EPIDEMIOLOGY, DIAGNOSIS, AND PROGNOSIS OF Peripheral Arterial Disease and Cardio-Renal Syndrome

EVIDENCE FROM SYSTEMATIC REVIEWS AND DATA FROM ROUTINE CLINICAL PRACTICE



Cindy Porras

Epidemiology, diagnosis, and prognosis of Peripheral Arterial Disease and Cardio-Renal Syndrome

Evidence from systematic reviews and data from routine clinical practice

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Epidemiology, diagnosis, and prognosis of Peripheral Arterial Disease and Cardio-Renal Syndrome

Evidence from systematic reviews and data from routine clinical practice

Epidemiologie, diagnostiek en prognose van Perifeer Arterieel Vaatlijden en het Cardiorenaal Syndroom

Bewijs uit systematische reviews en routinematige klinische praktijkgegevens
(met een samenvatting in het Nederlands)

Epidemiología, diagnóstico y pronóstico de la Enfermedad Arterial Periférica y el Síndrome Cardiorrenal

Evidencia de revisiones sistemáticas y datos de la práctica clínica habitual
(con un resumen en Español)

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A mi madre, ***Teresa***

PART

I

Chapter

1

General Introduction & Thesis Outline

Peripheral arterial disease & the cardiorenal connection

The organs in the human body do not function in isolation. While each organ has its own specific role, they are interconnected through complex physiological pathways. If one organ deteriorates, this might affect the others. One clear example is the interaction between the heart and the kidneys: the cardiorenal connection. In this thesis, I will focus on a framework that captures the interactions between the heart, peripheral vasculature, and kidneys. These interactions are strongly influenced by metabolic risk factors such as hypertension, diabetes, and obesity, collectively referred to as the cardiovascular-kidney-metabolic (CKM) syndrome. These interconnected conditions further challenge the traditional compartmentalised approach to disease management.[1-4]

Cardiovascular diseases (CVDs) impose a substantial burden in the Netherlands. Nearly 1.8 million people in the Netherlands live with some form of heart and vascular disease, with coronary disease and stroke being the most common conditions recorded in general practice.[5] Heart failure (HF) is a particularly impactful contributor to this burden. In 2024, approximately 240,000 people were living with a diagnosis of HF, and the condition accounted for 8,236 deaths. This represents approximately 22% of all deaths attributed to heart and vascular diseases nationwide.[6] A critical precursor of HF is left ventricular diastolic dysfunction (LVDD), often associated with ageing, hypertension, and vascular stiffness. While specific population-based prevalence estimates for LVDD in the Netherlands are limited, its occurrence increases with advancing age and common comorbidities such as hypertension and diabetes, which are prevalent in the Dutch population.

Another important contributor to the cardiovascular burden in the Netherlands is peripheral arterial disease (PAD). In 2024, 429 deaths were attributed to PAD (201 men and 228 women), accounting for approximately 1% of all heart and vascular disease deaths.[7] In the same year, there were 2,594 hospital admissions for PAD, with patients typically in their early seventies (**Table 1**).

Chronic kidney disease (CKD), which frequently coexists with CVD, further compounds this burden. A recent population-based study from the Netherlands estimated that approximately 8.9% of adults have CKD, with prevalence rising steeply with age.[8] CKD is strongly associated with cardiovascular conditions such as HF and PAD, and its coexistence significantly increases the risk of adverse cardiovascular and renal outcomes. Together, PAD, CKD and LVDD represent interconnected manifestations of systemic vascular and metabolic dysfunction. Their frequent coexistence not only exacerbates individual disease burden but also accelerates disease progression and worsens outcomes.

Table 1. *Cardiovascular disease in the Netherlands*

Condition	*Prevalence (Netherlands)*	*Mortality (Netherlands)*
All CVD	~1.78 million people living with ≥1 CVD condition (GP-registered prevalence, 2022)	
PAD	443,285 people with PAD recorded in primary care in 2022	429 deaths in 2024 (~1% of heart and vascular disease deaths)
HF	240,992 people living with HF in 2022	8,236 deaths in 2024 (~22% of heart and vascular disease deaths)
CKD	~8.9% of adults (~1.3-1.4 million people)	In 2016-2019, every year, about 5.0% of people with CKD died, while in 2020 and 2021 about 5.3% died.

CVD: cardiovascular disease; PAD: peripheral arterial disease; HF: heart failure; CKD: chronic kidney disease.

Why is the cardiorenal connection so strong?

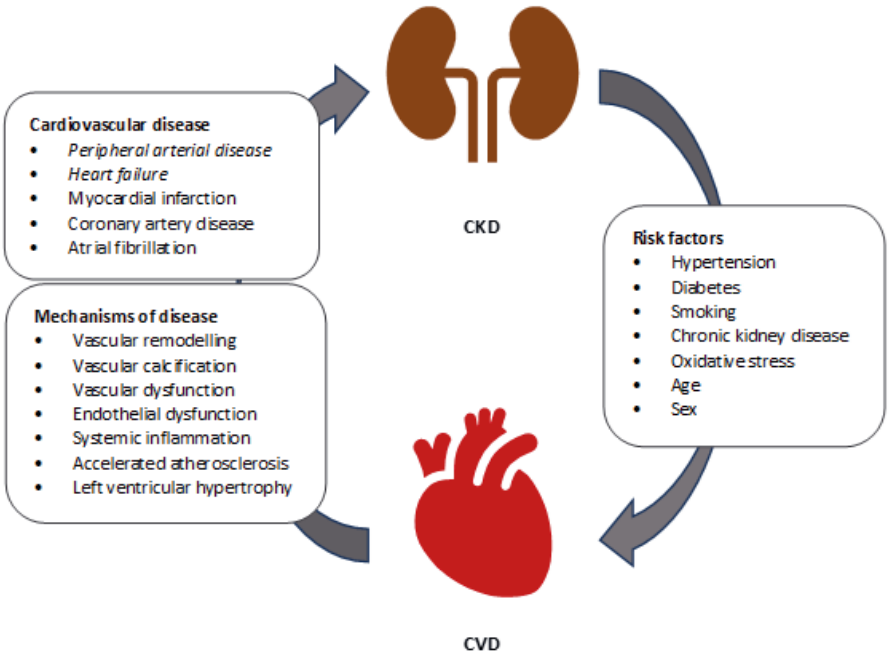
Disruptions in vascular integrity, whether through atherosclerosis, endothelial dysfunction, or altered haemodynamics, have far-reaching systemic consequences.[9] This vessel-centric perspective helps explain why PAD, CKD, and LVDD are interconnected manifestations of a shared underlying vascular pathology. In the context of the cardiorenal syndrome, vascular and haemodynamic changes, such as increased central venous pressure or reduced renal perfusion, can lead to kidney damage. Conversely, a reduction in estimated glomerular filtration rate (eGFR), often due to microvascular damage and uremic toxin accumulation, increases the risk of LVDD and eventually HF.[4,10,11] To make things even more complex, PAD, CKD, and LVDD share a series of modifiable and non-modifiable risk factors that collectively contribute to systemic vascular dysfunction, which in the end manifest in disease onset and progression (**Figure 1**). [1,12]

Among modifiable factors, one important player is hypertension. Hypertension affects approximately 30% of the adult population worldwide. It plays a central role in the pathogenesis and progression of cardiorenal syndrome by imposing chronic haemodynamic stress on the vascular system, which leads to structural and functional damage across multiple organs.[13-15] In the peripheral arteries, hypertension accelerates atherosclerosis by promoting endothelial injury, lipid infiltration, and inflammatory responses. Thus, it not only increases the risk of PAD but also worsens its prognosis by intensifying arterial stiffness and reducing tissue perfusion, which can lead to critical limb ischaemia and amputation.[16,17] In the kidneys, elevated blood pressure contributes to glomerular hypertension, endothelial dysfunction, and activation of the renin-angiotensin-aldosterone system (RAAS), all of which lead to glomerulosclerosis and progressive nephron loss.[18] In the heart, it induces left ventricular hypertrophy (LVH) and myocardial fibrosis, resulting in a reduction of ventricular compliance, impaired diastolic filling, and ultimately in LVDD.[19]

Another important risk factor is diabetes. Through mechanisms such as chronic hyperglycaemia, oxidative stress and systemic inflammation, DM accelerates both macrovascular and microvascular damage.[20] DM is a well-established risk factor for PAD, with epidemiological studies showing that for each 1% increase in haemoglobin A1c (HbA1c) there is a 26% increased risk of PAD.[21,22] In the kidneys, the story is not better, DM damages the glomerular microvasculature, leading to CKD progression, while in the heart, it contributes to myocardial stiffness and fibrosis, which impairs diastolic function, increasing the risk of LVDD and HF. [20,23,24]

CKD itself is not only a consequence but also a driver of vascular dysfunction. As kidney function declines, systemic changes such as increased arterial stiffness, vascular calcification, and endothelial dysfunction become more pronounced. These changes elevate the risk of cardiovascular events, including PAD and LVDD, and cardiovascular mortality.[25] Likewise, the prevalence of LVDD is significantly higher in patients with CKD, with studies showing an inverse relationship, meaning the risk of LVDD and HF increases as eGFR decreases.[26,27]

Figure 1. *Interconnection between cardiovascular and chronic kidney disease.*



CKD: chronic kidney disease; CVD: cardiovascular disease. Adapted from "Hallmarks for Thrombotic and Haemorrhagic Risks in Chronic Kidney Disease Patients," by Zeeba Saeed et al. (2024).

In addition to clinical risk factors, lifestyle behaviours such as smoking and physical activity are also relevant in the pathophysiology of the cardiorenal syndrome. Smoking, whether active or passive, acts as a potent systemic vascular toxin and is a well-established risk factor for multiple CVD conditions. Smoking promotes vasomotor dysfunction and thrombosis in multiple vascular beds. Smokers have more than double the risk of developing PAD compared to non-smokers, and it may take approximately 20 years of smoking cessation to reduce the risk of PAD to the level of those who have never smoked. Beyond its impact on peripheral arteries, smoking also contributes to renal microvascular damage, promoting CKD progression, and is linked to adverse cardiac remodelling, which can increase the risk of LVDD.[28,29] Similarly, sedentary behaviour is associated with increased arterial stiffness, impaired endothelial function, and heightened inflammation, all of which contribute to the development and progression of PAD, CKD, and LVDD.[30]

Adding another layer of complexity, the impact of these risk factors depends on the exposed individual, the duration of exposure and some genetic and environmental factors. Age and sex are key non-modifiable risk factors that significantly influence disease susceptibility and prognosis. Ageing is associated with physiological changes, including arterial stiffening, endothelial dysfunction and increased inflammation, all of which contribute to the development of PAD, CKD and LVDD.[31] Biological sex also influences vascular health. For example, vascular ageing differs between sexes, with oestrogens providing vascular protection in women, delaying the onset of endothelial dysfunction. These sex- and age-related differences in vascular biology not only affect susceptibility to PAD, CKD, and LVDD but also shape their clinical presentation, progression, and outcomes.[32-34]

The use of electronic health records in epidemiological research

Epidemiology plays a crucial role in advancing the understanding of PAD, CKD and LVDD and their interrelated progression. Epidemiological research aims to generate evidence that contributes, among others, to infer causality, improving prognostication and diagnostic approaches.[35] The epidemiological studies in this thesis apply different methodologies to datasets that were made fit-for-purpose. Among them, the innovative use of real-world data deserves special attention.

The introduction of electronic health records (EHRs) and the disclosure of the data within them for research purposes has revolutionised epidemiological studies.[36] In principle, EHRs offer access to large-scale patient data that can support rapid recruitment and generate real-world evidence. In certain contexts, particularly when randomised clinical trials (RCTs) are not a possible option for cost or ethical reasons, EHRs may support the modelling of intervention effects.[36,37,51] However, there are

challenges when it comes to reusing EHR data. Most of these challenges can be explained by the fact that the data were not originally collected for research purposes but include information collected by healthcare professionals from patients who seek medical attention in routine clinical practice. As EHR content depends on patients' conditions and what clinicians consider important during each visit, it often lacks standardisation, completeness, and consistency across patients and settings.[38] This issue is central to the concept of "fit for purpose" data, which emphasises that the quality of data must be evaluated in light of the specific research question because data that is suitable for one purpose may be inadequate for another.[39]

One of the most persistent challenges in working with EHR data is the proper handling of missing data. Although missing data always represent a significant statistical challenge, specifically in the context of EHRs, it is also a reflection that in clinical practice not all aspects of health can be fully captured in structured clinical records. Therefore, understanding the mechanism of missingness, i.e., whether data are missing completely at random (MCAR), at random (MAR), or not at random (MNAR), is critical for considering appropriate statistical methods,[40] especially because missingness in EHRs may itself be informative. For example, a missing smoking status might imply nonsmoking, or a missing body mass index value might suggest a normal measurement, and some information may be hidden in free-text fields rather than structured entries.

Simply deleting incomplete observations is common but often suboptimal, as it can introduce bias when excluded patients differ systematically from those with complete data. More robust approaches, such as imputation, are increasingly used to address this problem, but applying imputation techniques to EHR data requires careful consideration of both the clinical context and the underlying data architecture.

EHR data can also be messy and often require extensive cleaning and processing before it can be suitable for research. Although structured data such as laboratory values may appear ready for reuse, they are embedded in clinical and technical context that can introduce biases and inconsistencies. The accuracy of EHR data depends heavily on correct and consistent documentation, which is not always a priority in busy clinical settings. Errors can arise at multiple stages, from test ordering and specimen collection to analysis and data entry and may go unnoticed in large datasets.[41,42]

Science has limited value if it ends with a scientific paper in a journal. Patients are not treated by papers, they are treated by doctors, who might not be able to keep up with the vast and rapidly expanding body of literature. Hence, we need to do better at translating the findings of science into clinical practice.

In this thesis, I integrate the use of EHRs for research, and advocate for the adoption of learning health systems (LHS) to transform these insights into meaningful improvements in patient care.[43] LHS have been defined as health systems "*in which internal data and experience are systematically integrated with external evidence, and that knowledge is*

put into practice. As a result, patients get higher quality, safer, more efficient care, and healthcare delivery organisations become better places to work".[44] In essence, LHS are self-improving ecosystems where data from clinical care are systematically collected, analysed, and used to inform evidence-based decisions, which are then rapidly implemented and re-evaluated in a feedback loop.[45] This approach transforms the healthcare system into a dynamic ecosystem capable of learning and adapting in real time instead of remaining a static model where evidence generation and implementation are slow and disconnected from everyday clinical practice.[45]

The relevance of LHS is particularly evident in the management of complex, chronic, and interrelated conditions such as PAD, CKD and LVDD. These conditions require multidisciplinary care, long-term monitoring, and individualised treatment strategies. Within an LHS framework, continuous analysis of EHR data can help identify disease trajectories, detect care gaps, evaluate the effectiveness of interventions, and personalise treatment approaches for high-risk groups.[46] Furthermore, the iterative learning process of LHS allows for rapid hypothesis testing and implementation of best practices. This accelerates the translation of research findings into clinical care, reducing the longstanding gap between research discovery and clinical adoption.[47]

Research gaps and how this thesis contributes to filling these gaps

Despite the growing burden and interconnected nature of PAD, CKD, and LVDD, several important gaps remain in the current literature. In this thesis, I seek to address some of these gaps using real-world data. Information on specific patient groups is still missing, limiting the generalisability of current evidence. Recognising the importance of underrepresented and heterogeneous populations, I include them in our analyses to generate insights that can directly inform clinical practice and improve diagnostic and prognostic strategies in cardiovascular and kidney care. First, sex-specific differences in symptom presentation, disease progression, and healthcare utilisation are still insufficiently explored, particularly in PAD. Second, while the cardiorenal connection has been extensively studied in patients with reduced eGFR, much of this research is based on well-characterised cohorts or cross-sectional designs. Therefore, I will explore the connection between LVDD and CKD in a real-world clinical setting using both cross-sectional and longitudinal data. Third, although several prognostic models exist for cardiovascular and renal outcomes, they are often not implemented into clinical practice. The reasons are not fully understood, but one possibility is that current prognostic models often exclude clinically relevant variables, limiting their applicability across diverse patient populations. Finally, while the reuse of EHR data offers enormous

potential for real-world evidence, methodological challenges such as missing data, lack of standardisation, and contextual interpretation still limit its optimal use.

General aim

The overarching aim of this thesis is to improve the understanding of sex differences, prognostic factors, and longitudinal changes in PAD, CKD, and LVDD in real-world clinical practice. This thesis seeks to generate clinically relevant evidence that can support more personalised cardiovascular and renal care.

Thesis outline

This thesis is structured in four parts, each addressing a distinct but interconnected aspect of the epidemiology, diagnosis, and prognosis of PAD, CKD, and LVDD, with a particular focus on underrepresented populations and the reuse of real-world data.

PART I: Provides the clinical and epidemiological foundation of the thesis. It introduces PAD, CKD, and LVDD as interconnected manifestations of systemic vascular dysfunction and highlights their shared risk factors and underlying mechanisms.

> **Chapter 1** provides an overview of the epidemiology of PAD, CKD, and LVDD, emphasising their interrelationships and common vascular and metabolic risk factors.

PART II: Focuses on PAD as a key manifestation of systemic vascular disease and a central component of the cardiorenal connection. This part addresses gaps in understanding of symptom presentation, prognostic factors, and healthcare utilisation, with particular attention to sex-specific differences.

> **Chapter 2** presents a systematic review and meta-analysis on sex differences in symptom presentation among patients with PAD.
>
> **Chapter 3** reviews prognostic factors and prediction models for mortality in PAD, identifying limitations in current models and underused predictors.
>
> **Chapter 4** examines sex differences in general practitioner consultation patterns, exploring whether diagnostic disparities in PAD may be influenced by healthcare-seeking behaviour.

Chapter 5 analyses trends in mortality following first hospitalisation for PAD, identifying factors associated with survival.

