic PAD regardless of the diabetes status of the population. Studies were excluded if they were review articles or case reports.

### 2.2.2 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 and gender, 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 PubMed, EMBASE, and The Cochrane Library. The period of searching was restricted to publications from January 2000 to February 2021. Additionally, we restricted the search to papers written in English. Detailed search strategy can be found in **supplementary S1**.

Eligibility assessment, based on title/abstract and full text was performed independently by two reviewers (CP, RV) using the Rayyan web tool. A third author acted as an arbitrator in the case of disagreement between the reviewers (MB).

### 2.2.3 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 were 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 co-morbidities); and 4) outcome data (IC, rest pain, atypical leg symptoms). The first review author (CP) extracted the data from included studies, and the second author (RV) checked the data for correctness. The risk of bias of the included studies was assessed by two independent authors (CP, RV). Observational studies were 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.<sup>13,14</sup>

We used the GRADE system to assess the quality of evidence as high, moderate, low, or very low based on study design considerations. Observational studies start with low evidence and randomised trials with high evidence. Studies were downgraded based on their limitations, inconsistency, indirectness, and imprecision.

### 2.2.4 Statistical analysis

We performed the statistical analyses 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 relation between women and men were reported as odd ratios (OR) and 95% confidence interval (CI). Statistical significance was defined as a two-sided  $\alpha < 0.05$ . Given that we suspected clinical heterogeneity in patients and symptom-characteristics across the included studies, we applied a random-effect model for all outcomes.

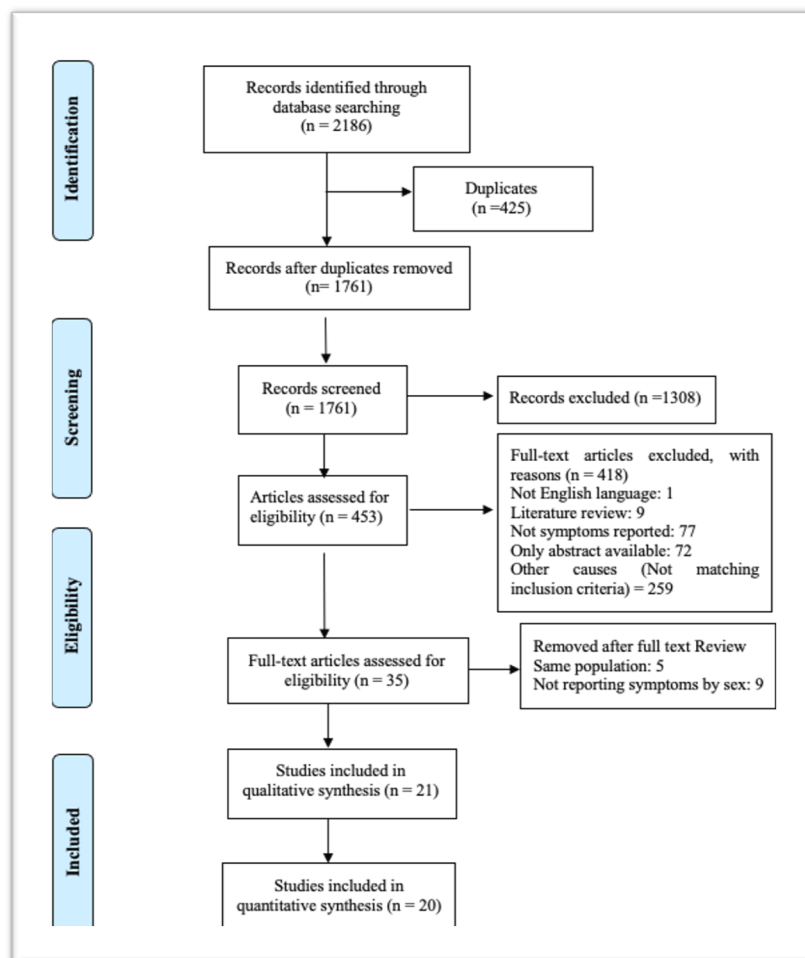
To explore whether existing heterogeneity can be explained by certain patient- and study characteristics, explorative subgroup analyses were performed. Subgroups were defined based on mean proportion of smokers ( $\leq 50\%$ ,  $\geq 50\%$ ), hypertension (we established the cut-off point for subjects with hypertension higher ( $\leq 70\%$ ,  $\geq 70\%$ ) because from the studies that reported hypertension only in two the prevalence was less than 50%), and diabetes mellitus ( $\leq 50\%$ ,  $\geq 50\%$ ) in the overall population. In addition, we performed a subgroup analysis 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. We performed sensitivity analyses to assess the contribution of each study to the pooled estimate by excluding individual studies one at a time and recalculating the pooled odd ratio estimates for the remaining studies.

## 2.3 Results

### 2.3.1 Literature search

A total of 2,186 studies were identified in the different databases, out of which we excluded 425 as being duplicate publications. After reviewing titles and abstracts, 453 studies were assessed for eligibility; and finally, we selected 35 articles for full-text review. During the full-text review, fourteen studies were discarded; five because they had the same population,<sup>15-19</sup> and nine because they did not stratify the symptoms by sex but by PAD status, race, or a different factor<sup>20-28</sup> (see **appendix 2**). **Figure 1** presents a flow diagram for the PRISMA process used to identify the included studies.



**Figure 1:** flow diagram of the literature search strategy. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.

### 1.3.2 Study and population characteristics

A total of thirteen cross-sectional,<sup>8,29-40</sup> six cohorts,<sup>41-46</sup> one case-control study,<sup>47</sup> and one randomised clinical trial<sup>48</sup> met the inclusion criteria and selected for detailed analyses. Together these studies report on 1,950,169 patients (1,929,966 with confirmed PAD). The studies were 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 twenty-one included studies, fourteen<sup>8,29,31-33,35,37,41-46,48</sup> provided sex-specific data, out of which two primarily focused on differences in symptoms by sex, and the others reported it as a secondary objective. For the latter studies, we often had available a relatively small section of each article for the review itself, and limited data reported in tables. Due to the lack of a specific focus on symptom presentation in most of the articles included in our review, we did not find a single study that stood out as contributing significantly more than others. Instead, the articles as a whole described differences in symptoms. See **table 1**.

Author	Year of publication	Country	Study design	Inclusion criteria	NOS / Cochrane risk of bias	Sample size	Confirmed PAD
McDermott et al	2003	United States	Cross-sectional	ABI < 0,90	7	460	460
Dang et al	2013	China	Cross-sectional	Elderly with DM2	7	323	323
Smolderen et al	2009	The Netherlands	Cross-sectional	ABI < 0,90	7	628	628
Collins et al	2006	United States	Cross-sectional	People > 50 years old	7	403	67
Brevetti et al	2008	Italy	Cross-sectional	ABI < 0,90	8	231	231
Behrendt et al	2019	Germany	Cross-sectional	PET of PAD	8	23 715	23 715
Kumakura et al	2011	Japan	Cross-sectional	ABI < 0,90	6	730	730
Gardner et al	2002	United States	Cross-sectional	Fontaine stage II	8	560	560
Murabito et al	2002	United States	Cross-sectional	People > 40 years old	8	3 313	118
Vliegenthart et al	2002	The Netherlands	Cross-sectional	People > 55 years old	8	3 975	557
Krishnan et al	2017	India	Cross-sectional	People ≥ 20 and ≤79 y/o	9	1 148	299
Sigvant et al	2007	Sweden	Cross-sectional	People ≥ 60 and ≤90 y/o	9	5 080	914
Tekin et al	2011	Turkey	Cross-sectional	Patients at a geriatric center	6	507	30
Jelani et al	2020	Several countries	Cohort	Patients ABI < 0,90	7	1 243	1 243
Choi et al	2019	Korea	Cohort	Patients treated with EVT	7	3 073	3 073
Sartipy et al	2019	Sweden	Cohort	Patients ABI < 0,90	9	5 080	957
Lo et al	2014	United States	Cohort	PAD + revascularization	8	1 797 885	1 797 885
Al-Zoubi et al	2019	Saudi Arabia	Cohort	DM2 + symptomatic PAD	6	364	364
Peters et al	2020	Germany	Cohort	≥ 40 + symptomatic PAD	8	83 867	83 867
Brevetti et al	2004	Italy	Case-control	People ≥ 40 and ≤80 y/o	8	3 699	60
Haine et al <sup>5</sup>	2020	International	RCT	Patients ≥ 50 y/o with PAD	Low risk	13 885	13 885

**Table 1:** Studies characteristics. Characteristics of all the studies included. NOS: Newcastle-Ottawa score, PAD: peripheral artery disease, ABI: Ankle-brachial Index, DM2: diabetes mellitus type 2, PET of PAD: patients who underwent percutaneous endovascular treatment of PAD, EVT: endovascular treatment for symptomatic PAD.

Overall, women represented 43.9% of the total population with confirmed PAD. Thirteen studies<sup>32-34,36,37,39,45-50,52</sup> reported age by sex, but only eleven<sup>32,34,36,37,39,45-47,49-50,52</sup> reported mean, and SD. 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 OR: 0.52 (95% CI: 0.40; 0.68,  $p < .001$ ,  $I^2 = 96\%$ ) and had lower prevalence of coronary heart disease OR: 0.67 (95% CI: 0.61; 0.74,  $p < .001$ ,  $I^2 = 92\%$ ) than men. On the other hand, hypertension was reported more often in women OR: 1.27 (95% CI: 1.19; 1.35,  $p < .001$ ,  $I^2 = 72\%$ ). A complete description of the baseline characteristics is found in **Table 2**.