PART III: Investigates the cardiorenal interaction in more detail. It examines the association between kidney function and diastolic function, using both cross-sectional and longitudinal real-world data, and it assesses the possibility of using prognostic models for heart failure risk using EHR.

Chapter 6 evaluates the use of echocardiography to assess diastolic function in patients with varying degrees of kidney dysfunction.

Chapter 7 examines longitudinal changes in echocardiographic parameters to better understand the progression of LVDD across stages of CKD.

Chapter 8 assesses how different approaches to handling missing data affect the applicability and stability of risk predictions in EHR settings.

PART IV: Integrates the findings of the preceding chapters and places them in a broader clinical and methodological context, highlighting implications for research, clinical practice, and learning health systems.

Chapter 9 summarises the main findings, discusses their clinical and methodological implications, and outlines directions for future research and implementation.

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PART

II

Chapter

2

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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ABSTRACT

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

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.

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 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 showing 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, 11, 12, 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/or 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 (≤ 50%, ≥ 50%), hypertension (the cut off point for subjects with hypertension was higher [≤ 70%, ≥ 70%] because in only two studies that reported hypertension, was the prevalence <

50%), and diabetes (≤ 50%, ≥ 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 a time. For rest pain, Peter et al. and Haine et al. were excluded, and for atypical leg symptoms, McDermott et al. was excluded.

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.

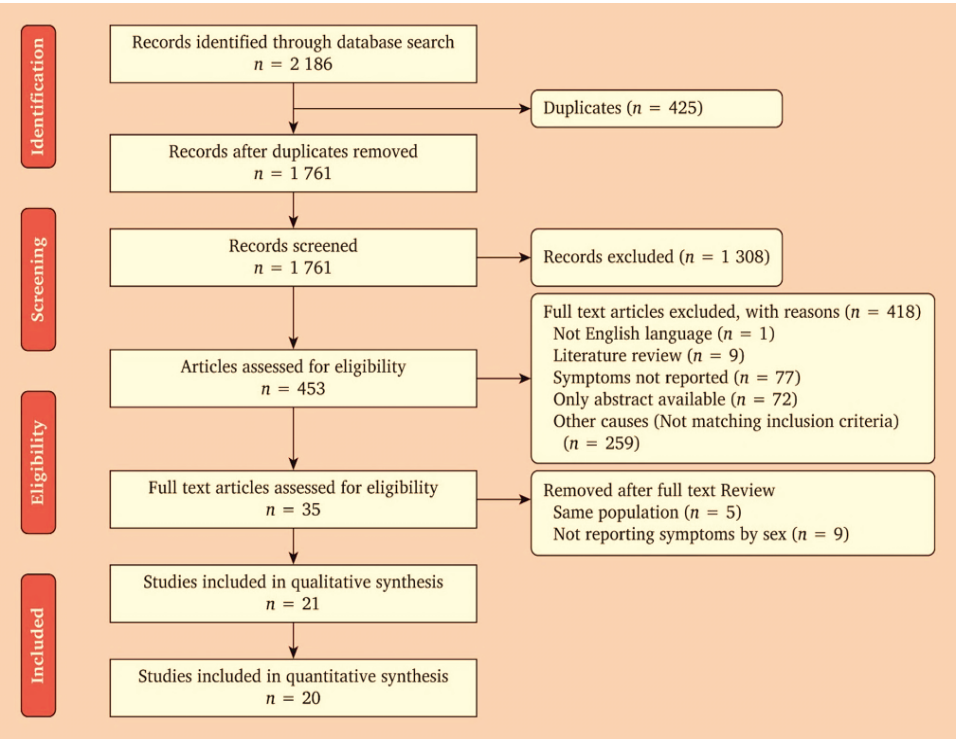
During the full text review, 14 studies were discarded: five because they studied the same population,[18, 19, 20, 21, 22] and nine because they did not stratify the symptoms by sex but by either PAD status, race, or a different factor.[23, 24, 25, 26, 27, 28, 29, 30, 31] **Supplementary Table S2** gives the characteristics of the studies excluded.

Study and population characteristics

A total of 13 cross sectional,[32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44] six cohort, [45, 46, 47, 48, 49, 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 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, 36, 37, 39, 41, 45, 46, 47, 48, 49, 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, 33, 34,36,37,39,45, 46, 47, 48, 49, 50,52] reported age by sex, but only 11 [32,34,36,37,39,45, 46, 47,49,50,52] reported mean and standard deviation.

***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.*



Women were slightly older with a mean difference 2.25 years (95% CI 0.13 – 4.37, p = .03, I2= 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, I2=96%). Prevalence of coronary heart disease (35.5% *vs.* 43.9%) OR 0.67 (95% CI 0.61 – 0.74, p < .001, I2=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, I2=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, I2=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 (I2=86%) (**Figure 2**). These results were consistent in subgroup analyses by smoking and diabetes prevalence (**Figure 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, $p < .001$, I2=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, $p = .010$, I2=71%) in the studies from 2000 to 2005 to OR 0.82 (95% CI 0.76 – 0.89, $p < .001$, I2=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 Figure S1**).

***Table 1**. Studies characteristics.*

Author	*Study design*	*Inclusion criteria*	*RoB*	*Sample size – n*	*PAD – n*
McDermott et al. (2003)[32]	Cross-sectional	ABI < 0.90	7	460	460
Dang et al. (2013)[36]	Cross-sectional	Elderly with DM2	7	323	323
Smolderen et al. (2009)[42]	Cross-sectional	ABI < 0.90	7	628	628
Collins et al. (2006)[35]	Cross-sectional	> 50 y	7	403	67
Brevetti et al. (2008)[34]	Cross-sectional	ABI < 0.90	8	231	231
Behrendt et al. (2019)[33]	Cross-sectional	PET of PAD	8	23 715	23 715
Kumakura et al. (2011)[39]	Cross-sectional	ABI < 0.90	6	730	730
Gardner et al. (2002)[37]	Cross-sectional	Fontaine stage II	8	560	560
Murabito et al. (2002)[40]	Cross-sectional	> 40 years old	8	3 313	118
Vliegenthart et al. (2002)[44]	Cross-sectional	> 55 years old	8	3 975	557
Krishnan et al. (2017)[38]	Cross-sectional	≥ 20 and ≤ 79 y	9	1 148	299
Sigvant et al. (2007)[41]	Cross-sectional	≥ 60 and ≤ 90 y	9	5 080	914
Tekin et al. (2011)[43]	Cross-sectional	At a geriatric centre	6	507	30
Jelani et al. (2020)[47]	Cohort	ABI < 0.90	7	1 243	1 243
Choi et al. (2019)[46]	Cohort	Treated with EVT	7	3 073	3 073
Sartipy et al. (2019)[50]	Cohort	ABI < 0.90	9	5 080	957
Lo et al. (2014)[48]	Cohort	PAD + revascularisation	8	1 797 885	1 797 885
Al-Zoubi et al. (2019)[45]	Cohort	T2 + symptomatic PAD	6	364	364
Peters et al. (2020)[49]	Cohort	≥ 40 y + symptomatic PAD	8	83 867	83 867
Brevetti et al. (2004)[51]	Case control	≥ 40 and ≤ 80 y	8	3 699	60
Haine et al. (2020)[52]	RCT	≥ 50 with PAD	LR	13 885	13 885

RoB: Risk of bias; RoB includes Newcastle–Ottawa score and Cochrane risk of bias; ABI = Ankle brachial Index; T2D = diabetes mellitus type 2; PET = percutaneous endovascular treatment; EVT = endovascular treatment for symptomatic PAD; RCT = randomised clinical trial.

***Table 2**. Characteristics of the population from the 21 included studies.*

Author	*PAD – n*	*Female, %*	*Age, MD (95% CI)*	*HT, OR (95% CI)*	*DM, OR (95% CI)*	*CHD, OR (95% CI)*	*Smoking, 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 met 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)

Table 2. *Continued*

Author	*PAD – n*	*Female, %*	*Age, MD (95% CI)*	*HT, OR (95% CI)*	*DM, OR (95% CI)*	*CHD, OR (95% CI)*	*Smoking, OR (95% CI)*
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)	NR	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
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; HT: hypertension; DM: diabetes mellitus; CHD = coronary heart disease. ∗ The quality of this evidence was downgraded due to serious inconsistency (high I^2 statistic test), and serious indirectness.

***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.*

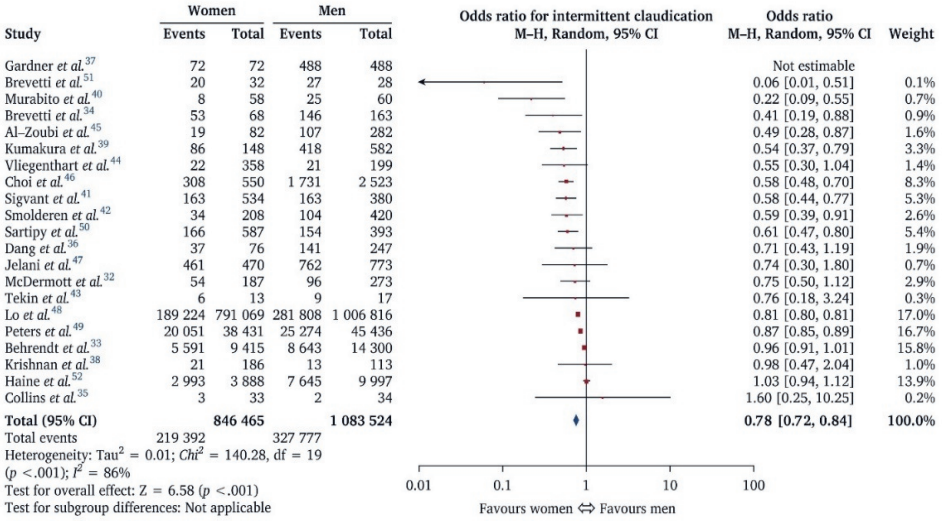
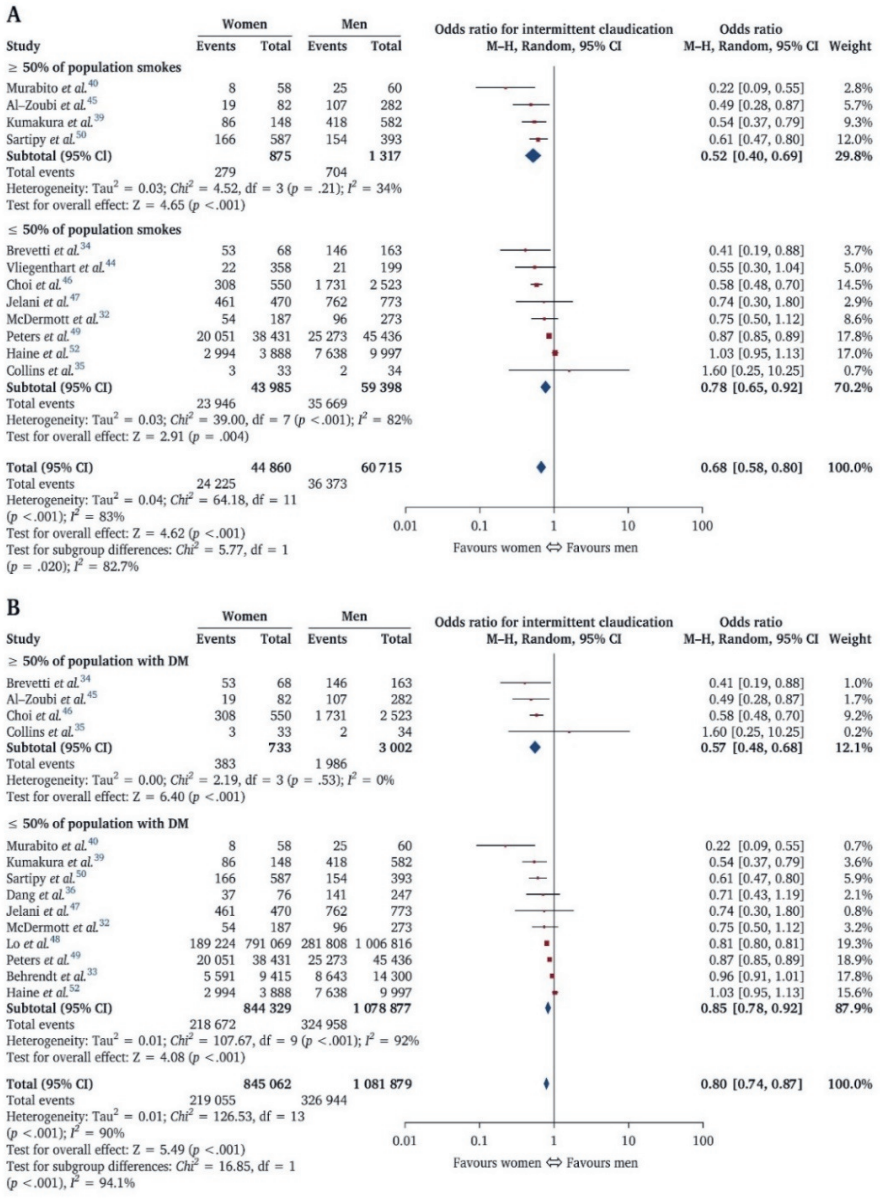


***Figure 3**. Forest plot of (A) 12 studies reporting intermittent claudication (IC) differences by sex in patients with peripheral artery disease in populations with ≥ 50% or ≤ 50% of smokers, and (B) 14 studies reporting IC in populations with ≥ 50% or ≤ 50% of people with diabetes mellitus (DM).*



OR = odds ratio; M-H = Mantel–Haenszel; CI = confidence interval.

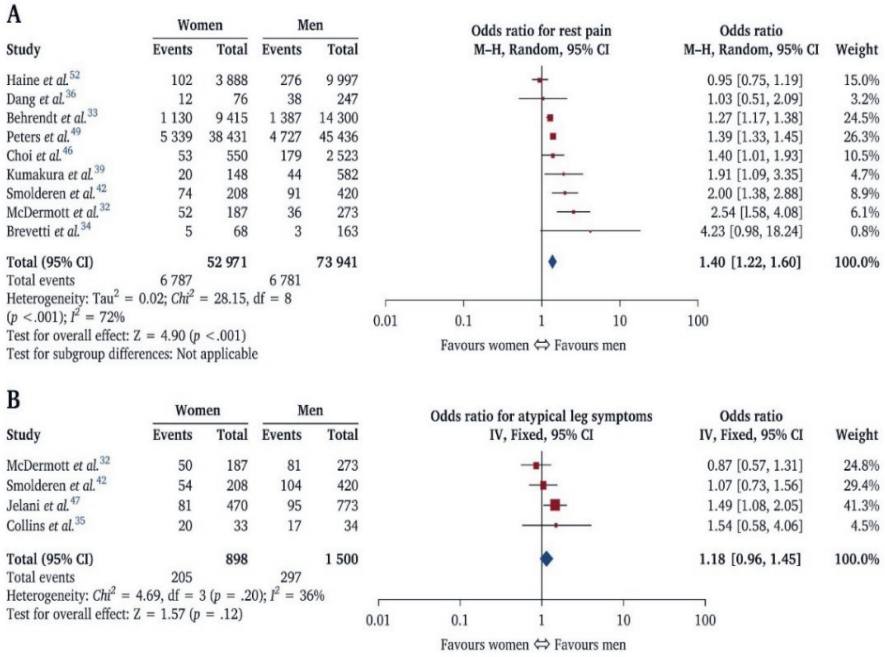
Finally, four studies[36,46,47,52] described the grades of IC among women and men. Mild claudication was reported less often in women OR 0.74 (95% CI 0.61 – 0.91, *p* = .003, I2=0%) and considered very low quality of evidence due to imprecision and indirectness. The subgroup analyses for moderate and severe claudication were not statistically significant, and the quality of evidence was considered very low due to inconsistency and indirectness (**Supplementary Figure S1**).

Nine of 20 studies reported on rest pain.[32, 33, 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, I2=72%) (**Figure 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 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, I2= 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, I2 = 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, I2= 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 I2=36%. The quality of evidence was considered very low, downgraded due to inconsistency, indirectness, and imprecision (**Figure 4B**).

***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.

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, I2=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, I2=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**).

Table 3. *Sensitivity analysis of the 21 studies on symptom differences by sex in patients with PAD with exclusion of studies one a time.*

	Studies	*Patients*	*OR (95% CI)*	*p*	*I^2 – %*	*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. ∗ Downgraded due to serious inconsistency (high I^2 statistic test), and serious indirectness (the study outcome is a surrogate for a different outcome). † 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

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 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.