Author	Confirmed PAD (N)	Female %	Age	Hypertension	Diabetes	Coronary heart disease	Smoking
			MD, 95% CI	OR, 95% CI	OR, 95% CI	OR, 95% CI	OR, 95% CI
McDermott et al	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	323	23.5	5.95 (3.62; 8.28)	NR	2.51 (1.48; 4.25)	NR	NR
Smolderen et al	628	33.1	NR	NR	NR	NR	NR
Collins et al	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	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	23 715	39.7	NR	NR	0.67 (0.61; 0.72)	NR	NR
Kumakura et al	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	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	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	557	64.3	NR	NR	NR	NR	0.39 (0.27; 0.57)
Krishnan et al	299	62.2	NR	NR	NR	NR	NR
Sigvant et al	914	58.4	NR	NR	NR	NR	NR
Tekin et al	30	43.3	NR	NR	NR	NR	NR
Jelani et al	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	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	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	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	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	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	60	53.7	NR	NR	NR	NR	NR
Haine et al	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)
<b>TOTAL</b>	<b>1 929 966</b>	<b>43.9</b>	<b>2.25 (0.13; 4.37)</b> <b>p&lt;.001, I<sup>2</sup>= 100%</b>	<b>1.27 (1.19; 1.35)</b> <b>p&lt;.001, I<sup>2</sup>= 72%</b>	<b>1.00 (0.85; 1.16)</b> <b>p&lt;.001, I<sup>2</sup>= 98%</b>	<b>0.67 (0.61; 0.74)</b> <b>p&lt;.001, I<sup>2</sup>= 92%</b>	<b>0.52 (0.40; 0.68)</b> <b>p&lt;.001, I<sup>2</sup>= 96%</b>
<b>(GRADE)</b>			⊕○○○ Very low*	⊕○○○ Very low*	⊕○○○ Very low*	⊕○○○ Very low*	⊕○○○ Very low*

**Table 1:** Population baseline characteristics. Characteristics of the population from the included studies. The comparison are women vs men. N: total number of patients with PAD, MD: mean difference, 95% CI: 95% confidence interval, OR: odd ratio, NR: no reported. The total at the bottom gives the pooled data across studies.

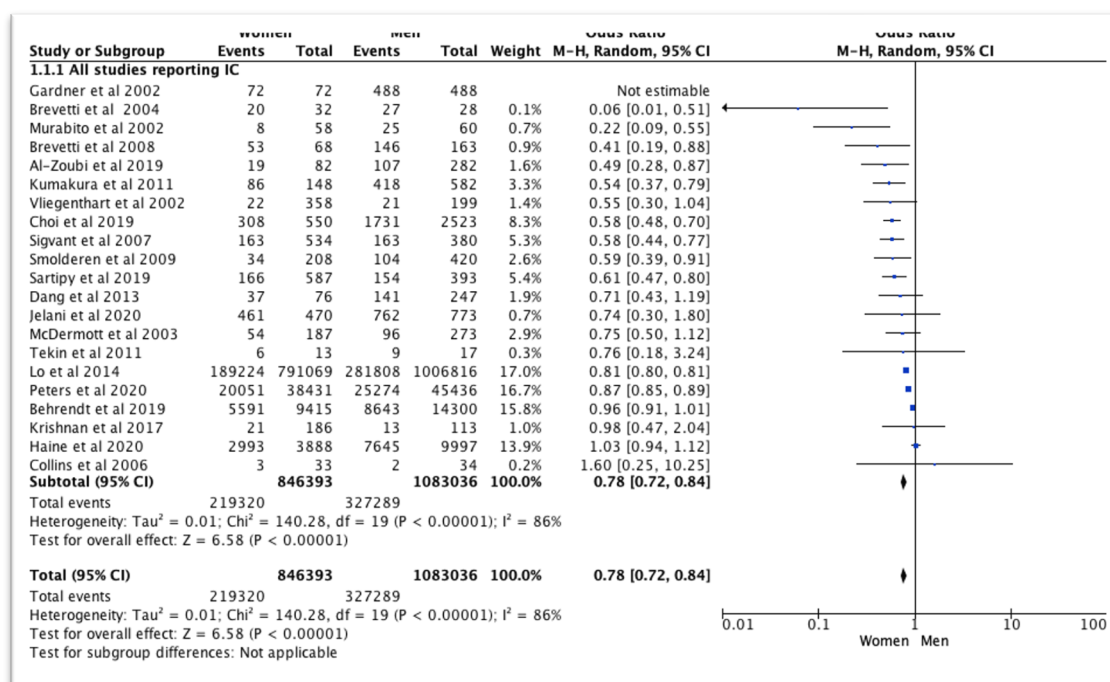
### 3.3.3 Quality of the included studies

We assessed the quality among the observational studies using the NOS. There was a significant heterogeneity in sample size, setting, and inclusion criteria. The only randomised study included had a low risk of bias.

### 2.3.4 Intermittent claudication

For IC symptoms, twenty studies involving 1,929,429 patients were included. The study by Gardner et al. was excluded from the quantitative analysis because one of its inclusion criteria was that the participants 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 bias our results. The included studies

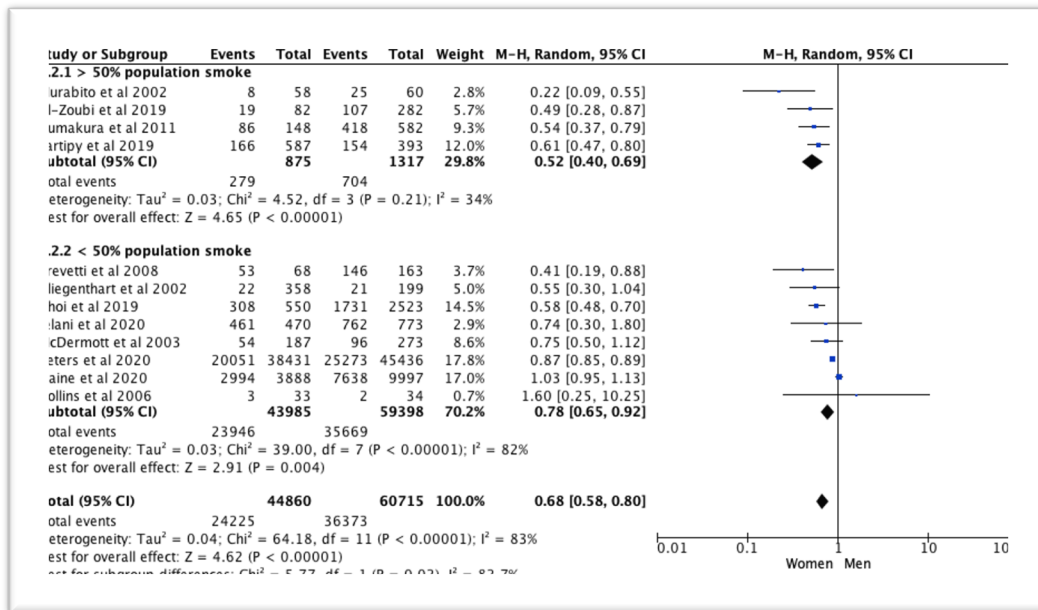
showed that among the symptomatic patients, women had less IC, OR: 0.78 (95% CI: 0.72 - 0.84,  $p < .00$ ,  $I^2=86\%$ ) **Figure 2**. According to the GRADE approach, the quality of evidence was very. It was downgraded due to inconsistency (unexplained heterogeneity of results) and indirectness (differences in the population between studies). See **supplementary material S3**.



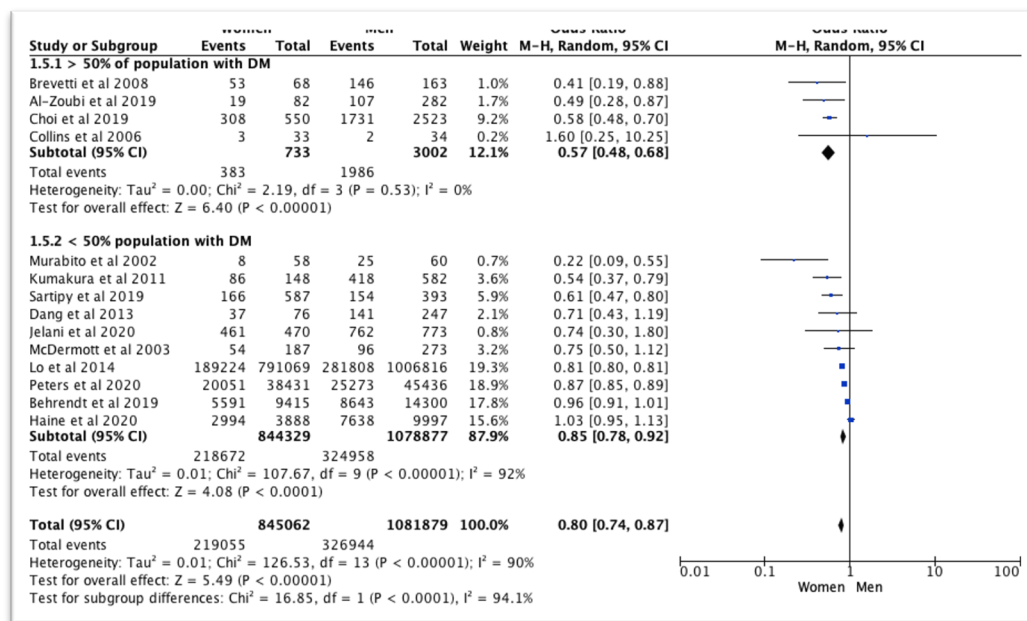
**Figure 1:** forest plot of twenty studies reporting intermittent claudication.

Subgroup analyses by the proportion of smokers in the population  $\geq 50\%$ ,<sup>35,36,41,46</sup> and  $\leq 50\%$ ,<sup>8,30,31,40,42,43,45,48</sup> showed fewer rates of IC in women,  $\geq 50\%$  OR: 0.52 (95% CI: 0.40 - 0.69,  $p < .001$ ,  $I^2 = 36\%$ );  $\leq 50\%$  OR: 0.78 (95% CI: 0.65 - 0.92,  $p = .002$ ,  $I^2 = 83\%$ ). Similarly, IC was less commonly reported in women among studies with diabetes prevalence  $\geq 50\%$ <sup>30,31,41,42</sup> OR: 0.56 (95% CI 0.47; 0.67,  $p < .00$ ,  $I^2 = 0\%$ ). In studies with more than 70% of the population with hypertension, we found IC less frequently in women, OR: 0.79 (95% CI: 0.72 - 0.86,  $p < .001$ ), see **figures 3**. 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) in the studies from 2000-2005 to OR: 0.82 (95% CI: 0.76 - 0.89) in the studies from 2011 onwards. Finally, four studies<sup>32,42,43,48</sup> described the grades of IC among women and men. Women reported less mild claudication OR: 0.74 (95% CI: 0.61 - 0.90,  $p = .003$ ,  $I^2 = 0\%$ ).

a)



b)



**Figure 2:** a) forest plot of 12 studies reporting intermittent claudication, the studies were subgroup by those that reported ≥ 50% and ≤ 50% of smokers in their population; b) forest plot of 14 studies reporting intermittent claudication, the studies were subgroup by those that reported ≥50% and ≤50% of people with diabetes in their population. Comparison is women vs men. OR: odd ratio, M-H: Mantel-Haenszel statistic, 95% CI: 95% confidence interval

### 2.3.5 Rest pain

Nine studies reported rest pain<sup>8,29,30,32,35,38,42,45,48</sup>. In these studies, women more frequently reported rest pain than men OR: 1.40 (95% CI: 1.22 - 1.60, p= <.001, I<sup>2</sup>= 72%), see **Figure 4**. This evidence was also downgraded due to serious inconsistency.

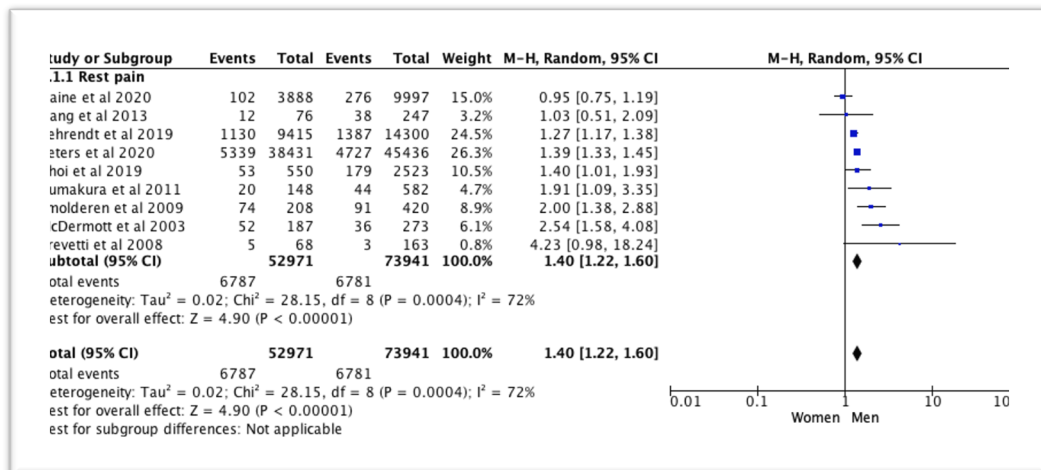


We performed separate subgroup analyses by grouping the studies according to the proportion of subjects with diabetes mellitus and hypertension in their population. Rest pain in women was more prevalent in studies with a lower prevalence of diabetes mellitus ( $\leq 50\%$ ), OR: 1.33 (95% CI: 1.15 - 1.53,  $p < .001$ ,  $I^2 = 77\%$ ), and in those with  $< 70\%$  of hypertension in their population, OR: 1.43 (95% CI: 1.20 - 1.72,  $p = < .001$ ,  $I^2 = 18\%$ ). 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 - 2.06,  $p = .001$ ,  $I^2 = 67\%$ ).

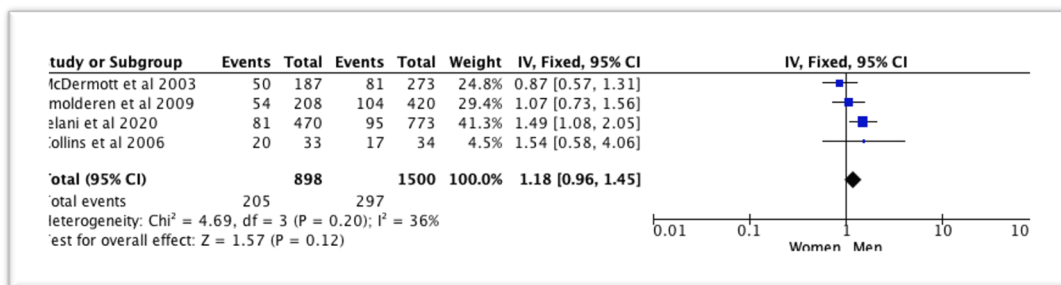
2.3.6 Atypical leg symptoms

Four studies reported atypical leg symptoms.<sup>8,31,38,43</sup> Women had more often atypical leg symptoms with an OR: 1.18 (95% CI: 0.96 - 1.45), and the heterogeneity seems low  $I^2 = 34\%$ ; however, these results were not statistically significant  $p = .12$ . See **Figure 4**.

a)



b)



**Figure 4:** a) forest plot of nine studies reporting rest pain; b) forest plot of four studies reporting atypical leg symptoms. Comparison is women vs men. OR: odd ratio, M-H: Mantel-Haenszel statistic, 95% CI: 95% confidence interval.

### 2.3.7 Sensitivity analyses

Some of the included studies were very large and was suspected they might dominate the results. Therefore, we created separate meta-analysis models by excluding individual studies one at a time. For the outcome, IC symptoms, the exclusion of the study by Lo et al. resulted in a reduction of IC for women OR: 0.72 (95% CI: 0.65 - 0.81,  $p < .001$ ,  $I^2 = 81\%$ ). We repeated this procedure and excluded the study with the second largest population, Peters et al., resulting in very similar findings; women reported less IC, OR= 0.71 (95% CI: 0.64 - 0.80,  $p < .001$ ,  $I^2 = 85\%$ ). Finally, we removed from the analysis the study by Behrendt et al., and these results were also quite similar. We also performed sensitivity analyses, 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 our previous findings. Women reported less IC with an OR: 0.79 (95% CI: 0.73 - 0.85). 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. **Table 3** shows the results.

<b>Exclusion of studies with the largest population one a time</b>						
	Number studies	Total patients	OR (95% CI)	P-value	I <sup>2</sup> Statistics (%)	GRADE
<b>Intermittent Claudication</b>						
All studies	20	1 929 429	0.78 [0.72; 0.84]	< .001	86	⊕○○○
Exclusion Lo et al	19	131 544	0.72 [0.65; 0.81]	< .001	81	Very low*
Exclusion Peters et al	19	1 845 562	0.71 [0.64; 0.80]	< .001	84	
Exclusion Behrendt et al	19	1 905 714	0.75 [0.70; 0.81]	< .001	83	
<b>Rest pain</b>						
All studies	9	126 912	1.40 [1.22; 1.60]	< .001	72	⊕○○○
Exclusion Peters et al	8	43 045	1.48 [1.18; 1.86]	.008	72	Very low*
Exclusion Haine et al	8	113 027	1.46 [1.29; 1.65]	< .001	62	
<b>Atypical leg symptom</b>						
All studies	4	2 398	1.18 [0.96; 1.45]	.12	36	⊕○○○
Exclusion McDermott et al	3	1 938	1.31 [1.03; 1.66]	.03	0	Very low**
<b>Exclusion of studies with NOS score &lt;7 or with moderate or high risk of bias</b>						
	Number studies	Total patients	OR (95% CI)	P-value	I <sup>2</sup> Statistics (%)	GRADE
<b>Intermittent claudication</b>						
NOS ≥ 7	17	1 928 305	0.79 [0.73; 0.85]	< .001	88	⊕○○○
						Very low*
<b>Rest pain</b>						
NOS ≥ 7	8	126 182	1.37 [1.20; 1.58]	< .001	74	⊕○○○
						Very low*
<b>Atypical leg symptoms</b>						
NOS ≥ 7	4	2 398	1.18 [0.96; 1.45]	.12	34	⊕○○○
						Very low**

**Table 2:** Sensitivity analysis. Exclusion of studies with the largest population one a time. Exclusion of studies with NOS score <7 or with moderate or high risk of bias. NOS: Newcastle-Ottawa score, OR: Odd ratio, 95% CI: 95% confidence interval.