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SUPPLEMENTARY MATERIAL

Supplementary Table S1. *Search strategy*

	PUBMED. Date: February 15 2021	***Studies found.***
# 1	("peripheral arterial disease"[MeSH Terms] OR "peripheral arterial disease"[Title/Abstract] OR "Peripheral artery disease"[Title/Abstract] OR "arterial occlusive diseas*"[Title/Abstract] OR "peripheral vascular diseas*"[Title/Abstract]) AND "English"[Language] AND 2000/01/01:2021/12/31[Date - Publication]	22 990
#2	(("Sex Characteristics"[Mesh] OR "Sex"[tiab] OR "Gender"[tiab] OR "Gender specific"[tiab] OR "Male AND Female"[tiab] OR "Men AND Women"[tiab]) AND (English[Language])) AND (("2000/01/01"[Date - Publication] : "2021"[Date - Publication]))	716 651
#3	(("Intermittent Claudication"[Mesh] OR "Symptom*"[tiab] OR "Intermittent claudication" [tiab] OR "Claudication" [tiab] OR "Claudication intermittent" [tiab] OR "Rest pain" [tiab] OR "Pain" [tiab]) AND (English[Language])) AND (("2000/01/01"[Date - Publication] : "2021"[Date - Publication]))	1 201 521
#4	#1 AND #2 AND #3	635
	EMBASE. Date: February 15 2021	***Studies found.***
# 1	('peripheral arterial disease*':ti,ab,kw OR 'peripheral artery disease':ti,ab,kw OR 'arterial occlusive diseas*':ti,ab,kw OR 'peripheral vascular diseas*':ti,ab,kw) AND [english]/lim AND [2000-2021]/py	35 253
#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	***Studies found.***
# 1	Peripheral arter* disease OR Arterial Occlusive Diseas* OR Peripheral Vascular Diseas*] 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

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

Author	*Year*	*Rob*	*Country*	*Study design*	*Sample size*	*PAD*	*Reason for exclusion*
Sigvant et al	2009	8	Sweden	C-S	4 926	880	Population
McDermott et al	2010	9	United States	Cohort	731	415	Population
McDermott et al	2001	8	United States	C-S	590	460	Population
Roumia et al	2017	8	United States	Cohort	1 274	1 274	Population
McDermott et al	2002	8	United States	C-S	740	460	Population
Dörenkamp	2016	7	The Netherlands	C-S	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	C-S	1 485	37	Reporting
Rucker-Whitaker et al	2004	6	United States	C-S	442	442	Reporting
Vural et al	2020	8	Turkey	C-S	250	44	Reporting
Weragoda et al	2015	9	Sri Lanka	C-S	2 912	88	Reporting
Okello et al	2014	6	Uganda	C-S	229	55	Reporting
Wang et al	2005	7	UNITED STATES	C-S	3 629	875	Reporting

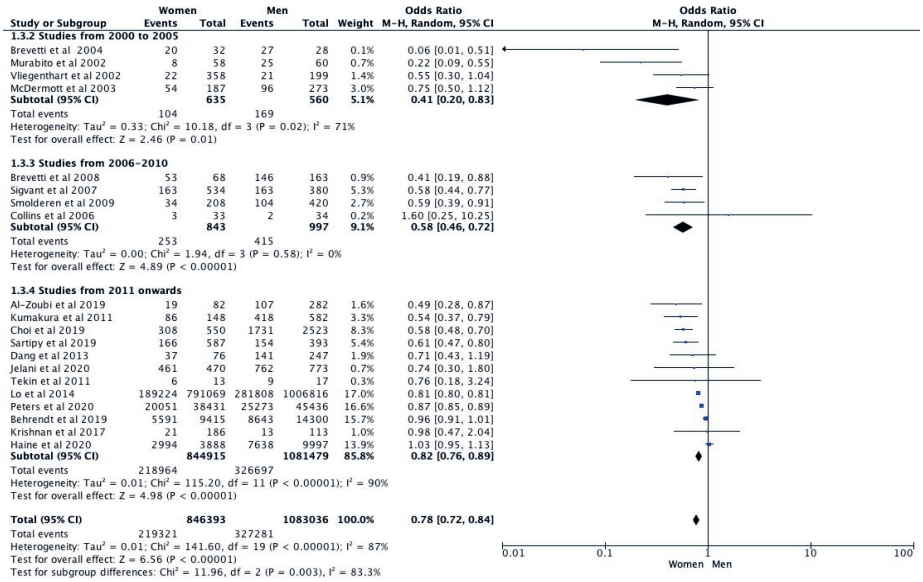
***Supplementary Table S3**. GRADE methodology*

Outcome	*N of studies*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*	*Women (n)*	*Men (n)*	*Effect, or (95% ci)*	*Quality*
Intermittent claudication	20	Not serious	Serious[1]	Serious[2]	Not serious	846393	1083036	0.78 (0.72,0.84)	Very low
Intermittent claudication (hypertension)	11	Not serious	Serious[3]	Serious[2]	Not serious	830375	1053569	0.78 (0.72, 0.85)	Very low
Intermittent claudication (diabetes)	14	Not serious	Serious[4]	Serious[2]	Not serious	845062	1081879	0.80 (0.74, 0.87)	Very low
Intermittent claudication (smoking)	12	Not serious	Serious[5]	Serious[2]	Not serious	44860	60715	0.68 (0.58, 0.80)	Very low
Rest pain	9	Not serious	Serious[6]	Serious[2]	Not serious	52971	73941	1.40 (1.22, 1.60)	Very low
Rest pain (hypertension)	5	Not serious	Serious[7]	Serious[2]	Not serious	43085	58701	1.34 (1.05, 1.70)	Very low
Rest pain (diabetes)	8	Not serious	Serious[8]	Serious[2]	Not serious	52763	73521	1.34 (1.18, 1.54)	Very low
Rest pain (smoking)	6	Not serious	Serious[9]	Serious[2]	Not serious	43272	58974	1.48 (1.15, 1.90)	Very low
Atypical leg Symptoms	4	Not serious	Serious[10]	Serious[2]	Serious[11]	898	1500	1.18 (0.96, 1.45)	Very low

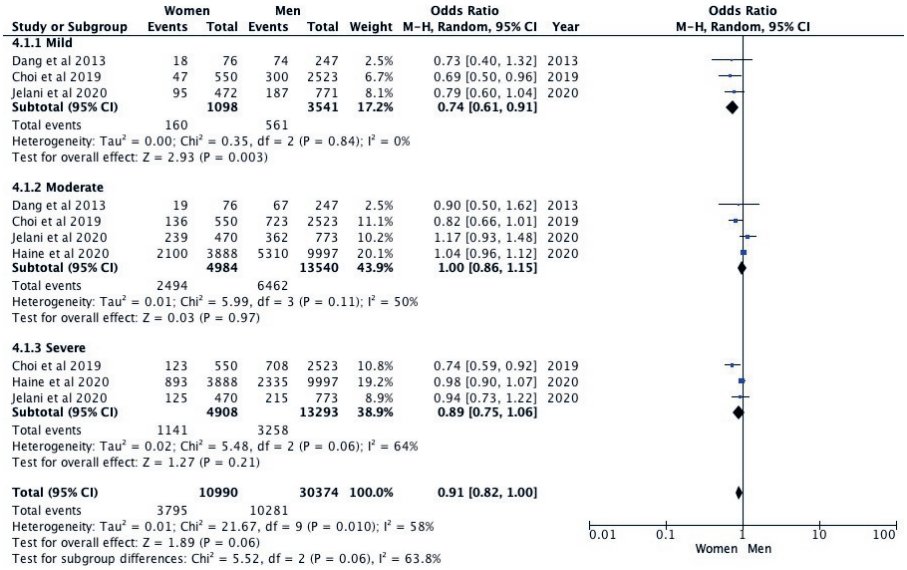
The quality of evidence was assessed using the GRADE approach. Explanations: GRADE Working Group grades of evidence. High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate: The true 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.

Supplementary figure S1: A) *forest plot of 20 studies reporting intermittent claudication, the studies were subgroup by year of publication; B) forest plot of studies reporting grade of intermittent claudication. Comparison is women vs men. OR: odd ratio, M-H: Mantel-Haenszel statistic, 95% CI: 95% confidence interval.*

A)



B)



Chapter

3

Prognostic Factors and Models to Predict Mortality Outcomes in Patients with Peripheral Arterial Disease

A Systematic Review

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ABSTRACT

Aim: Predicting adverse outcomes in patients with peripheral arterial disease (PAD) is a complex task owing to the heterogeneity in patient and disease characteristics. This systematic review aims to identify prognostic factors and prognostic models to predict mortality outcomes in patients with PAD Fontaine stage I - III or Rutherford category 0 - 4.

Methods: PubMed, Embase, and Cochrane Database of Systematic Reviews were searched to identify studies examining individual prognostic factors or studies aiming to develop or validate a prognostic model for mortality outcomes in patients with PAD. Information on study design, patient population, prognostic factors, and prognostic model characteristics was extracted, and risk of bias was evaluated.

Results: Sixty-nine studies investigated prognostic factors for mortality outcomes in PAD. Over 80 single prognostic factors were identified, with age as a predictor of death in most of the studies. Other common factors included sex, diabetes, and smoking status. Six studies had low risk of bias in all domains, and the remainder had an unclear or high risk of bias in at least one domain. Eight studies developed or validated a prognostic model. All models included age in their primary model, but not sex. All studies had similar discrimination levels of > 70%. Five of the studies on prognostic models had an overall high risk of bias, whereas two studies had an overall unclear risk of bias.

Conclusion: This systematic review shows that a large number of prognostic studies have been published, with heterogeneity in patient populations, outcomes, and risk of bias. Factors such as sex, age, diabetes, hypertension, and smoking are significant in predicting mortality risk among patients with PAD Fontaine stage I - III or Rutherford category 0 - 4.

INTRODUCTION

Peripheral arterial disease (PAD) affects over 236 million people worldwide and is the third most common manifestation of atherosclerosis following coronary artery disease and stroke.[1,2] The prognosis for individuals with PAD is generally poor, with mortality rates of around 30% at five years[3, 4, 5] and over 50% at 10 years.[6] Additionally, the risk of major adverse cardiovascular and limb events is high, especially in those with chronic limb threatening ischaemia (CLTI).[7]

Predicting adverse outcomes in patients with PAD is challenging because of the wide range of factors that vary across patients, such as symptom presentation and patient characteristics.[8, 9, 10] Prognostic factors refer to the parameters that are associated with the risk of future outcomes in individuals with a specific health condition.[11] These factors are combined in mathematical algorithms to estimate individual risk of a particular outcome, resulting in prognostic models.[12]

Some prognostic factors, such as demographic characteristics and comorbidities, have been identified as predictors of health outcomes in PAD. For instance, age is a well-established prognostic factor, as older individuals have a higher risk of adverse outcomes such as amputation, cardiovascular events, and death.[13,14] Diabetes is also a significant predictor of worse outcomes in PAD, including a higher risk of amputation.[1,6,15,16]

Despite studies investigating the prognostic value of patient disease characteristics and new models that aim to improve prognostication in patients with PAD, more clarity on all existing predictor factors and models is needed to predict mortality outcomes accurately in this high-risk population.[17] Lack of a comprehensive overview of published research on this topic may explain this. Therefore, this systematic review aimed to investigate prognostic factors and prognostic models of mortality outcomes, such as all-cause mortality, cardiovascular related mortality, short term mortality, or in hospital mortality in patients with PAD Fontaine stage I – III or Rutherford category 0 – 4.

METHODS

The protocol for this systematic review was registered with PROSPERO (CRD42022353663). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used to ensure transparent reporting of review methods (**Supplementary Table S1**).[18]

Search strategy and eligibility criteria

A literature search was conducted on 1 August 2022 in PubMed, Embase, and Cochrane Database of Systematic Reviews. Studies that were published between 1 January 2010 and 1 August 2022 were searched (**Supplementary Table S2**). On 21 November 2023, an

update search was conducted using the same strategy for studies published between August 2022 and November 2023 (**Supplementary Table S3**). Inclusion of studies was restricted to those published from 2010 onwards, as studies on the prognosis of PAD before 2010 would not inform current clinical practice.

The eligible studies were those that investigated factors predicting mortality outcomes in adult patients (> 18 years) with PAD Fontaine stage I – III or Rutherford category 0 – 4. The mortality outcomes included all-cause mortality, in hospital mortality, short term mortality, long term mortality, cardiovascular mortality, and non-cardiovascular mortality. Studies that developed or validated prognostic models for predicting mortality outcomes were also considered. Studies that focused only on patients with CLTI or those who had previously undergone major amputation were excluded to minimise heterogeneity among the selected studies. For studies that included patients with all PAD stages, including CLTI, only the results for Fontaine stage I – III or Rutherford category 0 – 4 were reported. If a study did not conduct subgroup analysis by PAD stage, it was still included and the result from the entire population was reported. Finally, studies with limited sample sizes that prevented adjustment for traditional risk factors were excluded.

For the studies on prognostic models, internal validation, i.e., assessment of the performance of a prognostic model using the same data that were used to develop the model,[19] and external validation, i.e., testing the performance of a prognostic model on an independent dataset that was not used to develop the model,[12] were considered. The study selection process was conducted by two independent reviewers (C.P.P. and R.W.V.M.) who screened titles, abstracts, and full text articles to identify potentially eligible studies. In cases of disagreement, reviewers resolved the issue by reaching a consensus.

Data extraction and quality assessment

Data were extracted independently by two reviewers (C.P.P. and R.W.V.V.) and cross checked for accuracy. From all the included studies, the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) guidance[20] was followed, and data related to general information, i.e., authors, year of publication, and title, were extracted. Other data extracted included study characteristics (study design, sample size, eligibility criteria, and outcome definition) and information about single predictors and model characteristics (predictor under study, number of predictors in the model, rationale for selecting the predictors, methods for internal or external validation, and performance measures).

The predictors were classified into six groups: demographics (age, sex, and race), medical history (comorbidities), clinical features (body mass index [BMI], blood pressure, ankle brachial index [ABI]), medication (antiplatelets, antihypertensives, and

lipid lowering drugs), biomarkers and laboratory measurements (C reactive protein [CRP], estimated glomerular filtration rate [eGFR]), and other factors (scores, arterial stiffness assessed by systolic pulse wave analysis, and flow mediated dilation assessed by ultrasound).

The quality of studies evaluating prognostic factors was assessed independently by two reviewers (C.P.P. and R.W.M.V.) using the Quality in Prognosis Studies (QUIPS) tool,[21] resulting in a low, unclear, or high risk of bias for each domain. To assess the risk of bias and applicability of studies to prognostic models, the Prediction model Risk Of Bias ASsessment Tool (PROBAST) was used.[22] Each model was evaluated on four domains (participants, predictors, outcome, and analysis), and bias and applicability per domain was rated as low, unclear, or high. Finally, the overall risk of bias and applicability based on the level of concern in each domain were evaluated.

Data synthesis

A descriptive analysis of the identified prognostic factors and model studies was conducted. From the studies on prognostic factors, all the predictors included in the multivariable model were extracted, along with their effect estimates, i.e., hazard ratio (HR), risk ratio, odds ratio (OR), or area under the receiver operating characteristic curve (AUC) with respective 95% confidence interval (CI). Furthermore, all the variables used for adjustment in the final multivariable models were extracted. For the studies on prognostic models, the model characteristics were thoroughly examined, including all the predictors considered and their validation methods. Discriminatory values were assessed, such as concordance statistic (C statistic) or AUC, indicators of a model's predictive accuracy. Additionally, calibration was evaluated to understand how predicted outcomes align with observed outcomes. Because of the expected differences in patient demographics, disease characteristics, outcome definitions, and investigated predictors, a decision was made not to conduct a meta-analysis. The varied methodologies and outcome measures used by the studies could introduce significant variability, making statistical pooling unsuitable.

RESULTS

Literature search results

A total of 4 538 unique studies were reviewed, from which 4 390 were excluded after the screening of titles and abstracts. Subsequently, 148 full text articles were assessed. Among these, 86 articles were excluded for various reasons, such as the availability of only abstracts, incorrect outcome or population, or inadequate sample size (**Supplementary Table S4**). The first phase of the search included 56 studies focusing on

prognostic factors, along with six studies (comprising five models) dedicated to developing or validating a prognostic model.
In a subsequent search update, 699 studies were identified, and 31 studies were chosen for full text evaluation. Of these, 15 studies met the inclusion criteria, encompassing 13 on prognostic factors and two on prognostic models. A total of 77 studies were included, with 69 studies on prognostic factors [23-91] and eight studies developing or validating prognostic a model [92-99] for mortality outcomes (**Figure 1**).

Study characteristics

Among the studies investigating prognostic factors, 44 (64%) were prospective cohorts, 22 (32%) were retrospective cohorts, and three (4.3%) were case–control studies. The sample size across these studies ranged from 101 – 134 081 patients, with the proportion of men varying from 42 – 100%. The mean age ranged from 61 – 79 years, and the mean follow up duration spanned from 1 – 135.6 months.
The prevalence of hypertension was significantly variable, ranging from 27 – 90%, whereas seven studies (10%) did not report it. Similarly, the prevalence of diabetes varied from 13 – 78%, with seven studies (10%) omitting the reporting of diabetes prevalence. Chronic kidney disease showed a wide range, from 0.8 – 75%; 31 studies (45%) did not provide information on its prevalence (**Table 1**). Regarding mortality outcomes under study, the most frequently studied was all cause mortality in 38 studies (55%), cardiovascular mortality in 24 studies (35%), and overall mortality in 13 studies (19%) (**Table 2**).
In the studies that described prognostic models, the sample size varied from 129 – 150 921. The male population ranged from 0 – 76%, and the mean age ranged between 69 years and 72 years. The prevalence of hypertension ranged from 39 – 97%, with one study (13%) not reporting it. The prevalence of diabetes ranged from 21 – 53%. Chronic kidney disease was reported in four studies (50%), with a prevalence ranging from 6 – 33% (**Table 3**).