## 2.4 Discussion

This systematic review provides evidence for differences in symptoms of PAD between women and men. The meta-analysis suggests that women with PAD present less often with

IC and more often with rest pain compared to men. These effects are consistent across different subgroups (i.e., year of publication, percentage of the population with hypertension, diabetes, and smokers). The study by Lo et al., with more than a million participants, had more weight compared to the other studies; however, we found the relations in all the outcomes to be the same after its removal in sensitivity analyses.

These results suggest that PAD presents differently among sexes, which could partially explain differences in outcome and treatment of PAD between women and men.

Our results are consistent with those described by other literature reviews without meta-analysis who report that women have lower rates of IC and, in contrast, tend to be asymptomatic or have atypical leg symptoms.<sup>1,3,7</sup> However, the reasons for this are still unclear. Some authors suggest that women experience symptoms differently, are less physically active (and therefore do not experience IC),<sup>16</sup> or that they may tend to report their symptoms less often than men.<sup>49</sup>

Existing systematic reviews focus on sex differences in mortality or long-term cardiovascular outcomes in patients with PAD.<sup>50</sup> They show that outcomes after endovascular interventions were worse in women compared to men, and differences in treatment options were also reported.<sup>7,10</sup> We expand that evidence by showing that the severity of symptoms at presentation in women is already worse, as they more often present with rest pain instead of IC. Therefore, it seems likely that women present with a more advanced stage of PAD.

Furthermore, the exploration of subgroups allowed to confirm that the presentation of IC is lower in women; in contrast, rest pain and atypical leg symptoms are more frequent in them. These findings were consistent through the different subgroups, including studies with a high proportion of DM, hypertension, and smokers.

The strengths of our 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 our 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, the included studies did not focus on sex differences in symptom presentation but rather on sex differences in risk factors or prevalence of PAD. Second, although we have used a broad search strategy, we only analysed studies written in English, and we may have missed other studies where authors have not fully reported their findings in published articles. Finally, not all the studies reported the outcomes of interest; while 20 studies reported IC, only four reported atypical leg symptoms. This difference in reporting could be because the definition of atypical leg symptoms may vary between studies. While Smolderen et al. defined atypical symptom as “atypical exertional leg

pain, characterized as either exertional calf symptoms that do not begin at rest but are otherwise not consistent with Rose intermittent claudication; or exertional leg symptoms that do not begin at rest and do not include the calves”, Collins et al. identified it as “pain at rest, non-calf exercise leg pain, and “non-Rose” exercise calf pain, or Rose claudication”. We believe that the absence of agreement on the definition of atypical leg symptoms may affect the reporting of this symptom. This lack of reporting limited some analyses; for example, subgroup analyses were not possible for the outcome of atypical leg symptoms. However, these limitations are unlikely to influence the results because the observation of a lower prevalence of IC in women was consistent over several subgroups and remained after sensitivity analyses.

### 2.5 Conclusion

This systematic review and meta-analysis evaluated the literature on sex differences in symptom presentation in patients with PAD. Women with PAD more often present with rest pain, while the prevalence of IC is lower. They also tend to present more atypical leg symptoms. More studies are needed to understand the possible reasons for differences in clinical presentation in women and men with PAD and how this influences diagnosis, treatment and ultimately and most important, outcome.

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## 2.7 Supplementary material

PubMed. Date: February 15 2021		Records found.
# 1	("peripheral arterial disease"[MeSH Terms] OR "peripheral arterial disease"[Title/Abstract] OR "Peripheral artery disease"[Title/Abstract] OR "arterial occlusive diseases"[Title/Abstract] OR "peripheral vascular diseases"[Title/Abstract]) AND "English"[Language] AND 2000/01/01:2021/12/31[Date - Publication]	22 990
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#4	#1 AND #2 AND #3	635
EMBASE. Date: February 15 2021		Records found.
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#2	('sex':ti,ab,kw OR 'sex specific':ti,ab,kw OR 'gender specific':ti,ab,kw OR 'male* and female*:ti,ab,kw OR 'men and women':ti,ab,kw) AND [english]/lim AND [2000-2021]/py.	720 170
#3	('intermittent claudication':ti,ab,kw OR 'symptom*:ti,ab,kw OR 'claudication':ti,ab,kw OR 'claudication intermittent':ti,ab,kw OR 'rest pain':ti,ab,kw OR 'pain':ti,ab,kw) AND [english]/lim AND [2000-2021]/py	1 884 063
#4	#1 AND #2 AND #3	736
Cochrane. Date: February 15 2021		Records found.
# 1	Peripheral arter* disease OR Arterial Occlusive Diseases* OR Peripheral Vascular Diseases*] AND 2000/01/01:2021/12/31[Date - Publication]	1 354
#2	Sex OR gender OR gender specific OR Men AND Women OR Male* AND Female*	7 713
#3	Intermittent Claudication OR Symptom* OR Claudication OR Claudication intermittent OR Rest pain OR Pain	7 728
#4	#1 AND #2 AND #3	815

Table S 1: Search strategy

Author	Year of publication	NOS/Cochrane risk of bias	Country	Study design	Sample size	Confirmed PAD	Reason for exclusion
Sigvant et al	2009	8	Sweden	Cross-sectional	4 926	880	Population
McDermott et al	2010	9	United States	Cohort	731	415	Population
McDermott et al	2001	8	United States	Cross-sectional	590	460	Population
Roumia et al	2017	8	United States	Cohort	1 274	1 274	Population
McDermott et al	2002	8	United States	Cross-sectional	740	460	Population
Dörenkamp	2016	7	The Netherlands	Cross-sectional	2 995	2 995	Reporting
Oka et al	2003	Low risk	United States	RCT	97	97	Reporting
Noyes et al	2018	6	Several countries	Cohort	1 258	1 248	Reporting
Passos et al	2001	8	Brazil	Cross-sectional	1 485	37	Reporting
Rucker-Whitaker et al	2004	6	United States	Cross-sectional	442	442	Reporting
Vural et al	2020	8	Turkey	Cross-sectional	250	44	Reporting
Weragoda et al	2015	9	Sri Lanka	Cross-sectional	2 912	88	Reporting
Okello et al	2014	6	Uganda	Cross-sectional	229	55	Reporting
Wang et al	2005	7	United States	Cross-sectional	3 629	875	Reporting

Table S2: Characteristics of the excluded studies. Population: same population than other study already included. Reporting: symptoms reported by other than sex.

Outcome	Quality assessment									Quality
	Number of studies	Study design	Limitations	Inconsistency	Indirectness	Imprecision	Women (n)	Men (n)	Effect OR (95% CI)	
Intermittent claudication	20	19 Observational studies and 1 randomised trial	Not serious	Serious <sup>1</sup>	Serious <sup>2</sup>	Not serious	846393	1083036	0.78 (0.72, 0.84)	⊕○○ ○ Very low
Intermittent Claudication (Population with hypertension)	11	10 Observational studies and 1 randomised trial	Not serious	Serious <sup>3</sup>	Serious <sup>2</sup>	Not serious	830375	1053569	0.78 (0.72, 0.85)	⊕○○ ○ Very low
Intermittent Claudication (population with diabetes)	14	13 Observational studies and 1 randomised trial	Not serious	Serious <sup>4</sup>	Serious <sup>2</sup>	Not serious	845062	1081879	0.80 (0.74, 0.87)	⊕○○ ○ Very low
Intermittent Claudication (smoking population)	12	11 Observational studies and 1 randomised trial	Not serious	Serious <sup>5</sup>	Serious <sup>2</sup>	Not serious	44860	60715	0.68 (0.58, 0.80)	⊕○○ ○ Very low
Rest pain	9	8 Observational studies and 1 randomised trial	Not serious	Serious <sup>6</sup>	Serious <sup>2</sup>	Not serious	52971	73941	1.40 (1.22, 1.60)	⊕○○ ○ Very low
Rest pain (population with hypertension)	5	4 Observational studies and 1 randomised trial	Not serious	Serious <sup>7</sup>	Serious <sup>2</sup>	Not serious	43085	58701	1.34 (1.05, 1.70)	⊕○○ ○ Very low
Rest pain (population with diabetes)	8	7 Observational studies and 1 randomised trial	Not serious	Serious <sup>8</sup>	Serious <sup>2</sup>	Not serious	52763	73521	1.34 (1.18, 1.54)	⊕○○ ○ Very low
Rest pain (smoking population)	6	5 Observational studies and 1 randomised trial	Not serious	Serious <sup>9</sup>	Serious <sup>2</sup>	Not serious	43272	58974	1.48 (1.15, 1.90)	⊕○○ ○ Very low
Atypical leg symptoms	4	Observational	Not serious	Serious <sup>10</sup>	Serious <sup>2</sup>	Serious <sup>11</sup>	898	1500	1.18 (0.96, 1.45)	⊕○○ ○ Very low

**Table S3:** GRADE methodology

Explanations: GRADE Working Group grades of evidence.