***Figure 1**. Preferred reporting items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram of the literature search strategy.*

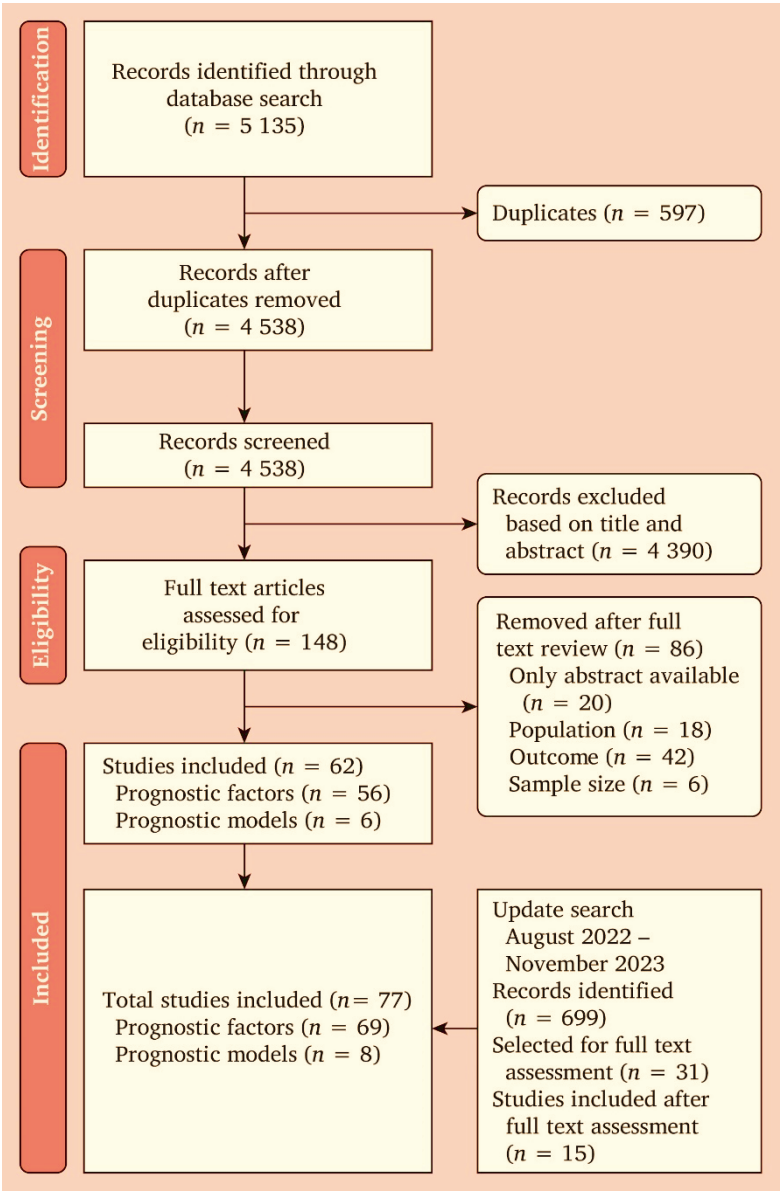


Table 1. *Baseline characteristics of 69 studies of prognostic factors in patients with peripheral arterial disease.*

Author (year)	*Outcome*	*Sample size*	*Men – %*	*Mean age – y*	*HT –%*	*DM – %*	*Smoking – %*	*HF – %*	*CAD – %*	*CKD – %*
Criqui et al. (2010)[32]	All cause, CV and non-CV death at 2 and 6.6 y	397	87	68.7†	77†	36†	NR	NR	NR	NR
de Liefde et al. (2010)[33]	All cause and CV death at 5 y	261	62	61†	36†	23†	40†	6†	NR	5†
McDermott et al. (2011)[64]	All cause death and mobility loss at 97 mo	440	57	NR	NR	32	16	21	24	NR
Singh et al. (2010)[75]	All cause death at 5 y	410	60	71.8 (8.2)†	NR	36†	14†	27†	27†	NR
Skau et al. (2020)[76]	All cause death	436	59	70.1 (7.2)	78	25	76	NR	18	NR
Winkel et al. (2010)[89]	CV death at 2 y	3 655	75	67.7 (9.6)†	61†	NR	20†	42†	NR	NR
de Liefde et al. (2012)[34]	Long term death	2 165	67	62 (11)†	37†	19†	32†	6†	NR	7†
Mui et al. (2011)[67]	Death at 12 y	488	68	66 (11.3)†	58†	31†	60†	NR	23†	NR
Urbonaviciene et al. (2011)[82]	All cause and CV death at 120 mo	295	58	67 (9.6)	51	15	60	NR	15	NR
Urbonaviciene et al. (2011)[83]	All cause at 100 mo	378	61	65.7 (8.8)†	56†	24†	56†	NR	18†	NR
Ye et al. (2011)[90]	All cause death	13 039	61	69.5 (11.9)†	74†	35†	81†	16†	56†	9.8†
Jain et al. (2012)[48]	Long term all-cause and CV death	679	56	72.7 (8.4)†	NR	35†	20†	26†	23†	NR
Urbonaviciene et al. (2012)[81]	All cause and CV death at 120 mo	463	58	65.6 (9.5)†	51†	13†	58†	NR	14	NR
Valentijn et al. (2012)[84]	Death at 4 y	1 172	73	68.6 (10.1)†	70†	23†	45†	9†	NR	31†
Jain et al. (2013)[47]	Long term death	442	58	72.7 (8.2)†	27†	32†	17†	20†	24†	NR
Leeper et al. (2013)[59]	All cause and CV death at 12 y	725	98	62 (9.1)	65	16	67	8	NR	NR
de Vos et al. (2014)[35]	Death at 5 y	252	73	66 (11)	91	29	50	NR	28	NR
Desormais et al. (2014)[36]	Combined 1 y death and major amputation	925	71	71 (12.8)	77	44	25	13	38	NR

Table 1. *Continued*

Author (year)	*Outcome*	*Sample size*	*Men – %*	*Mean age – y*	*HT – %*	*DM – %*	*Smoking – %*	*HF – %*	*CAD – %*	*CKD – %*
Erturk et al. (2014)[37]	CV death	508	81	64 (57–71)*	61†	42†	52†	NR	41†	21.6†
Kals et al. (2014)[52]	Death at 8 y	117	100	62.1 (7.6)†	39†	NR	97†	NR	20†	NR
Linnemann et al. (2014)[61]	Total death at 1 y	1 041	63	70.7 (10.8)	85	41	24	NR	45	38
Mueller et al. (2014)[66]	All cause death	487	70	70 (38–94)*	61	NR	41	NR	31	NR
Pohlhammer et al. (2014)[68]	All cause death	235	100	58.3 (6.3)	86	16	52	NR	29	NR
Jones et al. (2015)[51]	Composite of death, MI, and stroke at 8 y	908	57	68.6 (10.1)	89	41	31	NR	14	21
Kim et al. (2015)[53]	All cause of death	240	81	66.8 (11.3)	73	48	55	NR	38	NR
Lacroix et al. (2013)[57]	Death at 1 y	1 010	71	70.7 (2.8)	77	44	25	13	37	NR
Smolderen et al. (2015)[77]	CV and other causes of death at 60 mo	756	65	65 (9.8)	60	24	50	5	19	9
Staniszewska et al. (2015)[78]	All cause death at 10 y	238	66	69 (62–75)	65	14	NR	NR	31	NR
Amrock et al. (2016)[26]	Long term all-cause and CV death	556	50	70.9 (11.3)	78	30	22	NR	NR	31
Hackl et al. (2016)[42]	Death at 5 y	184	67	68 (61–76)*	81	35	40	NR	21	NR
Jalkanen et al. (2016)[49]	Death at 36 mo	887	57	72.4	70	43	27	NR	43	10
McDermott et al. (2016)[63]	All cause and CV death at 70 mo	951	61	71.29 (9.14)	34	34	21	20	23	NR
Senthong et al. (2016)[73]	All cause death at 5 y	821	66	66 (10)	83	43	74	NR	90	NR
Ali et al. (2018)[24]	30 d death after LE bypass surgery	4 704	64	67.9 (11.7)	85	NR	41	NR	NR	7
Amrock et al. (2017)[25]	All cause and CV death	647	42	67.8	77	30	25	NR	NR	30
Chowdhury et al. (2017)[31]	CV and all cause death	220	66	69 (63–88)	71	23	86	NR	36	17
Senda et al. (2018)[72]	All cause and CV death at 5 y	441	81	74 (67–80)	74	43	59	10	31	NR

Table 1. *Continued*

Author (year)	*Outcome*	*Sample size*	*Men – %*	*Mean age – y*	*HT – %*	*DM – %*	*Smoking – %*	*HF – %*	*CAD – %*	*CKD – %*
Senthong et al. (2017)[74]	All cause death at 5 y	771	66	66 (10)	83	43	74	31	90	NR
Wickström et al. (2017)[87]	All death at 80 mo	887	NR	72.4	NR	NR	NR	NR	NR	NR
Wickström et al. (2017)[88]	All cause and CV death at 40 mo	732	58	72 (11)	40	41	29	NR	43	10
Esteban et al. (2019)[38]	Death and amputation	518	80	NR	79	57	63	11	26	26
Hemstra et al. (2018)[43]	CV death	286	57†	67	49†	16†	58†	NR	NR	NR
Higashitani et al. (2018)[44]	All cause, CV, and non-CV death, and MACE	2 238	72	73.3 (9.3)	83	57	23	12	47	27
Höbaus et al. (2018)[45]	All cause of death at 5 y	366	66	69 (10)	NR	NR	NR	NR	32†	NR
Hu et al. (2019)[46]	Long term death	16 888	53	63.4 (14.5)	68	26	NR	10	NR	19
Pourafkari et al. (2018)[69]	All cause death at 10 y	1 228	99	67†	77†	52†	NR	9†	55†	32†
Tern et al. (2018)[80]	All cause death at 90 mo	678	60	74 (64–82)*	NR	42	NR	11	NR	NR
Mizobuchi et al. (2019)[65]	Any death at 1 000 d	628	69	69 (10)	83	71	38	NR	NR	75
Roncal et al. (2019)[71]	CV death at 96 mo	262	87	70 (11)	74	53	32	NR	28	39
Golledge et al. (2020)[41]	All cause death	1 533	75	69†	75†	35†	31†	NR	45†	0.8†
Malik et al. (2020)[62]	All cause death at 4 y	765	58	68.4 (9.7)	89	39	31	14	NR	15
Chi et al. (2021)[30]	All cause and CV death	195	66	66.4 (13)†	82†	42†	12†	NR	NR	NR
Fukase et al. (2021)[40]	All cause of death, MACE	335	82	72 (8)	84	56	89	NR	NR	36
Koivunen et al. (2021)[54]	CV death	729	58	74.9 (10.5)	70	41	29	NR	43	9
Rammos et al. (2021)[70]	Death at 24 mo	246	59	75 (6.5)†	90†	36†	23†	NR	54†	39†
Al-Damluji et al. (2022)[23]	Peri-operative death	134 081	60	68.4 (11.1)	88	52	79	19	32	14
Aursulesei et al. (2022)[27]	Death risk at 10 y	101	52	70.6 (9.2)	76	38	43	26	24	17

Table 1. *Continued*

Author (year)	*Outcome*	*Sample size*	*Men – %*	*Mean age – y*	*HT –%*	*DM – %*	*Smoking – %*	*HF – %*	*CAD – %*	*CKD – %*
Balasundaram et al. (2023)[28]	30 d death after revascularisation	11 947	60	69*	84	56	30	4	NR	10
Kotov et al. (2022)[55]	All death and MACE	4 354	68	69 (62–77)	NR	37	20	17	16	22
Lapébie et al. (2022)[58]	All cause death, and MACE	2 494	75	70.6 (12.8)	86	40	25	12	37	40
Vieira-Cardoso et al. (2023)[85]	All cause death	107	95	62.2 (8.8)	65	32	90	12	29	15
Chang et al. (2023)[29]	All cause of death, MACE	504	47	79.9 (6.2)†	88†	67†	28†	14†	39†	70
Evans et al. (2023)[39]	All cause and CV death	202	78	68*	96	49	26	NR	73	26
Jang et al. (2023)[50]	Death at 1, 2, 3, 4, and 5 y	214	53	71.2 (11.8)	84	78	38	16	53	40
Kurokawa et al. (2023)[56]	Death, MALE, MACE	288	77	73 (9)	85	46	22	NR	30	24
Leiherer et al. (2023)[60]	All cause and CV death	379	72	67*	94	40	31	NR	NR	20
Tasbulak et al. (2022)[79]	Long term death	723	89	61.6 (9.3)	74	58	58	NR	66	24
Welch et al. (2023)[86]	All cause death at 6 mo	148	61	70.3 (11)	72	NR	75	NR	30	10
Zierfuss et al. (2023)[91]	All cause and CV death	1 028	61	68 (9.0)†	90†					

*HT: hypertension; DM: diabetes mellitus, HF: heart failure, CAD: coronary artery disease; CKD: chronic kidney disease; CV: cardiovascular; MI: myocardial infarction; LE: lower extremity; NR: not reported; MACE: major adverse cardiovascular event; MALE: major adverse limb event. * Median. † Pooled results.*

***Table 2**. Predictors identified in 69 studies assessing prognostic factors to predict death in patients with peripheral arterial disease.*

Prognostic factor	***Studies-69 (%)***	***Mortality outcomes described in the included studies***						
		All cause-38 (55%)	CV death-24 (35%)	Death-13 (19%)	Long term-7 (10%)	30 d-3 (4%)	In hospital-2 (3%)	Non-CV-1 (1%)
Age	63 (91)	39	16	11	3	3	1	1
Sex	40 (58)	32	8	5	2	2		
Race/ethnicity	9 (13)	6	1			3		
Diabetes mellitus	44 (64)	20	11	8	2		1	
Smoking history	32 (47)	19	11	7	1			
CAD	24 (35)	11	6	5	1	2	1	
Heart failure	20 (29)	20	3	4	1		1	
Hypertension	17 (25)	7	7	4	1			
Stroke or TIA	13 (19)	8	2	2	1			
Dyslipidaemia	13 (19)	5	3	3	2			
CKD	11 (16)	6	2	5				1
Renal failure	11 (16)	3	3	2	1	1	1	
COPD	8 (12)	4	1	2	1			
Dialysis	7 (10)	4		1		2		
LVEF	6 (9)	4		1		1		
Intervention	6 (9)	2		2		1	1	
Non-specified CVD	5 (7)	3	2					
History of cancer	5 (7)	4		1				
History of angina	4 (6)	2	1			1		
Amputation	4 (6)	1		1	1		1	
Atrial fibrillation	3 (4)	1	1	1				
Anaemia	2 (3)	1		1				
Musculoskeletal disease	1 (1)			1				
Previous PAD	1 (1)				1			
Post-operative complications	1 (1)			1				
BMI	24 (35)	15	4	1				
ABI	18 (26)	12	5	1		1		
PAD stage	15 (22)	7	2	6				
Functional performance	8 (12)	6	1	1				
Blood pressure	9 (13)	8	1					
Heartbeat	3 (4)	2	1	1				

Site and N of lesions	3 (4)	2	1					
Physical activity	3 (4)	3	1					
Weight	2 (3)	1		1				
Toe pressure	3 (4)		2			1		
Toe brachial index	2 (3)		2					
Crural index	2 (3)		1	1	1			
Clinical symptoms	2 (3)	1	1					
Depressive symptoms	2 (3)	2	1					
Pulse pressure	1 (1)	1	1					
GFR or creatinine	18 (26)	11	4	2				
Non-HDL cholesterol	11 (16)	10	3	1				
High sensitivity CRP	11 (16)	6	2	2				1
BNP and NT-proBNP	6 (9)	6		1				
HDL cholesterol	5 (7)	4	1					
High NLR	4 (6)	3	1					
Haemoglobin	3 (4)	1		2				
Cardiac troponin	3 (4)	2		1				
Cystatin level	3 (4)	3	2					
Glucose or HbA1C	3 (4)	2		1				
Triglycerides	2 (3)	1		1				
Red cell distribution width	2 (3)	2						
High trimethylamine N-oxide	2 (3)	1	1					
Urea	1 (1)	1						
High homocysteine	1 (1)	1						
Albumin: creatinine ratio	1 (1)	1	1					
White blood cell count	1 (1)	1						
Angiopoietin-2	1 (1)	1						
Symmetric dimethylarginine	1 (1)	1						
α-Defensin	1 (1)	1	1					
TNF and or sTWEAK	1 (1)		1					
Skin autofluorescence	1 (1)	1						
Protein biomarkers	1 (1)	1						
Microfibril associated glycoprotein 4	1 (1)		1					

Lipid lowering drug use	12 (18)	7	3	4	1		
Antiplatelet agent use	7 (10)	3		3			
ACEi or ARB use	4 (6)	3	1		1		
Beta blocker use	2 (3)			1	1		
Diuretic	1 (1)	1			1		
Antihypertensive	1 (1)	1					
RAAS inhibitors	1 (1)			1			
Anticoagulants	1 (1)	1					
Hyperbaric oxygen	1 (1)			1			
Scores	13 (19)	6	2	3	1	2	
Frailty index	3 (4)			1			
Apolipoprotein	2 (3)	2				2	
Myeloperoxidase	2 (3)	2					
QT interval	1 (1)	1					
Flow mediated dilatation	1 (1)			1	1		
Renal artery stenosis	1 (1)						
LDL cholesterol	1 (1)	1			1		
Small arterial stiffness	1 (1)	1					
Aortic valve calcium	1 (1)						1
Chronic stress	1 (1)			1			
Financial situation	1 (1)						

Data are presented as n *(%) or* n. *The cells that are empty indicate that the prognostic factor in the first column was not included in any study investigating that specific mortality outcome. COPD: chronic obstructive pulmonary disease; ABI: ankle-brachial index; CKD: chronic kidney disease; CVD: cardiovascular disease; PAD: peripheral arterial disease; BMI: body mass index; CRP: C reactive protein; BNP: B type natriuretic peptide; NT-proBNP: N-terminal pro B type natriuretic peptide; s/TWEAK: serum tumour necrosis factor like weak inducer of apoptosis; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; RAAS: renin–angiotensin–aldosterone system.*

Prognostic factors for mortality outcomes

In multivariable models, over 80 prognostic factors were associated with increased mortality outcomes (**Supplementary Table S5**).

Sixty-three studies (91%) investigated the predictive value of age.[23-30, 32-55, 57, 59-78, 80-84, 86-91] Twenty-two studies included age as a predictor in the primary model; [24, 28, 32, 35, 37-39, 43, 44, 49, 50-52, 59, 62, 63, 65, 67, 69, 76, 80, 89] the remainder adjusted their multivariable model for age. Of the studies that included age in their primary model, 21 showed that as age increased, mortality risk increased. One study's results were not statistically significant (HR 1.04, 95% CI 1.00 – 1.1).[4]

Sex or gender was the second most examined demographic factor, included in 40 (58%) studies, with 31 studies [23, 25, 26, 30, 33, 34, 36, 40, 41, 45- 48, 53, 54, 57, 60, 64, 71-74, 77, 78, 81-84, 86, 90, 91] adjusting their multivariable model for sex or gender, and nine studies [27, 32, 37, 43, 50, 62, 63, 65, 89] including it as a predictor. In terms of the prognostic relevance of sex or gender, two studies established that females faced a lower mortality risk at six years (women vs. men, HR 0.45, p < .05;32 men vs. women, HR 1.73, 95% CI 1.27 – 2.3763), whereas the remaining studies did not yield statistically significant results.

Race/ethnicity was a predictor included in nine studies (13%), where five adjusted their multivariable model for race, [26, 47, 48, 64, 75] whereas four included it in their primary model. [24, 28, 62, 63] In one study, other races (compared with White people) had a lower mortality risk (OR 0.69, p = .022).[28] The results from the other studies, however, were not statistically significant.

Factors related to previous and current medical history were also predictors of mortality outcomes. Forty-four studies (64%) reported the predictive value of diabetes. [25-27, 30, 32-34, 36, 37, 40, 41, 44, 46, 49, 51, 53, 54, 55, 57, 58, 60-64, 66, 67, 69, 71, 73, 74, 75, 77-83, 87-91] Twenty-nine adjusted their multivariable model for diabetes status and 15 studies [25, 27, 32, 37, 44, 49, 51, 58, 62, 63, 67, 69, 79, 80, 89] included it as a predictor. The results on the effect of diabetes differed among the studies. Although seven studies showed that diabetes increased mortality risk, [27, 32, 49, 51, 58, 69, 79] others did not show a significant association.

Thirty-eight studies (55%) assessed the predictive value of smoking status.[23, 25-27, 32, 33, 37, 40, 41, 43, 47-49, 51, 52, 54, 55, 57, 59-64, 67, 68, 71, 73, 74, 77, 81-83, 87-91] Twelve included it as a predictor [25, 27, 32, 37, 43, 49, 51, 59, 62, 63, 67, 89] and the remainder adjusted for it in the multivariable model. Four studies showed a higher mortality risk among smokers. [25, 27, 49, 89] In other studies, however, no statistically significant differences were found between smokers and non-smokers.

History of coronary artery disease, including myocardial infarction and ischaemic heart disease, was assessed in 24 (35%) studies. [23, 24, 29, 36-38, 49-51, 54, 62, 63, 67, 69, 73, 75-77, 80, 81, 83, 87-89] Of these, 13 assessed the predictive value of coronary artery disease, [24, 37, 38, 49-51, 62, 63, 67, 69, 76, 80, 89] but only five found that history of coronary artery disease increased mortality risk. [24, 38, 62, 69, 76]

BMI was assessed in 24 studies (35%). Nine of these 24 studies examined its predictive value, [25, 30, 43, 44, 50, 52, 63, 65, 72] whereas 15 adjusted their multivariable model for it. [26, 29, 47, 48, 60, 64, 75, 77, 78, 81-83, 86, 90, 91] Two studies reported that underweight (BMI < 18 kg/m2) was associated with higher all-cause mortality and cardiovascular mortality risk compared with normal weight. [44, 72] BMI was also assessed as a continuous variable in five studies. [30, 43, 52, 63, 65] Chi et al. [30] showed that a decrease in BMI was associated with a lower overall mortality risk (HR 0.94, 95% CI 0.88 – 0.99). The study by McDermott et al. [63] also showed a lower all-cause mortality risk associated with BMI (HR 0.96, 95% CI 0.93 – 0.99), but no information was available about the direction of the effect. The studies by

Amrock et al. [25] and Senda et al. [72] compared BMI > 30 kg/m2 vs. 18.5 ≤ BMI < 25.0 kg/m2, but their results were not statistically significant.

The predictive value of ABI was assessed in 18 studies (26%). [25, 32-34, 47-49, 54, 62-64, 75-78, 81-83] Nine studies adjusted their multivariable analyses for it and nine studies assessed ABI as a primary predictor. Abnormally low ABI was associated with higher mortality risk in four studies. [33, 49, 54, 76] Two studies showed that ABI > 0.90 was associated with a lower all-cause mortality risk (HR 0.14, p < .05;[32] and HR 0.35, 95% CI 0.13 – 0.96[34]). The results from the remaining three studies were not statistically significant.

Toe pressure and toe brachial index were assessed in three [49, 54, 88] and two [54, 88] studies, respectively. Toe pressure < 30 mmHg vs. > 50 mmHg was found to be associated with a higher risk of cardiovascular death (HR 2.31, 95% CI 1.36 – 3.94; [54] and HR 2.84, 95% CI 1.75 – 4.61 [88]). Similarly, toe brachial index < 0.25 vs. > 0.50 was associated with a higher risk of cardiovascular death (HR 3.20, 95% CI 1.34 – 7.63;[54] and HR 3.68, 95% CI 1.48 – 9.19 [88]).

PAD stage assessed by Rutherford classification or Fontaine stage was investigated in 15 studies (22%). [23, 28, 29, 36, 37, 39, 44, 50, 53, 55, 57, 61, 82, 83, 91] Of five studies that included the PAD stage as a predictor, four found that a worse PAD stage was associated with a higher risk of mortality outcomes. [28, 37, 39, 44]

Clinical factors, such as blood pressure measurements, were evaluated in nine studies (12%), but different measures, including systolic, diastolic, or mean blood pressure, were used to assess its predictive value. [25, 26, 30, 33, 45, 52, 73, 74, 77] Six studies adjusted their multivariable model for blood pressure, and three [25, 30, 52] investigated its predictive value. Kals et al. [52] showed that including mean arterial blood pressure in a model aiming to predict all cause and cardiovascular mortality rate incremented the discrimination abilities of the model (AUC 0.70, 95% CI 0.60 – 0.80). The results from Chi et al. [30] and Amrock et al.[25] were not statistically significant.

Laboratory values such as creatinine, eGFR, and CRP were predictors of mortality outcomes in 18 (26%) [27, 45, 51, 53, 57, 61, 65, 67, 68, 71-74, 76, 78, 82, 83, 91] and 14 (20%) studies, [25, 26, 32, 40, 50, 57, 66, 71-74, 76, 81, 83] respectively. Two studies showed that eGFR < 30 mL/min/1.73m^2 was associated with higher mortality risk compared with eGFR > 90 mL/min/1.73m2.[51, 57] The prognostic value of brain natriuretic peptide (BNP), haemoglobin, and anaemia were evaluated in six (9%) [65, 66, 68, 70, 74, 91] and five (7%) [36, 57, 65, 72, 90] studies, respectively. High BNP levels were associated with higher mortality risk in four studies. [65, 66, 70, 91] Other factors such as scores, e.g., CHADS2, R2CHADS2, and lower limb arterial calcification scores, and chronic stress were assessed in 13 studies (19%) [23, 28, 30, 31, 42, 46, 49, 51, 55, 65, 80, 86, 87] and one study (1%), [62] respectively.

***Table 3**. Baseline characteristics of prognostic models of patients with peripheral arterial disease (PAD).*

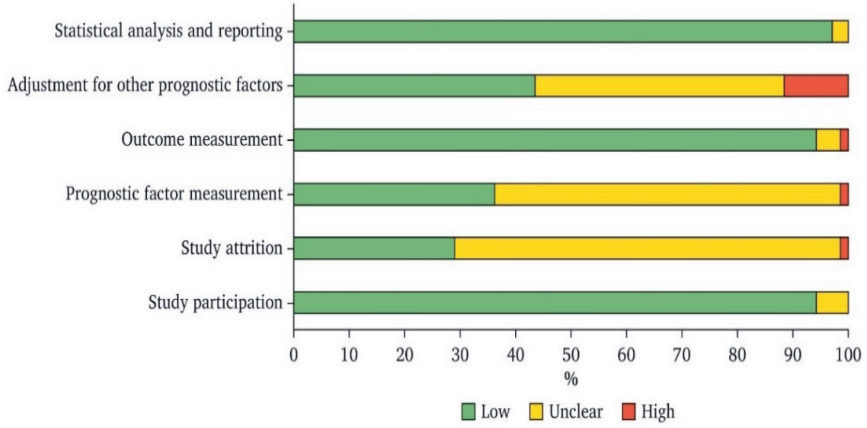
Author	*Predictors included in final model*	*Sample size*	*Men – %*	*Age (mean)*	*HT– %*	*DM – %*	*Smoking – %*	*HF – %*	*CAD – %*	*CKD – %*
Abbas et al. (2011)[92]	Age, CHF, pre-procedural creatinine	292	0	71 (11)	97	47	61	27	76	26
Dopheide et al. (2020)[94]	Age, Rutherford class, atherosclerosis extent	1310	64	72 (11.7)	85	30	62	NR	43	NR
Gupta et al. (2012)[95]	Age, chronic corticosteroid use, COPD, SIRS, dialysis dependence, functional status, rest pain	9556	64	68 (60–77)*	84	21	42	2	2	6
Hackl et al. (2015)[96]	Age, history of MI, CRP, ABI, eGFR, and APA, statin, and RAASi use	129	71	66 (60–76)*	78	31	40	NR	9	NR
Pros et al. (2013)[97]	Age, history of MI, CRP, ABI, eGFR, and APA, statin, and RAASi use	D: 640; V: 517	D: 68; V: 76	D: 70.2 (13); V: 70.5 (12)	D:70; V: 71	D: 42; V: 48	D: 26; V: 23	D: 11; V: 11	NR	D: 17; V: 14
Wisman et al. (2015)[98]	Age, CLI, DM, vascular intervention	D: 482; V: 2088	D: 65; V: 64	D: 69 (10); V: 69 (10)	D: 39; V: 39	D: 23; V: 27	D: 60; V: 53	NR	D: 16; V: 18	NR
Cox et al. (2022)[93]	Physiological high-risk factors, elective surgery, functional status, creatinine, INR, BUN, DM, claudication, haematocrit, age, renal comorbidities, albumin	14 444	59	69.1 (11.4)	83†	53†	30†	NR	NR	NR
Zhang et al. (2022)[99]	ICD-10 diagnoses, total of ICD-10 procedure, age, endovascular revascularisation, CHF, DM, region of the hospital, teaching status of the hospital, ED use record	150 921	60	67.2 (12.9)	NR	38	NR	74	14	33

D: development cohort; V: validation cohort; HT: hypertension; DM: diabetes mellitus; HF: heart failure; CAD: coronary artery disease: CKD: chronic kidney disease; PAD: peripheral arterial disease; NR: not reported; COPD: chronic obstructive pulmonary disease; SIRS: systemic inflammatory response syndrome; CRP: C reactive protein; ABI: ankle brachial index; eGFR: estimated glomerular filtration rate; APA: antiplatelet agent; RAAS: renin–angiotensin–aldosterone system; INR: international normalised ratio; ICD-10: International Classification of Diseases, 10th revision. ED: emergency department. ∗Median. † Pooled results

Risk of bias assessment of studies on prognostic factors

Six studies had low risk of bias in all domains [29, 58, 60, 62, 77, 80] and the remainder had an unclear or high risk of bias in at least one domain. Most of the studies were downgraded due to inadequate reporting of differences between participants who completed the study and those who did not, lack of description of loss to follow up, or no explanation of how missing data were handled by the authors (**Figure 2**).

***Figure 2**. Quality in Prognosis Studies risk of bias for studies on prognostic factors. Low = low risk of bias; unclear = unclear risk of bias; high = high risk of bias.*



Prognostic models

Eight studies were identified on prognostic models to predict mortality outcomes. The number of predictors included in each model ranged between three and 12. Age was the only predictor present in all models. Sex and race were not included in the final models. Each model contained at least one medical history factor, such as diabetes, history of myocardial infarction, and chronic obstructive pulmonary disease. Laboratory measurement factors, specifically creatinine and CRP, were included in four (50%) and two (25%) models, respectively. Two studies used machine learning techniques to predict 30 day and in hospital mortality rates, respectively. [93, 99] These studies identified physiological high-risk factors and total number of International Classification of Diseases, Tenth Revision (ICD-10) diagnoses as the most important predictors for 30 day and in hospital mortality rate, respectively.

All models demonstrated acceptable discrimination with AUC from 0.70 – 078. Five studies (50%) conducted internal model validation, split population was used in four models, and bootstrapping in one study. [93, 94, 95, 98, 99] Two studies externally validated the Cohort de Patients Artériopathes (COPART) risk score in an external cohort in

another country. [96, 97] In both populations, the model had a satisfactory performance in discrimination (C statistic 0.74) and calibration. All studies provided a statistical syntax, a web interface, or a simple scoring system to calculate an individual risk.

Risk of bias assessment of studies on prognostic models

Five of the studies describing a prognostic model had an overall high risk of bias, whereas two studies had an overall unclear risk of bias. [98, 99] Particularly, the items regarding analyses were suboptimal, including the categorisation of continuous variables, lack of reporting on missing data, and the use of univariable analysis for selecting predictors. Most of the studies were considered of low concern for applicability, meaning that the participants, predictors, and outcomes reflected clinical practice. Except for the study by Abbas et al., [92] applicability was unclear owing to inadequate information on participants and settings (**Table 4**).

***Table 4**. The Prediction model Risk Of Bias ASsessment Tool (PROBAST) for studies on prognostic factors.*

Study	***Risk of bias***				***Applicability***			***Overall***	
	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	RoB	Applicability
Pros et al. (2013)[97]	+	+	+	–	+	+	+	–	+
Hackl et al. (2015)[96]	+	+	+	–	+	+	+	–	+
Abbas et al. (2011)[92]	–	?	+	–	?	?	+	–	?
Wisman et al. (2015)[98]	+	+	+	?	+	+	+	?	+
Dopheide et al. (2020)[94]	+	+	+	–	+	+	+	–	+
Gupta et al. (2012)[95]	–	?	+	–	+	+	+	–	+
Cox et al. (2022)[93]	+	?	+	+	+	+	+	+	+
Zhang et al. (2022)[99]	+	?	+	?	+	+	+	?	+

RoB: risk of bias; (+) = low risk of bias and low concern about applicability; (–) = high risk of bias and high concern about applicability; (?) = unclear risk of bias and unclear concern about applicability.

DISCUSSION

This systematic review summarises evidence from 69 studies that investigated prognostic factors for death in PAD, as well as eight studies that developed or validated prognostic models. Over 80 single prognostic factors were identified, with age, sex, diabetes, hypertension, and smoking status consistently emerging as predictors of mortality outcomes. These factors can be considered when deciding which models provide incremental predictive accuracy and are more precise and suitable for specific patient populations or outcomes.

Prognostic factors

Age, which constitutes an essential and natural prognostic factor, was the only factor present in more than 90% of the studies. It has been found that in patients with PAD, mortality risk increases after the age of 65 years, with each year reflecting worse outcomes in older patients. This suggests that early diagnosis and intervention might provide benefits, such as reducing the severity of symptoms, improving physical functioning and quality of life, and lowering the mortality risk.

Smoking and diabetes are recognised risk factors for PAD and are associated with disease severity. [100,101] In this systematic review, several included studies described the predictive value of these factors, and their findings confirmed the associations between diabetes and smoking status and poor outcomes in patients with PAD. It is surprising, however, that over 40% of the studies did not include them as variables in their analyses. While this discrepancy could be caused by population differences, study designs, and specific research objectives, it raises a critical concern about the potential oversight of crucial determinants that significantly contribute to accurate risk prediction in patients with PAD. Refining predictive models for PAD is imperative, and including smoking status and diabetes as essential variables in future research ensures that predictive models accurately capture the multifaceted nature of PAD and its associated risk factors.

In the included studies, elevated levels of CRP and BNP were associated with increased mortality risk. A notable challenge arises in determining cutoff levels, specifically for predictors with a continuous unit of analysis, or changing units that effectively discriminate between individuals at high and low risk of death. This challenge is attributed to differences in statistical modelling approaches and the unique characteristics of diverse study populations. This complicates the clinical interpretation of CRP and BNP levels and hinders their seamless integration into routine risk stratification practices for patients with PAD. Future research efforts should focus on establishing consensus on standardised cutoff levels or changing units, considering variations in statistical methodologies and population demographics.

Prognostic factors such as race, ethnicity, and socio-economic status were barely assessed in any study. Only 13% and 1% of studies, respectively, have reported on these factors, despite their known significant roles in health disparities and outcomes. For instance, Asian American patients with PAD have been found to have higher in hospital mortality rates, whereas Black and Hispanic patients have a higher percentage of CLTI than non-Hispanic White patients. [102]

Additionally, low socio-economic status has been linked to an increased risk of amputation. [103] Neglecting these factors can lead to an incomplete understanding of how they affect the overall prognosis of PAD. Therefore, to ensure that medical interventions are tailored to the needs of a diverse patient population, they need to be explored further.

Prognostic models

Relying on a single prognostic factor often falls short in providing a comprehensive prognosis for all patients with PAD. [104] A more informative approach involves integrating relevant factors into existing models, and ideally externally validating them. Eight studies were identified on prognostic models to predict mortality outcomes with similar discrimination and calibration abilities. Although all models had methodological limitations, particularly in statistical analyses, including handling missing data and predictor selection, future prognostic models can improve their methodological approaches by addressing these specific concerns.

From a clinical perspective, the identified prognostic models are easy to use in clinical practice because simple scoring systems with points or percentages to assign risk levels are used, with predictors that are commonly available in clinical practice. All the models included age in the primary model and at least one of the identified medical history factors and or clinical factors. Sex was notably absent from all models except for the study conducted by Abbas et al.,[92] which was specifically developed for a female population. The absence of sex as a variable in most models raises questions about the comprehensiveness and applicability of existing prognostic tools across diverse populations. The unique physiological characteristics of women and men, and potential differences in clinical presentation, emphasise the necessity of incorporating sex specific factors into prognostic models.

The investigation of prognostic models developed for other cardiovascular diseases offers a promising avenue for exploration in the context of PAD. Chi et al. [30] evaluated the predictive value of CHADS2, R2CHADS2, and CHA2DS2-VASc scores, originally designed for assessing stroke risk in patients with atrial fibrillation, within the context of patients with both low and abnormally high ABI. They found that CHADS2, R2CHADS2, and CHA2DS2-VASc scores were significant predictors of cardiovascular and all-cause mortality and, had additional predictive values to conventional parameters for

predicting cardiovascular and all cause death. The results of this research approach show the potential applicability of predictive models across different cardiovascular conditions.