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is markedly different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be markedly different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be markedly different from the estimate of effect.

CI: confidence interval; OR: odds ratio.

1: downgraded for inconsistency because substantial heterogeneity identified ( $I^2=86\%$ ).

2: downgraded for indirectness because clinically relevant differences identified in population, treatment in clinical care, and measurement of outcomes across the studies.

3 downgraded for inconsistency because substantial heterogeneity identified ( $I^2=89\%$ ).

4: downgraded for inconsistency because substantial heterogeneity identified ( $I^2=90\%$ ).

5: downgraded for inconsistency because substantial heterogeneity identified ( $I^2=83\%$ ).

6: downgraded for inconsistency because substantial heterogeneity identified ( $I^2=72\%$ ).

7: downgraded for inconsistency because substantial heterogeneity identified ( $I^2=71\%$ ).

8: downgraded for inconsistency because substantial heterogeneity identified ( $I^2=71\%$ ).

9: downgraded for inconsistency because substantial heterogeneity identified ( $I^2=75\%$ ).

10: downgraded for inconsistency because substantial heterogeneity identified ( $I^2=36\%$ ,  $p = .20$ ).

11: downgraded for imprecision because the effect estimate come from 4 small studies with few events.

## CHAPTER 3

### Differences between women and men in primary health care contact preceding diagnosis of peripheral artery disease

#### 3.1 Introduction

Primary health care consists of services sought by individuals and delivered by providers to protect health and treat basic and uncomplicated diseases, illnesses and injuries, especially those that are public health priorities in terms of disease burden that can be alleviated through cost-effective and affordable interventions and programmes.<sup>1</sup>

In the Netherlands, healthcare insurance is mandatory, and all the inhabitants are obliged to register with a general practitioner (GP), who acts as a "gatekeeper". As gatekeepers, the GPs have the responsibility to control costs by limiting the number of referrals to specialists.<sup>2</sup> Thus, before contacting a specialist, the patients must obtain a referral letter from their GPs, except in the case of acute conditions.

The Centraal Bureau voor de Statistiek (CBS) in The Netherlands indicated that in 2013 Dutch inhabitants had on average 4.1 contacts with the GP in the last 12 months. Nevertheless, it is unclear if the number of GP visits varies months before the event triggering the referral. A study conducted in Norway between 2012 and 2013 by Skarshaug et al., found that the estimated percentage of GP contact increases in the last three months before hospital admission for heart failure and in the month before hospital admission for myocardial infarction and pneumonia.<sup>3</sup>

Peripheral artery disease (PAD) is the third most common clinical manifestation of atherosclerosis after coronary artery disease and stroke, and it affects approximately 236.6 million people worldwide;<sup>4</sup> therefore, PAD is a common cause of referral to a specialist.

Exists studies that evidenced the differences between women and men with PAD concerning symptoms, treatment, and outcomes.<sup>5-7</sup> However, it is unknown whether there are discrepancies between gender and the number of health care contact preceding the diagnostic of PAD, and in case of differences at what moment the number of GP visits increases in women and men.

Consequently, this retrospective cohort study aims to investigate to what extent exists potential differences between women and men in the frequency of primary health care contact prior to diagnosis of PAD. In addition, we pursue to determine at what point the increase in the number of consultations before suspected PAD occurs.

## 3.2 Methods

### 3.2.1 Data source

In this study, we retrieved data from the Julius General Practitioner's Network (JGPN). The JGPN is a collaboration between the Julius Center and the network's general practitioners (GP) practices in The Netherlands. This database contains information on each patient-physician consultation in the involved clinics. All contacts are registered according to a systematic format with information on symptoms, signs, diagnostic test results, diagnosis, and treatment of the patient, including prescription of medication and referral to hospital specialists. Diagnoses are entered following the International Classification of Primary Care (ICPC) coding, hospital referrals are coded according to specialist, and prescribed medication is registered in anatomical therapeutic coding (ATC).<sup>8</sup>

### 3.2.2 Population

We included patients older than 18 years. Eligible PAD patients were women and men with the first suspicion of PAD - patients with ICPC codes K91 (other diseases of the peripheral arteries) and K91.01 (intermittent claudication), seen by a GP between January 2013 and February 2020. To compare differences in primary health care contact between women and men, we used a reference population. Each patient in the PAD cohort was matched to a reference in terms of age, sex, and general practice. Eligible references were women and men without suspicion of having PAD by the time of matching.

Each included patient had an index date. For the PAD cohort, the index date was the time of the first PAD-related diagnosis, and for the reference cohort, it was the index date of the patient with PAD to which each reference belonged. The population was stratified by age at the index date as follows: <50, ≥50 - <70, ≥70 - <85, and >85 years.

### 3.2.3 Data extraction

We extracted information on sex, age, medical history, and the number of GP contacts for both cohorts. Age was defined as the age of the patient at the index date. For the medical history at baseline and number of GP contacts, we used the ICPC codes. Thus, history of hypertension was defined as patients with codes K86 and K87, diabetes mellitus T90, T90.01, T90.02, hyperlipidaemia T93, T93.01, T93.02, T93.03, T93.04, renal impairment U99.01, vascular disease K89 and K90, rheumatic disease L88, L88.01, L88.02, heart disease K75 and K76, musculoskeletal problems L14, L15, L18, L19, L28, L90, and smoking abuse ICPC-code P17. Finally, the number of GP contacts was defined as the number of ICPC codes reported up to 6 months before the index date. A summary table with the ICPC codes used in the baseline can be found in the **supplementary table S1**.

### 3.2.4 Variables of interest

The dependent variable of this study,  $y$ , was the number of health care contacts. Factors that were expected to be associated with the number of health care contacts in this study were age and medical history of diabetes mellitus, hypertension, hyperlipidemia, musculoskeletal problems, vascular disease, myocardial infarction, and smoking abuse. The definition of these variables is described in **supplementary table S2**.

### 3.2.5 Statistical analyses

To perform the statistical analyses, we used RStudio (2020): Integrated Development for R. RStudio, Inc., Boston, MA.

At baseline, continuous variables were presented as mean and standard deviation (SD) or as the median and interquartile range (IQR) depending on the distribution. Additionally, we presented categorical variables as absolute and relative frequencies. To evaluate the demographic and clinical features between women and men, we used the t-test or Chi-square test, as appropriate.

We defined the outcome as the number of health care contacts before the index date. To know the number of health contacts in women and men included in both cohorts, we used the ICPC-codes recorded in their medical records before the index date. We counted each ICPC-code as one contact moment. The index date was considered independent, so we did not take it as a GP contact. We classified the reason for contact into six groups according to body systems. Thus, category A: general symptoms, K: cardiovascular, P: psychological, S: skin, T: endocrine/metabolic, and U: urological symptoms. We did not include contact moments related to pregnancy ICPC-codes (W codes).

We fit four different count models (Poisson, negative binomial (NB), zero-inflated poisson (ZIP), and zero-inflated negative binomial (ZINB)). The Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used to identify the best fitting model.

Finally, we run interactions models between sex and covariates to investigate the association between these interactions and health contact. All tests were two-sided, and a p-value less than 0.05 was considered statistically significant.

## 3.3 Results

A total of 4,044 were patients with PAD and 15,033 reference patients without PAD. However, 4,547 (30.2%) of the references were duplicated. After removing the duplicated references, the final reference cohort included 10,486 patients, with a relation PAD-Reference of 1: 2.59. Women represented 43.5% and 46.3% of the population in the PAD and reference cohort,

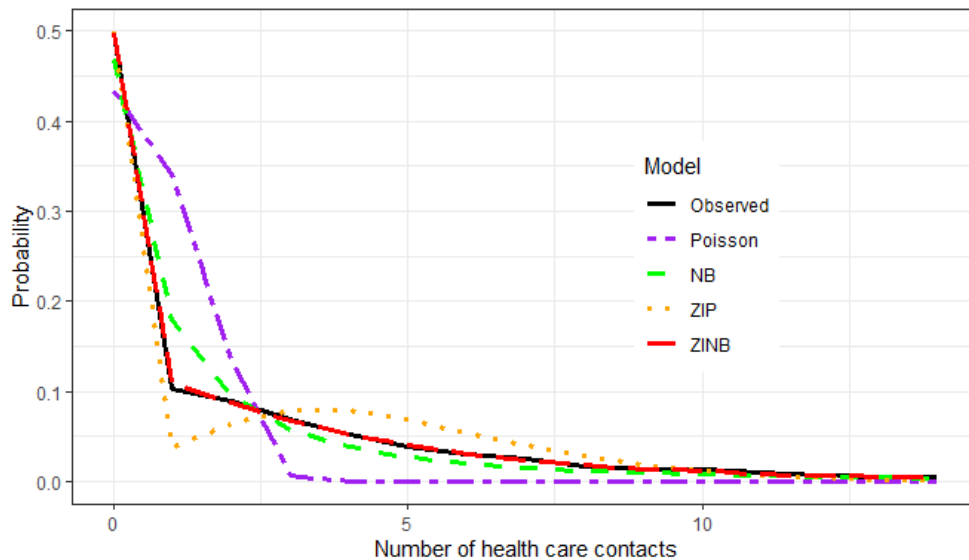
respectively. Their mean age was higher than men's mean age (69.23 (13.74) vs 67.55 (11.67) in the and 67.08 (14.25) vs 65.22 (12.24), PAD cohort and reference cohort, respectively). At baseline, women in both PAD and reference groups had a higher prevalence of hypertension, hyperlipidemia, renal impairment, rheumatic disease, and musculoskeletal problems than men, while men tended to have a higher history of diabetes mellitus and myocardial infarction. **Table 1.**