The use of machine learning techniques in medical research has become increasingly popular, particularly in developing and validating models. In predicting mortality risks among patients with PAD, machine learning has been found to be effective. Two studies exemplify the application of machine learning in predicting mortality outcomes in patients with PAD. [93,99] These studies have shown that incorporating new predictors apart from traditional prognostic factors such as age can improve the predictive capacity of a model. For instance, Zhang et al. [99] found that the total number of ICD-10-CM diagnoses and the total number of ICD-10-CM procedures were top predictors of in hospital death. Similarly, Cox et al. [93] identified physiological high risk as the most important predictive factor of 30-day death. Interestingly, none of the identified studies that examined single prognostic factors assessed the predictive abilities of the abovementioned. These findings demonstrate the significance of machine learning in prognostic research. Machine learning has the potential to extract valuable insights that may not be noticeable through traditional statistical methods. Moreover, incorporating new parameters along with demographic and clinical characteristics can significantly enhance prognostic models.

Current recommendations and perspectives towards the future

The 2024 guideline of the European Society for Vascular Surgery (ESVS) on the management of asymptomatic lower limb PAD and intermittent claudication mentioned the role of some of the prognostic factors in relation to the prognosis of PAD. [105] This concerns all the factors that were identified in the present systematic review. For instance, biomarkers such as CRP and NT-proBNP (N-terminal prohormone of BNP) are discussed; however, because of insufficient data on the added value of prognosis, laboratory biomarkers are not recommended for clinical risk stratification. This was confirmed in the present systematic review, with only 16% and 9% of the identified studies investigating the predictive value of CRP and NT-proBNP, respectively. Tobacco smoking is described as an essential risk factor for progression and poorer outcomes in patients with PAD, and clear recommendations about smoking cessation are given to improve prognosis in this population. According to the guideline, the role of sex needs to be better identified, with conflicting research results, something that was confirmed in the review. One of the explanations for this may be the under representation of women in epidemiological studies. Therefore, the ESVS guideline recommends balancing the proportion of women and men in clinical studies.

The current guidelines do not recommend any prognostic model to be used in clinical practice in patients with PAD. Similarly, in the latest global vascular guideline for CLTI

management, the list of most important predictors of death is included as part of the patient risk estimation. [106] Similar to the present results, no specific tool or model is recommended because of the lack of studies prospectively testing their models across the spectrum of CLTI. This systematic review is a starting point for healthcare professionals to identify the current state of risk prediction tools in clinical practice, and to continue research efforts to refine and validate these tools, ultimately enhancing their utility and effect in guiding clinical decision making for patients with PAD and CLTI.

Strengths and limitations

To the best of our knowledge, this is the first systematic review investigating the prognostic factors and models for predicting mortality outcomes in patients with PAD. The main strength of the study is the rigorous systematic review methodology used to identify, describe, and assess the risk of bias of all studies. Some limitations are acknowledged in this systematic review. The studies were too heterogeneous to conduct any meta-analysis. The inherent variability in data presentation, outcome measures, and participant characteristics among the studies contributed to this heterogeneity. To improve this, it is recommended that authors adhere to reporting guidelines, such as the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, [107] to maintain the completeness of their reporting. Standardising outcome definitions to promote consistency among diverse studies is also advocated. And the stratification of patient groups based on relevant characteristics is also suggested, such as sex, disease stage, or comorbidities. This stratification will enable more refined subgroup analyses, allowing a deeper understanding of how a specific factor performs in different populations. Secondly, only studies published in English and Spanish were considered, potentially excluding relevant studies in other languages. Studies with small sample sizes were excluded; however, full text screening identified that all assessed predictors were also considered in the excluded studies. This systematic review only considered studies that were published from 2010 onwards. While this approach allowed us to focus on the most recent evidence, it may have resulted in the exclusion of relevant studies that were conducted before this period. Consequently, the ability to capture the complete range of prognostic factors and models in PAD may have been affected by this limitation. To determine whether many studies were missed, the same search strategy was conducted on PubMed to identify studies published between 1980 and 2009 that contained the keywords of interest in their title or abstract. This search yielded 190 studies, of which most could be excluded based on a quick scan. This is probably because prognostic research in the setting of PAD is rather novel. Therefore, not many references were missed by limiting the search to studies published from 2010 onwards. Furthermore, the review excluded studies that exclusively focused on patients with CLTI. This specific

exclusion criterion might limit the generalisability of the findings to this subset of patients. Patients with CLTI often represent a distinct and advanced stage of PAD, characterised by severe limb ischaemia and associated with higher morbidity and mortality rates. By excluding studies exclusively focused on CLTI, this systematic review may only partially capture the unique prognostic factors and models relevant to this specific subgroup. Researchers and clinicians should be aware of this exclusion when applying the findings to populations with CLTI. Future studies explicitly focusing on CLTI could provide valuable insights into prognostic factors specific to this severe manifestation of PAD. Although the identified prognostic models report acceptable performance abilities, they differ significantly in their outcome definitions, the included patient population, and the considered variables. Moreover, only two of the models were externally validated. Therefore, it cannot be conclusively determined which model would perform best in clinical practice. We urge clinicians to select a model that matches each patient's individual characteristics and emphasise that externally validated models are more likely to provide an accurate prediction.

CONCLUSION

Sex, age, diabetes, hypertension, and smoking are consistently identified as key prognostic factors that influence mortality outcomes in patients with PAD Fontaine stage I – III or Rutherford category 0 – 4. A strategic approach of continuously updating and validating existing models is recommended. This involves a dynamic process that periodically reviews and refines the models, considering the evolving nature of medical knowledge and patient demographics. We suggest exploring the integration of additional prognostic factors with robust predictive capabilities for mortality outcomes. This proactive approach aims to determine whether incorporating these factors significantly improves the refinement and precision of prognostication, leading to more reliable and relevant models.

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Chapter

4

The Frequency of Primary Healthcare Contacts Preceding the Diagnosis of Lower-Extremity Arterial Disease:

Do Women Consult General Practice Differently?

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ABSTRACT

***Background*:** Women with lower-extremity arterial disease (LEAD) are often underdiagnosed, present themselves with more advanced disease at diagnosis, and fare worse than men.

Aim: To investigate to what extent potential gender differences, exist in the frequency and reasons for general practitioner (GP) consultation six months prior to the diagnosis of LEAD, as potential indicators of diagnostic delay.

***Methods*:** Individuals older than 18 years diagnosed with LEAD, sampled from the Julius General Practitioner's Network (JGPN), were included and compared with a reference population, matched (1:2.6 ratio) in terms of age, sex, and general practice. We applied a zero-inflated negative binomial (ZINB) regression model.

***Results*:** The study population comprised 4044 patients with LEAD (43.5% women) and 10,486 subjects in the reference population (46.3% women). In the LEAD cohort, the number of GP contacts was 2.70 (95% CI: 2.42, 3.02) in women and 2.54 (2.29, 2.82) in men. In the reference cohort, 1.77 (95% CI: 1.62, 1.94) in women and 1.63 (95% CI: 1.50, 1.78) in men. In the LEAD cohort, 21.9% of GP contacts occurred one month prior to diagnosis. In both cohorts and both sexes, the most common cause of consultation during the last month before the index date was cardiovascular problems.

***Conclusions*:** Six months preceding the initial diagnosis of LEAD, patients visit the GP more often than a similar population without LEAD, regardless of gender. Reported gender differences in the severity of LEAD at diagnosis do not seem to be explained by a delay in presentation to the GP.

INTRODUCTION

Primary healthcare aims to protect health and treat diseases, illnesses, and injuries that can be alleviated through cost-effective and affordable interventions and programs. In the Netherlands, all inhabitants are obliged to register with a general practitioner (GP), who acts as a "gatekeeper" before contacting medical specialists. [1] GPs have the responsibility to control public healthcare costs by limiting the number of (unnecessary) referrals to specialists. [2] Recent studies find that the number of GP visits increases prior to hospitalisation for an acute event, such as heart failure, myocardial infarction, and pneumonia. [3, 4]

Lower-extremity arterial disease (LEAD)—also known as lower-limb peripheral artery disease—is the third most common clinical manifestation of atherosclerosis after coronary artery disease and stroke. It affects over 236 million people worldwide (52.23% women) [5] and is associated with a very high risk for major adverse cardiovascular (MACE) and limb events (MALE). [6] Previous studies have shown that women with LEAD present symptoms differently, are often underdiagnosed or not diagnosed expeditiously, and have a worse prognosis for life and limb. [7-10] Egorova et al. found that women are consistently less likely to be hospitalized for LEAD but are more prone than men to be admitted urgently. As a result, these findings could indicate that women are hospitalized with more advanced-stage disease, requiring emergent rather than elective medical treatment.

The GP is the first person to intervene at the early symptoms of LEAD. [11, 12] Nonetheless, it remains unclear whether differences in severity, delays in diagnosis, and differences in prognosis between women and men might be caused, potentially due to delays, in the early stages at the GP level. There is a lack of evidence concerning discrepancies, in terms of quantity and timing, in GP visits between women and men, as a potential indicator for delays in referral. Therefore, this study aims to investigate whether differences exist between women and men in the frequency of GP contact prior to diagnosis of LEAD. Furthermore, it pursues to determine whether and when there is an increase in the number of GP consultations preceding the diagnosis.

METHODS

Data source

For this study, we extracted data from the Julius General Practitioner's Network (JGPN). [13] This ongoing dynamic database contains information of approximately 370,000 individuals registered with the involved GP centres (n = 78). The current composition of the patient database and the geographical distribution of the participating practices in urban and (semi)rural regions make the JGPN population representative of the Dutch population. Gender, mean age, and age distribution of patients are comparable to the

Dutch population (47.9 vs. 49.5% males, 39.5 vs. 41.3 years). The number of participating GPs is higher than the Dutch average (60 vs. 44%), as is the number of group practices in JGPN (76 vs. 33% national average). [13]
All visits 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 referred specialism, and prescribed medication is registered using the anatomical therapeutic coding (ATC) system. [13]

Study population

We sampled individuals ≥18 years for two cohorts. (1) The LEAD cohort included all women and men diagnosed with LEAD for the first time, defined as ICPC codes K92 (other diseases of the peripheral arteries) or K92.01 (intermittent claudication), registered by a GP between January 2013 and February 2020. Date of LEAD diagnosis was considered the "index date". (2) A reference population (age-, sex-, and GP-matched (1:2.6 ratio)) from the JGPN registry to compare potential sex differences in primary healthcare contact in general. Each person in the reference group served only one time as a reference.

Data extraction

Information on sex, age, medical history, and the number of GP contacts was collected. Age was defined as the age at the index date and stratified as follows: <50, 50–69, 70–84, ≥85. For the medical history at baseline and number of GP contacts, we used ICPC codes. History of hypertension was defined as patients with codes K86 and K87; diabetes, 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 tobacco abuse, ICPC code P17.

Variables of interest

The primary outcome of this study was the number of GP contacts; other healthcare professional contacts were not considered (i.e., nursing contact). We defined the outcome as the number of GP contacts up to six months prior to the index date by using ICPC codes recorded in their medical records. We counted each ICPC code as one contact moment. When the same ICPC code is used for multiple GP contacts, we have counted these each as unique GP contacts. The index date, i.e., time of LEAD diagnosis, was not counted as a GP contact. We classified the reason for GP consultation into six groups according to body systems, as generally is done in general practice; category A: general

symptoms (e.g., fever, pain general), K: cardiovascular, L: musculoskeletal, P: psychological, S: skin, T: endocrine/metabolic, and U: urological symptoms. Factors expected to be associated with the number of GP contacts in this study were: age, diabetes, hypertension, hyperlipidaemia, musculoskeletal problems, vascular disease, myocardial infarction, and smoking.[14, 15]

Statistical analyses

Continuous variables were presented as mean and standard deviation (SD) or as the median and interquartile range (IQR) depending on the distribution. Categorical variables were presented as absolute numbers and proportions.

Count data are assumed to have a Poisson distribution and are often analysed using the Poisson regression model. The Poisson model is a member of the Generalized Linear Models (GLM), which assumes that mean and variance are equal. Nevertheless, in some count data, the conditional variance exceeds the conditional mean (overdispersion) and an excess of zeros (i.e., for our study, no visit to the GP) exists. [16] To account for overdispersion and excess of zeros, negative binomial regression (NB) and zero-inflated Poisson (ZIP) are used, respectively. [17] When data exhibit both problems, zero-inflated negative binomial regression (ZINB) accounts for the excess of zeros and the heterogeneity in the positive outcome. The ZINB model has two parts: an NB regression part that examines how frequent the outcome occurs (count part), and a zero-inflated part (ZI) that predicts the odds ratio (OR) of not presenting the outcome (logit part). [18] We performed a ZINB model separately for the LEAD and reference cohort.

Because comorbidities such as hypertension, diabetes mellitus, or history of cardiovascular problems might increase the number of GP visits, [15] we ran interactions models between sex and these covariates to explore potential differences between women and men with different comorbidities in frequency of GP contact. Continuous covariate (i.e., age) was mean centred in all analyses, and all tests were two-sided; p-value less than 0.05 was considered statistically significant. All analyses were performed using RStudio (2020, Integrated Development for R. RStudio, Inc., Boston, MA, USA). [19]

RESULTS

In the JGPN, we identified 4044 LEAD patients and sampled 10,486 subjects for the reference cohort. Women represented 43.5% of the LEAD cohort and 46.3% of the reference cohort, and their mean age was higher than that of men (69.2 (SD 13.7) vs. 67.5 (SD 11.6) in the LEAD group and 67.0 (SD 14.2) vs. 65.2 (SD 12.2) years in the reference group, respectively). At baseline, in both cohorts, hypertension, rheumatic disease, and musculoskeletal problems were more common in women, while diabetes mellitus and myocardial infarction were more common in men (**Table 1**). Although the

prevalence of these conditions was higher in those with LEAD compared to the reference population, differences between women and men were in the same direction for both cohorts.

Table 1. *Baseline characteristics*

	LEAD Cohort [1]			***Reference Cohort***		
	Women	Men	p Value	Women	Men	p Value
N	1761	2283		4851	5635	
Age (mean (SD))	69.2 (13.7)	67.5 (11.6)	<.001	67.1(14.2)	65.2 (12.2)	<.001
Age group			<.001			<.001
<50 years (%)	159 (9.0)	159 (7.0)		561 (11.6)	589 (10.5)	
≥50 <70 years (%)	677 (38.4)	1107 (48.5)		2095 (43.2)	2990 (53.1)	
≥70 <85 years (%)	736 (41.8)	895 (39.2)		1730 (35.7)	1826 (32.4)	
≥85 years (%)	189 (10.7)	122 (5.3)		465 (9.6)	230 (4.1)	
Hypertension (%)	1111 (63.1)	1308 (57.3)	<.001	2163 (44.6)	2193 (38.9)	<.001
Diabetes (%)	494 (28.1)	823 (36.0)	<.001	815 (16.8)	1035 (18.4)	.038
Hyperlipidaemia (%)	487 (27.7)	624 (27.3)	.848	856 (17.6)	888 (15.8)	.010
Kidney disease (%)	262 (14.9)	307 (13.4)	.211	367 (7.6)	335 (5.9)	.001
Rheumatic disease (%)	105 (6.0)	67 (2.9)	<.001	193 (4.0)	139 (2.5)	<.001
Vascular disease[2] *(%)*	225 (12.8)	307 (13.4)	.563	310 (6.4)	405 (7.2)	.115
MI [3] *(%)*	182 (10.3)	450 (19.7)	<.001	202 (4.2)	500 (8.9)	<.001
Musculoskeletal (%)	1094 (62.1)	1180 (51.7)	<.001	2525 (52.1)	2421 (43.0)	<.001
Smoking [4] *(%)*	523 (29.7)	670 (29.3)	.835	467 (9.6)	577 (10.2)	.311

N: number of patients; SD: standard deviation; LEAD: lower-extremity arterial disease; p value: reflects the differences between women and men in the specific cohort; [1] LEAD is defined as ICPC codes K92 (other diseases of the peripheral arteries) or K92.01 (intermittent claudication); 2 vascular disease is defined as ICPC code K89 (Transient ischemic attack) and K90 (Stroke); [3] history of myocardial infarction; [4] smoking is defined as patients with ICPC code P17 at baseline.

GP contacts six months preceding the index date

In the LEAD cohort, 69.5% of the patients and 42.6% of the reference cohort had at least one GP contact in the six months preceding the index date (69.1% of women and 69.9% of men vs. 45.5% of women and 40.2% of men in the LEAD and reference cohort, respectively).

The median number of GP contacts in the LEAD 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. The number of GP contacts ranged from 0–79 in women and 0–66 in

men in the LEAD group and from 0–35 in women and 0–66 in men in the reference group (see **Supplementary Table S1**).

In the LEAD cohort, 3525 (21.9%) GP visits occurred one month prior to their diagnosis. During this period, women and men had the same median number of GP contacts, 2 (IQR: 2; p = 0.87). In the reference group, 3036 (16.2%) of the contacts occurred one month before the index date and the median number of the GP contacts for both women and men in the reference group was 1 (IQR: 1; p = 0.95).

For both women and men in the LEAD and reference cohort, the most common cause of consultation was cardiovascular problems, followed by endocrine/metabolic and musculoskeletal disorders. When comparing the two cohorts, the LEAD cohort had more visits due to musculoskeletal complaints than the reference group, 15% and 13% versus 12% and 8% for women and men, respectively (**Figure 1a, b**).

Within the LEAD cohort, the most common reason for GP visits due to musculoskeletal complaints were leg/thigh symptoms (72.3% in women and 70% in men). The reference cohort consulted more frequently due to knee symptoms (26.6% in women and 31.4% in men).