	PAD cohort <sup>1</sup>			Reference cohort		
	Women	Men	P value	Women	Men	P value
<b>N (%)</b>	1761 (43.5)	2283 (56.5)		4851 (46.3)	5635 (53.7)	
<b>Age (mean (SD))</b>	69.23 (13.74)	67.55 (11.67)	<b>&lt;.001</b>	67.08 (14.25)	65.22 (12.24)	<b>&lt;.001</b>
<b>Age group</b>			<b>&lt;.001</b>			<b>&lt;.001</b>
<b>&lt;50 years (%)</b>	159 (9.0)	159 (7.0)		561 (11.6)	589 (10.5)	
<b>≥50 &lt;70 years (%)</b>	677 (38.4)	1107 (48.5)		2095 (43.2)	2990 (53.1)	
<b>≥70 &lt;85 years (%)</b>	736 (41.8)	895 (39.2)		1730 (35.7)	1826 (32.4)	
<b>≥85 years (%)</b>	189 (10.7)	122 (5.3)		465 (9.6)	230 (4.1)	
<b>Hypertension (%)</b>	1111 (63.1)	1308 (57.3)	<b>&lt;.001</b>	2163 (44.6)	2193 (38.9)	<b>&lt;.001</b>
<b>Diabetes mellitus (%)</b>	494 (28.1)	823 (36.0)	<b>&lt;.001</b>	815 (16.8)	1035 (18.4)	<b>.038</b>
<b>Hyperlipidemia (%)</b>	487 (27.7)	624 (27.3)	.848	856 (17.6)	888 (15.8)	<b>.010</b>
<b>Renal impairment (%)</b>	262 (14.9)	307 (13.4)	.211	367 (7.6)	335 (5.9)	<b>.001</b>
<b>Rheumatic disease (%)</b>	105 (6.0)	67 (2.9)	<b>&lt;.001</b>	193 (4.0)	139 (2.5)	<b>&lt;.001</b>
<b>Vascular disease<sup>2</sup> (%)</b>	225 (12.8)	307 (13.4)	.563	310 (6.4)	405 (7.2)	.115
<b>MI<sup>3</sup> (%)</b>	182 (10.3)	450 (19.7)	<b>&lt;.001</b>	202 (4.2)	500 (8.9)	<b>&lt;.001</b>
<b>Musculoskeletal (%)</b>	1094 (62.1)	1180 (51.7)	<b>&lt;.001</b>	2525 (52.1)	2421 (43.0)	<b>&lt;.001</b>
<b>Tobacco abuse<sup>4</sup> (%)</b>	523 (29.7)	670 (29.3)	.835	467 (9.6)	577 (10.2)	.311

**Table 1:** Baseline characteristics : N: number of patients; SD: standard deviation; PAD: peripheral artery disease; P value: is reflecting the differences between women and men in the specific cohort; <sup>1</sup>PAD patients were defined as patient with ICPC code K91 or K91.01, <sup>2</sup> History of myocardial infarction; <sup>3</sup>History of tobacco abuse was defined as patients with ICPC code P17 at baseline; <sup>4</sup>Vascular disease is defined as ICPC codes K89 (Transient ischemic attack) and K90 (Stroke)

### 3.3.1 Evaluation of the model

NB and ZINB were the models that best corrected for overdispersion. However, ZINB was chosen as the final model because it exhibited the lowest AIC, BIC and predicted the highest number of zero health care contacts (**Figure 1**). The ZINB model has two parts. The first part, the NB regression part, examines the incidence rate ratio (IRR) of health care contacts. In contrast, the second part, the logistic regression part, predicts the odds ratio (OR) of having zero health care contacts.



**Figure 1:** comparison of count regression models. NB: negative binomial; ZIP: zero-inflated poisson; ZINB: zero-inflated negative binomial. **Poisson:** AIC: 70752.33; BIC: 70843.34; Predicted zeros: 3568 (42.2%); **NB:** AIC: 50991.92; BIC: 51090.51; Predicted zeros: 6795 (93.8%); **ZIP:** AIC: 57223.66; BIC: 57405.68; Predicted zeros: 7247 (100.02%); **ZINB:** AIC: 48162.81; BIC: 48352.41; Predicted zeros: 7209 (99.5%).

### 3.3.2 Health care contacts

51.7% of women and 48.8% of men included in both cohorts had at least one health care contact. The median number of GP contacts in the PAD cohort was 2 (IQR: 6) for women and 2 (IQR: 6) for men. The reference cohort had a lower median number of GP contacts, 0 (IQR: 3) for women and 0 (IQR: 2) for men. These data exhibited significant variability and dispersion (see **supplementary table S3**).

In the PAD cohort, the NB part of the model showed that the number of health care contacts for a woman was 2.70. This number is a factor of 0.94 (95% CI: 0.87, 1.01) in men; thus, men had 2.54 (95% CI: 2.29, 2.82) contacts with GP before referral. The number of GP contacts is a factor of 1.77 (95% CI: 1.65, 1.91) in patients with diabetes mellitus, 1.20 (95% CI: 1.10, 1.30) in hypertension, and 1.08 (95% CI: 1.01, 1.17) in patients with musculoskeletal symptoms. On the other hand, the zero-inflated model evidenced that the ORs of being among those never visiting the GP before suspicion of PAD for a woman is 2.70 (95% CI: 1.97, 3.68); for a man, the OR is a factor of 0.94 (95% CI: 0.70, 1.26); so, a man had an OR of 2.52 (95% CI: 1.90, 3.34), not statistically significant. Contrary, the presence of diabetes, hypertension, hyperlipidemia, musculoskeletal symptoms, and history of myocardial infarction decreased the ORs of having zero visits to the GP. **Table 3** shows the ZINB regression model for the PAD cohort.

In the reference cohort, the number of number of visits to the GP was 1.77 (95% CI: 1.62, 1.94) for a woman. This is a factor of 0.92 (95% CI: 0.87, 0.98) in men. All the other variables included in the regression model also increase the number of medical consultations. In

contrast, in the reference group, a woman had an OR of having zero GP contact of 6.96 (95% CI: 5.80, 8.36). The ORs of zero health care contact decreased on the different covariates except for sex (men), which increased the OR of zero contact by a factor of 1.16 (95% CI: 0.97, 1.38); that is, men had OR 8.06 (95% CI: 6.80, 9.57) of have zero GP contacts. **Table 3.**

To study the association of sex and other covariates with the number of health care contacts, we ran interaction models separately for the PAD cohort and the reference cohort. In patients with suspicion of PAD, none of the interactions between sex and covariates had statistically significant effect in the number of GP contacts. See **supplementary tables S4.**

Predictor	PAD cohort				Reference Cohort			
	Negative binomial model <sup>1</sup> (Count model)		Zero inflated model (Logit model)		Negative binomial model <sup>1</sup> (Count model)		Zero inflated model (Logit model)	
	Exp ( $\beta$ ) <sup>*</sup>	CI	Exp ( $\beta$ ) <sup>**</sup>	CI	Exp ( $\beta$ ) <sup>*</sup>	CI	Exp ( $\beta$ ) <sup>**</sup>	CI
Intercept <sup>+</sup>	2.70	2.42 – 3.02	2.70	1.97 – 3.68	1.77	1.62 – 1.94	6.96	5.80 – 8.36
Sex (men)	0.94	0.87 – 1.01	0.94	0.70 – 1.26	0.92	0.87 – 0.98	1.16	0.97 – 1.38
Diabetes	1.77	1.65 – 1.91	0.04	0.01 – 0.11	2.01	1.88 – 2.14	0.01	0.00 – 0.03
Hypertension	1.20	1.10 – 1.30	0.11	0.07 – 0.17	1.31	1.22 – 1.40	0.06	0.05 – 0.08
Hyperlipidemia	1.08	1.00 – 1.16	0.35	0.22 – 0.58	1.09	1.02 – 1.16	0.23	0.17 – 0.32
Musculoskeletal	1.08	1.01 – 1.17	0.39	0.29 – 0.52	1.08	1.01 – 1.15	0.34	0.28 – 0.42
Rheumatic disease	1.09	0.92 – 1.29	0.62	0.25 – 1.50	1.25	1.10 – 1.43	0.17	0.09 – 0.33
Vascular disease <sup>3</sup>	1.17	1.07 – 1.29	0.14	0.04 – 0.45	1.20	1.09 – 1.32	0.18	0.09 – 0.33
MI <sup>4</sup>	1.21	1.11 – 1.32	0.10	0.04 – 0.26	1.22	1.11 – 1.34	0.04	0.01 – 0.12
Tobacco abuse <sup>5</sup>	1.22	1.13 – 1.32	0.66	0.48 – 0.92	1.19	1.09 – 1.31	0.37	0.27 – 0.50
Age <sup>6</sup>	1.01	1.00 – 1.01	0.98	0.97 – 0.99	1.00	1.00 – 1.01	0.96	0.95 – 0.97

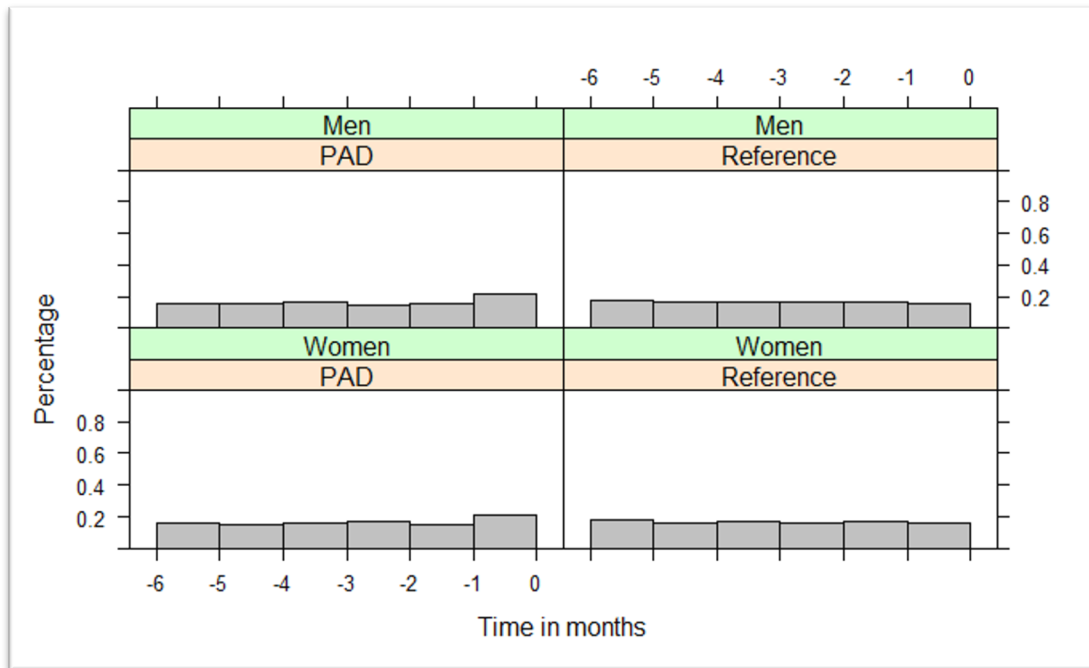
**Table 3:** ZINB Regression coefficients for the number of health care contact in the PAD and reference cohort; CI: 95% confidence interval; + **The intercept refers to a woman with mean age, the other exponent betas for the different predictor should be interpreted as factors.** \*Exponent beta in the negative binomial part of the model is interpreted as a count; \*\* Exponent beta in the zero inflated (logit model) is interpreted as an odd ratio; <sup>1</sup> Coefficients for the count part of the model are interpreted as predicted number of health care contact; <sup>2</sup> The logistic part of the model predicts non-occurrence of health care contact; <sup>3</sup> Vascular disease is defined as ICD codes K89 (Transient ischemic attack) and K90 (Stroke); <sup>4</sup> History of myocardial infarction; <sup>5</sup> History of tobacco abuse was defined as patients with ICD code P17 at baseline; <sup>6</sup> Age was mean centred for all analyses.

Regarding health care contact per month, six months before diagnosis of PAD, the percentage of contact with the GP increased during the last month before the index date for women and men in the PAD group. It remained stable in the reference group. See **figure 2.**

### 3.3.3 Zero health care contact

7,245 of the patients reported zero health care contacts. 6,013 (57,3%) of the reference cohort, and 1,232 (30.5%) of the patients in the PAD cohort. Of these, in the PAD cohort 44% were women and 56% men ( $p < .001$ ). These differences were also found in the reference cohort. **Supplementary Table S5** have the characteristics of patients without GP contact.





**Figure 2:** percentage of patients with at least one health care contact before suspicion or diagnosis of PAD.

### 3.4 Discussion

This study on sex differences in the number of contacts with primary care before diagnosis of PAD compared two cohorts within the dynamic cohort of patients belonging to the JGPN. Patients registered at JGPN are representative of the Dutch general population.

We aimed to determine whether gender influences the frequency and probability of having GP consultations. To achieve this goal, we implemented a ZINB model, which allowed us to identify if gender and other covariates may influence the number of visits while dealing with problems as the overdispersion and excess of zeros of our data.

Results showed that in patients with suspected or diagnosed PAD, the number of medical consultations does not differ between genders before the index date. Although covariates such as hypertension, diabetes mellitus, and musculoskeletal problems increased the number of visits and reduced the probability of having zero contact, this effect disappears in the interaction of gender with the covariates. On the other hand, for the reference group, the count model (NB part) evidenced that despite having a lower number of consultations compared to the PAD group, women in the reference group did consult more often than men. However, this effect only remains in the interactions between sex and hypertension and sex and history of myocardial infarction.

### 3.4.1 Strength and limitations

To our knowledge, this is the first study seeking the existence of sex differences in the number of health care contacts before diagnosis of PAD. Our study provides evidence on the non-influence of gender on the frequency of health care contact and reconfirmed something anteriorly described. Women in reference groups tend to consult more often than men.<sup>9</sup> Additionally, this study counted with a significant sample size representative of the Dutch general population. Finally, the implementation of the ZINB model solved the problems of overdispersion and zero excess and allowed to identify the factors that may influence the number of sanitary contact and those factors that may increase or reduce the probabilities of not having health care contact.

We also recognize some limitations in this study. First, our data were collected from the registers in the medical records made for the GPs in their consultation. Therefore, the quality of the information depends on the accuracy of the information in the medical records. Second, we did not have information about socioeconomic status, education, and ethnicity; these factors might influence the frequency of access to the healthcare services as described by Gerritsen et al., who found a lower frequency of GP contact in men from Morocco and the Netherlands Antilles than in women coming from the same places.<sup>10</sup> These limitations are unlikely to influence the results because our results reflect routine clinical care.

### 3.5 Conclusion

This study examined the effect of gender in primary health care contact in the population belonging to JGNP in The Netherlands. We found that patients in the PAD cohort consult more frequent than the reference cohort, but no differences in the number of health care contacts between sexes was observed.

For future research, the literature would benefit from the inclusion of data related to ethnicity, education, and socioeconomic status in the analyses, to investigate how these factors influence the primary care contact before suspicion or diagnosis of PAD.

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### 3.7 Supplementary material

Medical history	ICPC code
<b>Hypertension</b>	K86: Essential hypertension without organ damage
	K87: Essential hypertension without organ damage
<b>Diabetes</b>	T90: Diabetes mellitus
	T90.01: Diabetes mellitus type 1
	T90.02: Diabetes mellitus type 2
<b>Hyperlipidaemia</b>	T93: Fat Metabolism Disorder(s)
	T93.01: Hypercholesterolemia
	T93.02: Hypertriglyceridemia
	T93.03: Mixed hyperlipidemia
	T93.04: Familial hypercholesterolaemia/lipidaemia
<b>Renal impairment</b>	U99.01: Renal impairment/renal insufficiency
<b>Vascular disease</b>	K89: Transient cerebral ischemia/TIA
	K90: Cerebrovascular accident (CVA)
<b>Rheumatic disease</b>	L88: Rheumatoid arthritis/related condition(s)
	L88.01: Rheumatoid arthritis
	L88.02: Bechterew's disease (ankylosing spondylitis)
<b>Heart disease</b>	K75: Acute myocardial infarction
	K76: Other/chronic ischemic heart disease
<b>Musculoskeletal disease</b>	L14: Leg/thigh symptoms/complaints
	L15: Knee symptoms/complaints
	L18: Myalgia
	L19: Multiple/unspecified muscle symptoms
	L28: Disability/disability musculoskeletal system
	L90: Gonarthrosis
<b>Tobacco abuse</b>	P17: Tobacco Abuse

**Table S1:** overview of all the ICPC codes included to define baseline characteristics in the cohort. ICPC: International Classification of Primary Care

Variable	Description	Values
<b>Sex</b>	Biological sex	Male = 0; Female = 1
<b>Diabetes</b>	History of diabetes	No = 0; Yes = 1
<b>Hypertension</b>	History of hypertension	No = 0; Yes = 1
<b>Hyperlipidemia</b>	History of hyperlipidaemia	No = 0; Yes = 1
<b>Musculoskeletal</b>	History of musculoskeletal problem	No = 0; Yes = 1
<b>Rheumatic disease</b>	History of rheumatic disease	No = 0; Yes = 1
<b>Vascular disease</b>	History of vascular disease	No = 0; Yes = 1
<b>MI Smoking</b>	History of miocardial infarction	No = 0; Yes = 1
	History of tobacco abuse	No = 0; Yes = 1
<b>Age*</b>	Age in years	Continuous