ZINB model

In the LEAD cohort, the count part of the model (NB) shows that the number of GP contacts for women was 2.70 (95% CI: 2.42, 3.02). In men, this was a factor of 0.94 lower (95% CI: 0.87, 1.01); men had 2.54 (95% CI: 2.29, 2.82) contacts with the GP. The number of GP contacts was a factor of 1.77 (95% CI: 1.65, 1.91) times higher in patients with diabetes, 1.20 (95% CI: 1.10, 1.30) times higher in those with hypertension, and 1.08 (95% CI: 1.01, 1.17) for musculoskeletal symptoms.

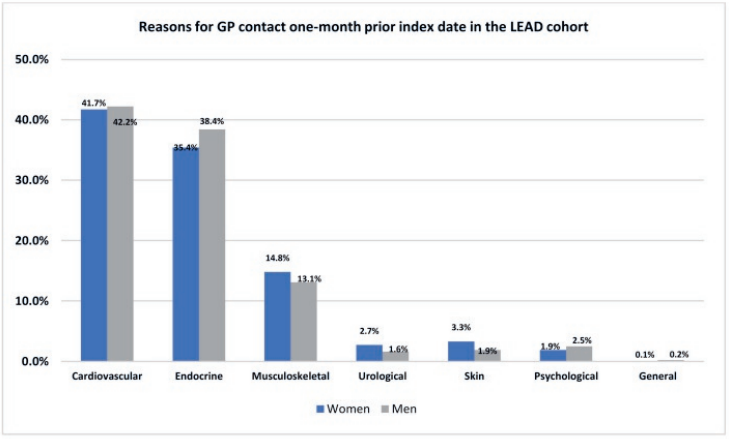
The zero-inflated (ZI) part of the model indicates that within this cohort, the odds ratio (OR) of having zero GP contact (as compared to more than one contact) was a factor 0.94 (95% CI: 0.70, 1.26) lower in men. The OR in women was 2.70 (95% CI: 1.97, 3.68) and 2.52 (1.90; 3.34) in men. Except for rheumatic diseases and sex (men), all the other covariates included in the model decreased the ORs of having zero visits to the GP. **Table 2** shows the ZINB regression model for the LEAD patients.

In the reference cohort, the number of visits to the GP for women was 1.77 (95% CI: 1.62, 1.94). In men, this was a factor 0.92 (95% CI: 0.87, 0.98) lower; thus, men had 1.63 (95% CI: 1.50, 1.78) contacts with the GP before the index date. The covariates included in the regression model incremented the rate for the number of GP visits for the reference cohort.

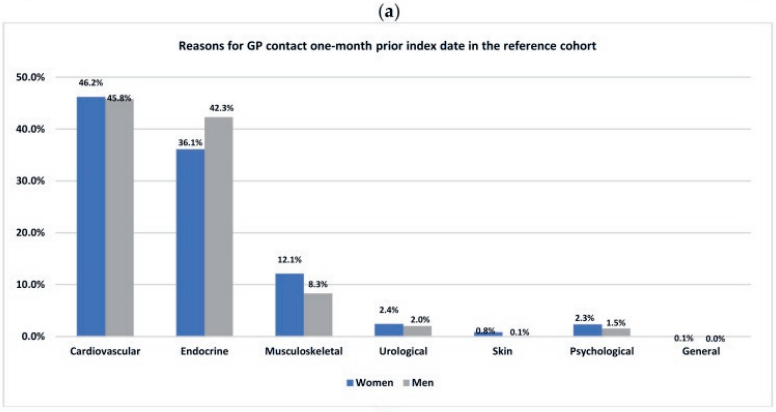
The OR of having no GP contact in women of the reference cohort was 6.96 (95% CI: 5.80, 8.36), lower compared with men, in which the OR of zero contact was a factor of 1.16 higher (95% CI: 0.97, 1.38); so, men had an OR 8.06 (95% CI: 6.80, 9.57) of having no GP contacts (**Table 2**).

Interactions between sex and covariates in the LEAD cohort were not statistically significant. In the reference cohort, interactions between sex and history of myocardial infarction and sex and hypertension decreased the number of GP contacts. None of the interactions in the ZI part of the model were statistically significant (**Supplementary Table S2**).

Figure 1. *(**a**) Reasons for GP contact one month prior to index date in the LEAD group. (**b**) Reasons for GP contact one month prior to index date in the reference group.*



(a)



(b)

DISCUSSION

Primary healthcare plays a critical role in the diagnosis and treatment path of patients with LEAD. GPs are the first to intervene at the earliest signs of the disease. Therefore, questions about differences in the pattern of consultations between women and men

are relevant and helpful to understand whether delays in diagnosis in women could be partially explained by differences in the number of GP contacts.

This study found that women and men did not differ in the frequency of GP contacts six months prior to LEAD diagnosis. An increase in GP visits was observed one month prior to diagnosis; however, this was seen in both women and men. Similarly, the reasons for GP contact did not appear to differ between them.

In the year 2020, Dutch inhabitants had on average 5.1 contacts with the GP (95% CI: 4.8, 5.3) per person. Women had a mean of 6.2 (95% CI: 5.7, 6.6) GP contacts and men 4.0 (95% CI: 3.7, 4.3). [20] These differences, albeit obtained over a 12-month period and for all ages, are consistent with our findings; in the reference population, matched to the LEAD cohort, during the six months previous to the index date, an average of 1.94 (3.39) visits to the GP for women occurred and 1.67 (3.32) for men.

Some studies have shown changes in the pattern of GP visits a short time before referral to a hospital due to a critical diagnosis, such as myocardial infarction or cardiac arrest. [3, 4, 21] This pattern was also observed in our study, in which the number of GP visits increased in the month before the index date; however, this was not different between women and men. Women had more GP contacts the month before the diagnosis, but there were no statistically significant differences between sexes. These results follow other studies that show that women and men with common morbidities have similar consultation patterns.[22, 23]

A considerable part of the GP contacts occurred one month prior to the index date and was labelled as a “disease of a musculoskeletal nature”. In patients with a history of atherosclerotic disease or cardiovascular risk factors (smoking, diabetes mellitus, overweight, high blood pressure, and increasing age), musculoskeletal complaints could be potential prodromal symptoms or atypical leg symptoms. [24] Unfortunately, we had no data from the free text in the clinical notes written during the GP visit. Further studies, preferably using text-mining techniques, are needed to identify which lower-limb-related musculoskeletal symptomatology could be considered as a potential prodromal symptom. This could help GPs to identify LEAD at an early stage and potentially lead to clues about avoiding possible delays in diagnosis and referral to specialist care.

Women with LEAD have a higher frequency to be asymptomatic [25] or present with either rest pain or atypical leg symptoms; [10] these factors could contribute to a delay in diagnosis and a worse prognosis. However, it was unclear whether this phenomenon could also be partially explained by differences in the number of GP contacts prior to the diagnosis of LEAD and by delays in referral to a hospital specialist. This study provides evidence that the number of GP visits up to six months before the diagnosis of LEAD is higher than that in a matched reference cohort. Nevertheless, differences between women and men were not observed. This evidence indicates that the pattern of GP

consultation was not gender-dependent; therefore, it is unlikely that the worse prognosis in women with LEAD is due to a delay in diagnosis by GPs.

Strength and limitations

The strengths of this study are its large sample size, its representativeness of the general Dutch population, and its reflection of routine clinical care. In addition, the use of state-of-the-art statistical models to solve analytical problems related to overdispersion and zero excess allowed for valid estimates.

We also acknowledge some limitations within this study. First, data were not collected primarily for research purposes. Therefore, its quality depends on the correct recording of the information by the GP. Second, we defined LEAD as patients with diagnosis codes K92 and K92.01 for the first time. The ICPC-1 code K92 refers to other diseases of the peripheral arteries, but within it, there are three subcategories: K92.01 (intermittent claudication), K92.02 (Raynaud's syndrome), and K92.03 (Buerger's disease). We classified all patients within this cohort as LEAD. However, we are uncertain how many patients classified as other diseases of the peripheral arteries (K92) have intermittent claudication (k92.01). Because we have no means of evaluating this, we cannot rule out misclassification.

Finally, 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 higher frequency of GP contact in women from Morocco and the Netherlands Antilles than in men coming from the same places. [26] Despite these limitations, this study is based on information that reflects routine clinical care. Therefore, we believe that it is unlikely that the limitations did influence the results significantly.

CONCLUSIONS

Patients with LEAD consulted the GP more frequently compared to the matched reference cohort, but no differences in the number of healthcare contacts between women and men were observed. Most of the consultations take place in the month before the diagnosis. Although the reasons for consultation in the last month preceding the index date were very similar, there was an increase in the number of GP visits due to musculoskeletal problems in patients with LEAD compared to the reference population. Further studies are needed to determine whether and which musculoskeletal problems could be potential early predictors of LEAD.

***Table 2**. ZINB regression coefficients for the number of healthcare contacts in LEAD and reference cohorts.*

Predictor	***LEAD Cohort***				***Reference Cohort***			
	Negative Binomial Model 1		Zero-Inflated Model 2		Negative Binomial Model 1		Zero-Inflated Model 2	
	Exp (β) *	CI	Exp (β)**	CI	Exp (β)*	CI	Exp (β)**	CI
Intercept +	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
Hyperlipidaemia	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 [3]	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 [4]	1.21	1.11–1.32	0.10	0.04–0.26	1.22	1.11–1.34	0.04	0.01–0.12
Smoking 5	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 [6]	1.01	1.00–1.01	0.98	0.97–0.99	1.00	1.00–1.01	0.96	0.95–0.97

*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 model is interpreted as a count; ** exponent beta in the zero-inflated is interpreted as an odd ratio; [1] coefficients for the count part of the model are interpreted as predicted number of healthcare contacts; [2] the logistic part of the model predicts non-occurrence of contact; [3] vascular disease is defined as ICPC codes K89 (Transient ischemic attack) and K90 (Stroke); [4] myocardial infarction; [5] defined as patients with ICPC code P17 at baseline; 6 age was mean centred for all analyses.*

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SUPPLEMENTARY MATERIAL

Table S1: *number of GP contacts six months prior to the index date*

Number of GP 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)
Total	1761	2283	4851	5635	6612	7918
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 S2**: Interaction regression model in the PAD and reference cohort*

	LEAD cohort				***Reference cohort***			
	Negative binomial model[1]		*Zero-inflated model2 (Logit model)*		*Negative binomial model[1]*		*Zero-inflated model[2] (logit model)*	
Predictors	Exp (b)*	CI	Exp (b)**	CI	Exp (b)*	CI	Exp(b)**	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	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
Hyperlipidaemia	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[3]	1.19	1.03 – 1.39	0.38	0.12 – 1.19	1.15	1.01 – 1.31	0.10	0.03 – 0.39
Mi4	1.19	1.01 – 1.39	0.17	0.03 – 0.96	1.41	1.21 – 1.64	0.05	0.01 – 0.31
Smoking[5]	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[6]	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*	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
*Sex * hyperlipidaemia*	0.99	0.84 – 1.15	0.63	0.24 – 1.63	0.95	0.83 – 1.09	2.45	1.23 – 4.88
*Sex * musculoskeletal*	1.07	0.92 – 1.25	1.04	0.57 – 1.88	0.92	0.81 – 1.04	1.02	0.70 – 1.49
*Sex * rheumatic disease*	0.92	0.65 – 1.31	1.22	0.14 – 10.84	0.86	0.66 – 1.12	1.17	0.31 – 4.49
*Sex * vascular disease[3]*	0.99	0.81 – 1.20	0.21	0.03 – 1.61	1.08	0.90 – 1.30	2.28	0.52 – 9.92
*Sex * mi[4]*	1.04	0.86 – 1.27	0.50	0.06 – 3.98	0.80	0.66 – 0.97	0.82	0.10 – 6.71
*Sex * smoking[5]*	1.14	0.97 – 1.33	0.85	0.43 – 1.66	1.07	0.89 – 1.28	0.91	0.48 – 1.71
*Sex * age[6]*	1.00	0.99 – 1.01	1.00	0.98 – 1.02	1.00	0.99 – 1.00	1.00	0.99 – 1.02

*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 in the negative binomial model is interpreted as a count. ** Exponent in the zero inflated is interpreted as an odd ratio. 1 Coefficients for the count part of the model are interpreted as predicted number of contacts. 2 The logistic part of the model predicts non-occurrence of contact.*

Chapter

5

Sex Differences in Mortality Risk After the First Hospitalisation with Lower Extremity Peripheral Arterial Disease

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ABSTRACT

Objective: Lower extremity peripheral arterial disease (PAD) is a severe condition that increases the risk of major adverse cardiovascular events, major adverse limb events, and all-cause mortality. This study aimed to investigate the mortality risk among females and males hospitalised for the first time with lower extremity PAD.

Methods: Three cohorts of patients who were admitted for the first time with lower extremity PAD in 2007 - 2010, 2011 - 2014, and 2015 - 2018 were constructed. For the 2007 - 2010 and 2011 - 2014 cohorts, the 28-day, one-year, and five-year mortality rates were calculated, assessing survival time from date of hospital admission until date of death, end of study period, or censoring. For the 2015 - 2018 cohort, only 28 day and one year mortality were investigated due to lack of follow up data. Mortality rates of these cohorts were compared with the general population using standardised mortality rates (SMRs), and the risk of death between sexes was evaluated using Cox proportional hazards models. Cox models were adjusted for age, cardiovascular disease, and diabetes mellitus to account for potential confounding factors.

Results: In total, 7 950, 9 670, and 13 522 patients were included in the 2007 - 2010, 2011 - 2014, and 2015 - 2018 cohorts, respectively. Over 60% of individuals in each cohort were males. Mortality rates at 28-day and one-year remained stable across all cohorts, while the five-year mortality rate increased for both males and females in the 2011 - 2014 cohort. The SMRs both of females and males with PAD were significantly higher than in the general population. Multivariable regression analyses found no significant differences in mortality risk between sexes at 28 day and one year. However, the five-year mortality risk was lower in females, with a hazard ratio of 0.89 (95% confidence interval [CI] 0.83 - 0.97) in the 2007 - 2010 cohort and 0.88 (95% CI 0.82 - 0.94) in the 2011 - 2014 cohort.

Conclusion: The five-year mortality risk has increased, and females face a lower mortality risk than males. Lower extremity PAD still carries unfavourable long-term consequences compared with the general population.

INTRODUCTION

Lower extremity peripheral arterial disease (PAD) is a health concern that impacts millions of individuals worldwide. This condition poses a significant threat due to its strong association with major adverse cardiovascular events and major adverse limb events as well as an increased all-cause mortality risk.[1-3] The global prevalence of individuals with lower extremity PAD has increased significantly, from 202 million in 2010 [4] to over 236 million in 2015.[5] Additionally, the long term mortality risk of lower extremity PAD is comparable with that of coronary heart disease.[6,7]

Compared with other cardiovascular diseases, patients with lower extremity PAD experience more undertreatment8 and underdiagnosis [9-11] as well as a lack of awareness about the predictors and risk factors for worse prognosis. [12-16] This disparity is even more prevalent in females, who face more underdiagnosis and undertreatment despite a similar incidence of lower extremity PAD. It is becoming increasingly recognised that sex may significantly influence the treatment and prognosis of lower extremity PAD. [17,18] In 2009, Vaartjes et al. reported that the five-year mortality risk was higher in males in a nationwide cohort of patients admitted for the first time with lower extremity PAD between 1997 and 2000. [19] These findings underline the urgency of understanding the prognosis in lower extremity PAD.

Over the past decades, there have been efforts to improve awareness and understanding of lower extremity PAD among healthcare providers and the general public. [20] These efforts include, for example, making ankle brachial index measurement a readily available diagnostic technique and promoting lifestyle modifications to reduce cardiovascular risk. [21] Additionally, diagnostic techniques and treatment options have improved. [22-25] Hence, the prognosis for patients with lower extremity PAD is assumed to have also improved.

This study aimed to investigate sex differences in mortality risk at 28 days, one year, and five years in three Dutch cohorts of patients who were admitted for the first time with lower extremity PAD between 2007 – 2010, 2011 – 2014, and 2015 – 2018.

METHODS

This study aligns with the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) Statement.[26]

Study population, data sources, and data linkage

The study population included individuals living in the Netherlands who were hospitalised for the first time with lower extremity PAD during three different time periods: 2007 – 2010, 2011 – 2014, and 2015 – 2018.

Lower extremity PAD hospital admissions were defined by the International Classification of Diseases, 10th edition (ICD-10)[27] primary diagnosis code I73.9 (i.e., peripheral vascular disease unspecified, intermittent claudication, or spasm of an artery), or the ICD-9 [28] primary diagnosis code 443.9 (i.e., peripheral vascular disease unspecified). A first hospital admission was defined as the initial admission related to lower extremity PAD, without prior hospitalisations for this condition within the preceding five years.

To construct the cohorts, information from the Dutch Hospital Discharge Registry (DHDR) and the Dutch Population Registry (PR) was linked. In brief, the DHDR is a nationwide database with admissions from all university and general hospitals in the Netherlands. Each record contains information about one hospital admission; therefore, each person can have multiple records. For each medical specialty involved during admission, at most one primary diagnosis was registered according to ICD-9 [28] or ICD-1027 code from 2013 onwards. This primary diagnosis code is deemed the most important reason for involvement of the medical specialist during the admission.