**Table S2:** Variables used in Count Regression Model. \* Continuous variables were mean centred for all analyses.

Number of health care contacts	PAD cohort		Reference cohort		Entire cohort	
	Women (%)	Men (%)	Women (%)	Men (%)	Women (%)	Men (%)
0	545 (31.0)	687 (30.1)	2646 (54.5)	3367 (60.0)	3191 (48.3)	4054 (51.2)
1	195 (11.1)	255 (11.2)	499 (10.3)	544 (9.6)	694 (10.5)	799 (10.1)
2	196 (11.1)	232 (10.2)	427 (8.8)	434 (7.7)	623 (9.4)	666 (8.4)
3	156 (8.8)	194 (8.5)	333 (6.9)	334 (5.9)	489 (7.4)	528 (6.7)
4	107 (6.1)	183 (8.0)	227 (4.8)	254 (4.5)	334 (5.1)	437 (5.1)
5	83 (4.7)	145 (6.3)	157 (3.2)	175 (3.1)	240 (3.6)	320 (4.0)
6	80 (4.5)	99 (4.3)	134 (2.8)	125 (2.2)	214 (3.2)	224 (2.8)
7	65 (3.7)	106 (4.6)	95 (1.9)	95 (1.7)	160 (2.4)	201 (2.5)
8	49 (2.8)	63 (2.7)	69 (1.4)	69 (1.2)	118 (1.8)	132 (1.7)
9	45 (2.5)	56 (2.4)	59 (1.2)	48 (0.9)	104 (1.6)	104 (1.3)
10	50 (2.8)	54 (2.4)	48 (1.0)	40 (0.7)	98 (1.5)	94 (1.2)
>10	190 (10.8)	209 (9.1)	157 (3.2)	150 (2.7)	347 (5.2)	359 (4.5)
<b>Total</b>	<b>1761</b>	<b>2283</b>	<b>4851</b>	<b>5635</b>	<b>6612</b>	<b>7918</b>
Minimum	0	0	0	0	0	0
Maximum	79	57	35	66	79	66
Mean	4.06	3.97	1.94	1.67	2.50	2.33
SD	5.44	5.17	3.39	3.32	4.15	4.08
Median	2	2	0	0	1	0
IQR	6	6	3	2	3	3
Variance	29.59	26.72	11.49	11.02	17.22	16.64
Skewness	3.29	2.74	2.95	4.58	3.49	3.71

Table S3 number of GP contacts six months prior to the index date

Predictors	PAD cohort				Reference cohort			
	Negative binomial model <sup>1</sup> (Count model)		Zero-inflated model <sup>2</sup> (Logit model)		Negative binomial model <sup>1</sup> (Count model)		Zero-inflated model <sup>2</sup> (Logit model)	
	Exp ( $\beta$ )*	CI	Exp ( $\beta$ )**	CI	Exp ( $\beta$ )*	CI	Exp ( $\beta$ )**	CI
Intercept*	2.77	2.36 – 3.25	2.45	1.68 – 3.56	1.53	1.36 – 1.72	6.86	5.45 – 8.62
Sex (men)	0.91	0.75 – 1.12	1.20	0.72 – 2.01	1.21	1.04 – 1.41	1.18	0.87 – 1.60
Diabetes mellitus	1.93	1.72 – 2.16	0.08	0.02 – 0.23	2.02	1.84 – 2.21	0.01	0.00 – 0.14
Hypertension	1.20	1.05 – 1.38	0.14	0.09 – 0.24	1.48	1.34 – 1.65	0.06	0.04 – 0.09
Hyperlipidemia	1.08	0.96 – 1.21	0.43	0.22 – 0.84	1.11	1.01 – 1.23	0.14	0.08 – 0.25
Musculoskeletal	1.04	0.92 – 1.17	0.36	0.24 – 0.56	1.12	1.03 – 1.23	0.34	0.26 – 0.45
Rheumatic disease	1.12	0.90 – 1.38	0.55	0.20 – 1.49	1.33	1.12 – 1.58	0.16	0.07 – 0.38
Vascular disease <sup>3</sup>	1.19	1.03 – 1.39	0.38	0.12 – 1.19	1.15	1.01 – 1.31	0.10	0.03 – 0.39
MI <sup>4</sup>	1.19	1.01 – 1.39	0.17	0.03 – 0.96	1.41	1.21 – 1.64	0.05	0.01 – 0.31
Tobacco abuse <sup>5</sup>	1.13	1.00 – 1.28	0.68	0.43 – 1.09	1.15	1.00 – 1.31	0.38	0.24 – 0.61
Age <sup>6</sup>	1.01	1.00 – 1.01	0.98	0.97 – 0.99	1.00	1.00 – 1.01	0.96	0.95 – 0.97
Sex * Diabetes mellitus	0.86	0.75 – 1.00	0.31	0.04 – 2.45	0.98	0.86 – 1.11	1.47	0.04 – 48.97
Sex * Hypertension	0.99	0.83 – 1.17	0.58	0.26 – 1.30	0.80	0.69 – 0.91	0.97	0.59 – 1.59

<b>Sex * Hyperlipidemia</b>	0.99	0.84 – 1.15	0.63	0.24 – 1.63	0.95	0.83 – 1.09	2.45	1.23 – 4.88
<b>Sex * Musculoskeletal</b>	1.07	0.92 – 1.25	1.04	0.57 – 1.88	0.92	0.81 – 1.04	1.02	0.70 – 1.49
<b>Sex * Rheumatic disease</b>	0.92	0.65 – 1.31	1.22	0.14 – 10.84	0.86	0.66 – 1.12	1.17	0.31 – 4.49
<b>Sex * Vascular disease<sup>3</sup></b>	0.99	0.81 – 1.20	0.21	0.03 – 1.61	1.08	0.90 – 1.30	2.28	0.52 – 9.92
<b>Sex * MI<sup>4</sup></b>	1.04	0.86 – 1.27	0.50	0.06 – 3.98	0.80	0.66 – 0.97	0.82	0.10 – 6.71
<b>Sex * Tobacco abuse<sup>5</sup></b>	1.14	0.97 – 1.33	0.85	0.43 – 1.66	1.07	0.89 – 1.28	0.91	0.48 – 1.71
<b>Sex * Age<sup>6</sup></b>	1.00	0.99 – 1.01	1.00	0.98 – 1.02	1.00	0.99 – 1.00	1.00	0.99 – 1.02

**Table S4:** interaction regression for PAD and reference cohort. CI: 95% confidence interval. + **The intercept refers to a woman with mean age, the other exponent betas for the different predictor and interactions should be interpreted as factors.** \* Exponent beta in the negative binomial part of the model is interpreted as a count.; \*\* Exponent beta in the zero inflated (logit model) is interpreted as an odd ratio; <sup>1</sup> Coefficients for the count part of the model are interpreted as predicted number of health care contact; <sup>2</sup> The logistic part of the model predicts non-occurrence of health care contact; <sup>3</sup>Vascular disease is defined as ICPC codes K89 (Transient ischemic attack) and K90 (Stroke); <sup>4</sup>History of myocardial infarction <sup>5</sup>History of tobacco abuse was defined as patients with ICPC code P17 at baseline; <sup>6</sup> Age was mean centred for all analyses.

	PAD <sup>1</sup>		Reference		Overall
	Women	Men	Women	Men	
<b>N</b>	545	687	2646	3367	7245
<b>Age (mean (SD))</b>	63.95 (15.93)	63.88 (12.97)	62.29 (14.69)	62.09 (12.40)	62.47 (13.62)
<b>&lt;50 years (%)</b>	102 (18.7)	94 (13.7)	500 (18.9)	513 (15.2)	1209 (16.7)
<b>≥50 &lt;70 years (%)</b>	227 (41.7)	352 (51.2)	1332 (50.3)	1968 (58.4)	3879 (53.5)
<b>≥70 &lt;85 years (%)</b>	180 (33.0)	213 (31.0)	665 (25.1)	795 (23.6)	1853 (25.6)
<b>≥85 years (%)</b>	36 (6.6)	28 (4.1)	149 (5.6)	91 (2.7)	304 (4.2)
<b>Hypertension (%)</b>	208 (38.2)	225 (32.8)	569 (21.5)	690 (20.5)	1692 (23.4)
<b>Diabetes (%)</b>	42 (7.7)	82 (11.9)	89 (3.4)	148 (4.4)	361 (5.0)
<b>Hyperlipidemia (%)</b>	89 (16.3)	124 (18.0)	238 (9.0)	328 (9.7)	779 (10.8)
<b>Renal impairment (%)</b>	29 (5.3)	48 (7.0)	62 (2.3)	65 (1.9)	204 (2.8)
<b>Rheumatic disease (%)</b>	23 (4.2)	19 (2.8)	54 (2.0)	52 (1.5)	148 (2.0)
<b>Vascular disease (%)</b>	37 (6.8)	49 (7.1)	81 (3.1)	135 (4.0)	302 (4.2)
<b>MI <sup>2</sup> (%)</b>	28 (5.1)	60 (8.7)	40 (1.5)	138 (4.1)	266 (3.7)
<b>Musculoskeletal (%)</b>	269 (49.4)	278 (40.5)	1082 (40.9)	1204 (35.8)	2833 (39.1)
<b>Tobacco abuse<sup>3</sup> (%)</b>	140 (25.7)	164 (23.9)	219 (8.3)	261 (7.8)	784 (10.8)

**Table S5:** Characteristics of patients with zero health care contact. N: number of patients; SD: standard deviation; PAD: peripheral artery disease; P value: is reflecting the differences between women and men in the specific cohort; <sup>1</sup> PAD patients were defined as patient with ICPC code K91 or K91.01; <sup>2</sup> History of myocardial infarction; <sup>3</sup> History of tobacco abuse was defined as; patients with ICPC code P17 at baseline; <sup>4</sup>Vascular disease is defined as ICPC codes K89 (Transient ischemic attack) and K90 (Stroke).