Information on the cause of death was derived from the National Cause of Death Registry (NCDR) of Statistics Netherlands. The NCDR captures all causes of death for persons in the Netherlands and is compiled on a statutory basis. Causes of death were coded using the ICD-10. [27] The PR comprises all individuals registered and living in the Netherlands. The PR, DHDR, and NCDR were linked to arrive at a dataset with one individual having one data record. Before 2013, the DHDR registry was linked to the PR based on a combination of date of birth, sex, and six-digit post code; after 2013 it was based on unique citizen service number. From the PR, DHDR, and NCDR registries, for each patient, information on age, sex, medical history (from hospital admissions up to five years prior to the current admission), length of hospitalisation, and (if dead) cause of death was extracted. The linkage occurred within the secure environment of Statistics Netherlands and according to the privacy rules and legislation of the Netherlands. The registers and linkage procedures have been described in detail in previous studies. [29,30]

Data analysis

Survival time was defined as the duration between hospitalisation and the date of death from any cause or the end of follow up, which was up to five years after the first hospitalisation for patients in the cohorts of 2007 – 2010 and 2011 – 2014, and up to one year for patients in the cohort of 2015 – 2018. Censoring occurred if the patient migrated outside the Netherlands, if their linkage key ceased to be unique during follow up (if no unique identifier is present in patients with the same six-digit postal code, date of birth, and sex [only before 2013]), or if the patient was still alive at the end of the follow up period.

The crude 28-day, one-year, and five-year mortality rates were calculated and expressed as percentages, stratified by age and sex according to the actuarial life table method. The mortality rate in females was compared with the mortality rate in males by calculating the relative risk with 95% confidence interval (CI).

To account for differences in mortality rates between patients with lower extremity PAD and the general population, standardised mortality rates (SMRs) were calculated. To do this, the number of observed deaths in patients with lower extremity PAD was divided by the expected number of deaths in the general population in 2007, taking the differences in age into account. The 95% CI of the SMR was computed using the Mid-P exact test, [31] which is based on the exact probability distribution of the observed number of deaths under the null hypothesis that the observed deaths follow a Poisson distribution with the expected number of deaths as the mean. To calculate the SMR between sexes, the SMR in females was divided by the SMR in males.

To study differences in mortality risk between sexes, Cox proportional hazards regression models were used, and the results were reported as hazard ratio (HR) and 95% CI. Age and comorbidities (i.e., previous admissions for cardiovascular disease [CVD] or diabetes mellitus [DM] complications) were adjusted for (see **Supplementary Table S1** for the ICD codes used to determine previous hospital admissions for other reasons). It was assumed that if a prior hospital admission was not recorded, it did not occur.

For the 2007 – 2010 and 2011 – 2014 cohorts, the 28-day, one-year, and five-year mortality rates were calculated. For the 2015 – 2018 cohort, five-year mortality could not be investigated owing to a lack of five year follow up data.

For privacy protection purposes, instances where the observed deaths were fewer than ten were removed from the tables. There were no missing values for sex and age.

All analyses were performed in RStudio 2020 (Integrated Development for R. RStudio, Inc., Boston, MA; http://www.rstudio.com/).

RESULTS

A total of 7 950, 9 670, and 13 522 patients were identified in the cohorts from 2007 – 2010, 2011 – 2014, and 2015 – 2018, respectively (**Table 1**). Across the cohorts, the proportion of males decreased slightly from 61.5% in 2007 – 2010 to 59.9% in 2015 – 2018. Mean ± standard deviation age at first hospitalisation increased for both sexes over time from, respectively, 68.76 ± 5.52 years and 66.94 ± 11.98 years for females and males in 2007 – 2010 to 71.37 ± 12.21 years and 69.03 ± 10.65 years in 2015 – 2018 (**Table 1**).

The prevalence of prior hospitalisation for cardiovascular conditions demonstrated an upward trend, increasing from 60.2% and 66.0% in the period 2007 – 2010 to 68.5% and

74.7% in the period 2015 – 2018 for females and males, respectively. Likewise, the prevalence of prior hospitalisation for complications related to DM also increased over time, increasing from 10.5% and 12.1% in 2007 – 2010 to 19.5% and 23.5% in 2015 – 2018 for females and males, respectively (**Table 1**).

Cause of death

CVD, specifically ischaemic heart disease, was the primary cause of death in both sexes. Nevertheless, in recent years there has been a decline in deaths due to CVD, including ischaemic heart disease, and a notable increase in deaths attributed to cancer and other causes, as outlined in **Supplementary Table S2**.

Twenty-eight-day mortality

The absolute mortality rate at 28-day for females and males, respectively, was 3.7% (n = 113) and 2.4% (n = 117) in 2007 – 2010, 3.2% (n = 124) and 2.6% (n = 153) in 2011 – 2014, and 2.9% (n = 157) and 2.1% (n = 171) in 2015 – 2018 (**Supplementary Table S3**).

The SMRs for females with lower extremity PAD in the 2007 – 2010, 2011 – 2014, and 2015 – 2018 cohorts were 13.52 (95% CI 11.19 – 16.19), 11.16 (95% CI 9.32 – 13.26), and 9.16 (95% CI 7.80 – 10.67), respectively, compared with the general population (**Table 2**; **Supplementary Table S4**). For males with lower extremity PAD in the same cohorts, the SMR values were 8.25 (95% CI 6.58 – 9.85), 8.30 (95% CI 7.06 – 9.69), and 6.21 (95% CI 5.32 – 7.18) respectively, compared with the general population (**Table 2**; **Supplementary Table S4**). When comparing the SMR in females vs. males with PAD, females had a statistically significantly higher SMR in the 2007 – 2010 cohort (SMR 1.63, 95% CI 1.01 – 2.54) (**Table 2**).

In the comparison of mortality risk between sexes, it was observed that the crude 28-day mortality risk was higher in females for the cohorts of 2007 – 2010 and 2015 – 2018, with HRs of 1.55 (95% CI 1.19 – 2.01) and 1.38 (95% CI 1.11 –1.71), respectively. However, after adjusting for age and previous admissions for CVD or DM complications, there were no statistically significant differences between females and males (**Table 3**).

Table 1. *Characteristics of patients with first hospital admission for lower extremity peripheral arterial disease between 2010 and 2018, by cohort.*

Characteristic	***2007–2010***			***2011–2014***			***2015–2018***		
	Females (n = 3 063, 38.5%)	Males (n = 4 887, 61.5%)	p ∗	Females (n = 3 858, 39.9%)	Males (n = 5 812, 60.1%)	p ∗	Females (n = 5 417, 40.1%)	Males (n = 8 105, 59.9%)	p ∗
Age at admission – y	68.76 ± 5.52	66.94 ± 11.98		70.01 ± 12.78	68.36 ± 10.94		71.37 ± 12.21	69.03 ± 10.65	
History of cardiovascular disease	1 844 (60.2)	3 226 (66.0)	<.001	2 493 (64.6)	4 108 (70.7)	<.001	3 710 (68.5)	6 054 (74.7)	<.001
Ischaemic heart disease †	630 (34.2)	1 507 (46.7)	<.001	877 (35.2)	2 002 (48.7)	<.001	1 432 (38.6)	3 018 (49.9)	<.001
Acute myocardial infarction †	250 (13.6)	735 (22.8)	<.001	355 (14.2)	919 (22.4)	<.001	555 (15.0)	1 376 (22.7)	<.001
Congestive heart failure †	237 (12.9)	371 (11.5)	.077	357 (14.3)	528 (12.9)	.090	623 (16.8)	1 002 (16.6)	<.001
Stroke †	273 (14.8)	544 (16.9)	<.001	458 (18.4)	812 (19.8)	<.001	710 (19.1)	1 131 (18.7)	.002
Other cardiovascular disease †	921 (49.9)	1 311 (40.6)	.004	1 190 (47.7)	1 565 (38.1)	<.001	1 615 (43.5)	2 259 (37.3)	.006
History of diabetes mellitus complications	321 (10.5)	589 (12.1)	.004	605 (15.7)	1 052 (18.1)	<.001	1 054 (19.5)	1 901 (23.5)	<.001
Length of hospital stay – d	6	5	.037	5	5	.23	5	4	.70
Origin, native ‡	2 881 (94.1)	4 556 (93.2)	.21	3 624 (93.9)	5 389 (92.7)	.038	5 054 (93.3)	7 458 (92.0)	.033

Data are presented as mean ± standard deviation or n (%). ∗ Age adjusted sex difference p value indicates the difference between females and males in the cohort. † Percentages are given out of those with a history of cardiovascular disease. ‡ Refers to Dutch nationals based on their place of birth

One-year mortality rate

The absolute mortality rate at one-year was 13.5% (n = 415) and 10.7% (n = 522) for females and males, respectively, in the 2007 – 2010 cohort. These mortality rates remained relatively stable in the 2011 – 2014 and 2015 – 2018 cohorts (**Supplementary Table S3**). Compared with the general population, the SMR was consistently higher in females with lower extremity PAD across all age groups, with the highest mortality rate observed in the age group 75 – 79 years for all cohorts. When comparing the SMR in females vs. males with PAD, no statistically significant differences were found (**Table 2**; **Supplementary Table S4**).

The one-year crude mortality risk was higher in females than males across all the cohorts, with HRs of 1.30 (95% CI 1.14 – 1.48), 1.19 (95% CI 1.06 –1.34), and 1.12 (95% CI 1.01 –1.24) for the 2007 – 2010, 2011 – 2014, and 2015 – 2018 cohorts, respectively. However, once adjusted for age and previous admissions for CVD or DM complications, there were no statistically significant differences in one year mortality risk between sexes (**Table 3**).

Five-year mortality rate

In the 2007 – 2010 cohort, the five-year mortality rates were 32.9% (n = 1 008) and 31.9% (n = 1 561), for females and males, respectively. These rates increased to 35.1% (n = 1 353) for females and 35.4% (n = 2 056) for males in the 2011 – 2014 cohort (**Supplementary Table S3**). The SMR across all group ages was higher in females with lower extremity PAD, with the highest mortality rate in the group aged 60 – 64 years compared with the general population (**Table 2**; **Supplementary Table S4**).

No statistically significant differences in five-year mortality risk were observed between the two sexes in the cohorts 2007 – 2010 (HR 1.05, 95% CI 0.97 – 1.14) and 2011 – 2014 (HR 0.99, 95% CI 0.93 – 1.07). After taking age and previous admissions for CVD or DM complications into account, females had a lower five-year mortality risk than males, with an HR of 0.89 (95% CI 0.83 – 0.97) for the 2007 – 2010 cohort and 0.88 (95% CI 0.82 – 0.94) for the 2011 – 2014 cohort (**Table 3**).

Table 2. *Standardised mortality rates (SMRs) for patients with lower extremity peripheral arterial disease (PAD), stratified by sex, compared with the general population (in 2007).*

Cohort	***Males***			***Females***			***SMR (95% CI) females vs. males†***
	Deaths– n	Expected deaths – n	SMR (95% CI)	Deaths – n	Expected deaths – n	SMR (95% CI)	
	First hospitalisation for lower extremity PAD 2007–2010						
28-day mortality	117	14.18	8.25 (6.58–9.85)	113	8.36	13.52 (11.19–16.19)	1.63 (1.01–2.54)
1 -year mortality	522	162.36	3.21 (2.94–3.5)	415	96.50	4.30 (3.90–4.73)	1.33 (0.68–2.72)
5-year mortality	1 561	791.53	1.97 (1.87–2.07)	1 008	481.81	2.09 (1.96–2.22)	1.06 (0.55–2.28)
	First hospitalisation for lower extremity PAD 2011–2014						
28-day mortality	153	18.43	8.30 (7.06–9.69)	124	11.11	11.16 (9.32–13.26)	1.34 (0.83–2.21)
1-year mortality	635	211.10	3.01 (2.78–3.25)	497	127.60	3.89 (3.56–4.24)	1.29 (0.53–2.40)
5-year mortality	2 056	1 022.46	2.01 (1.92–2.10)	1 353	633.00	2.14 (2.02–2.25)	1.06 (0.54–2.77)
	First hospitalisation for lower extremity PAD 2015–2018						
28-day mortality	171	27.56	6.21 (5.32–7.18)	157	17.15	9.16 (7.80–10.67)	1.47 (0.88–2.53)
1-year mortality	930	311.97	2.98 (2.74–3.17)	690	195.47	3.53 (3.28–3.81)	1.18 (0.54–2.42)

Expected death are the total number of deaths per 100.000 people in each time period. SMR = standardised mortality rate; CI = confidence interval; PAD = peripheral arterial disease.

∗ Full data are given in Supplementary Table S4. † SMR females vs. males were calculated by dividing the SMR in females by the SMR in males.

***Table 3**. Sex differences in short- and long-term all-cause mortality after a first hospital admission for lower extremity PAD in the Netherlands, by cohort.*

Mortality	***2007–2010***	***2011–2014***	***2015–2018***
	HR (95% CI) *	HR (95% CI) *	HR (95% CI) *
Crude			
28-day	1.55 (1.19–2.01)	1.23 (0.97–1.55)	1.38 (1.11–1.71)
1-year	1.30 (1.14–1.48)	1.19 (1.06–1.34)	1.12 (1.02–1.24)
5-year	1.05 (0.97–1.14)	0.99 (0.93–1.07)	–
Model 1†			
28-day	1.22 (0.93–1.59)	0.93 (0.73–1.19)	1.08 (0.87–1.35)
1-year	1.05 (0.92–1.19)	0.98 (0.87–1.10)	0.91 (0.83–1.01)
5-year	0.89 (0.83–0.97)	0.88 (0.82–0.94)	–

PAD = peripheral arterial disease; HR = hazard ratio; CI = confidence interval. ∗ Females vs. males. † Model 1: adjusted for age and comorbidities (previous admissions for cardiovascular disease or diabetes mellitus complications).

DISCUSSION

This nationwide record linkage study examined patients admitted for the first time with lower extremity PAD during three different time periods (2007 – 2010, 2011 – 2014, and 2015 – 2018). Mortality rates at 28-day and one-year remained stable across the cohorts for both females and males. However, the five-year mortality rate increased significantly in the 2011 – 2014 cohort both for females and males. The SMR standardised by age was significantly higher for both females and males with lower extremity PAD compared with the general population, with females having a higher SMR across all ages in all cohorts. Cox models assessing mortality risk between sexes showed no statistically significant differences in 28-day and one-year mortality risk, while the five-year mortality risk was consistently lower in females than males.

Previously, Vaartjes et al. [19,32] reported the one-year mortality risk after first hospital admission for lower extremity PAD was around 10% in both sexes, and the five-year (long term) risk was 27% for females and 31% for males. The present study found similar results for the 28 day and one year mortality rate, but an increase in five-year mortality risk, with one in three patients dying within five years of the first hospitalisation. Several mechanisms may have contributed to this worsening in long term prognosis, including an older population and higher prevalence of previous CVD and DM. In the later cohorts, individuals experienced their first hospitalisation at an older age and there was an increase in the number of hospitalisations with lower extremity PAD. This could be attributed to several factors. First, population growth has resulted in more people seeking medical care and being hospitalised for a variety of conditions, including PAD.

As the population grows, health problems are expected to increase, and PAD is no exception. Second, improved methods of data collection and record linkage, especially since 2013, have contributed to the recognition of patients hospitalised with PAD. A clear indicator of this improvement is the successful linkage of patient records. Effective record linkage is crucial to accurately capture and track individual cases across health encounters. The impressive 99.7% rate achieved in 2019 demonstrates the progress made in refining the registration process and minimising potential gaps in data capture.[33]

Sex may not play a significant role in short term mortality risk; however, at five years, mortality risk continues to be higher in males. The reason for this sex difference remains unclear, but some potential factors could explain this observation, including differences in comorbidities, [34] risk factors, [34] disease presentation [35] (i.e., females with PAD are more often asymptomatic), and referral patterns. [17] For instance, smoking, a known risk factor for the development and progression of PAD, [36] is more common in males with PAD than in females with PAD. [37] Additionally, evidence suggests that males with PAD receive more aggressive treatment and undergo surgical interventions more often than females.[17,18] The higher rate of aggressive treatment for males might be considered beneficial, however, it may also carry a higher risk of complications, which could contribute to the higher mortality risk. [38]

These findings provide a comprehensive overview of the evolving landscape of lower extremity PAD and its implications, offering valuable insights that resonate strongly with the European Society for Vascular Surgery (ESVS) guidelines on PAD. [39] By delineating temporal trends in PAD prevalence and mortality rates across different cohorts, the escalating burden of PAD over time is underscored, a trend consistent with the growing global prevalence outlined in the ESVS guidelines. Moreover, the identification of demographic shifts as well as risk factors such as age, sex, and comorbidities (i.e., DM and CVD) showed their role in driving PAD progression and shaping clinical outcomes and highlight the multifactorial nature of PAD aetiology and risk stratification approaches. Additionally, mortality outcomes were reported at various time intervals, including 28 days, one year, and five years, which serves as a stark reminder of the substantial cardiovascular morbidity and mortality associated with PAD, reinforcing the urgency emphasised in the ESVS guidelines for implementing comprehensive management strategies aimed at optimising patient care, reducing limb loss, and improving overall survival rates. Thus, the findings of this study not only enrich our understanding of PAD epidemiology and mortality but also underscore the need for coordinated efforts guided by ESVS recommendations to address the multifaceted challenges posed by this debilitating vascular condition.

The strengths of this study include its large sample size, which includes a nationwide population. Additionally, it was possible to link the DHDR with the PR and NCDR,

allowing for complete follow up and investigation of age and sex stratified prognosis. Some limitations should also be acknowledged. First, ICD codes do not provide information about disease severity or whether the hospital admission was intervention related. However, the cohorts consisted of hospitalised patients, which might suggest that they probably had moderate to severe disease and had an indication for surgical intervention or other specialised treatment. First hospital admission was defined by examining the five years before the current hospital admission. If an individual had an admission with lower extremity PAD more than five years before the current admission, this definition could have resulted in classifying a hospital admission as first instead of recurrent admission. Thus, if patients with more than one admission have a higher mortality risk, this could have resulted in mortality risk overestimation. This, however, would not bias the sex difference analyses. To construct the cohorts and to make the study comparable with studies published in the past regarding lower extremity PAD in the Dutch population, [19,32,33] only primary diagnosis codes from hospital admissions (ICD-10 code I73.9 or ICD-9 code 443.9) were used. This means that if lower extremity PAD was not the primary issue but a secondary one, it would not be included in this study. Additionally, although the primary ICD codes aimed to identify cases where PAD was the main reason for hospitalisation, it is acknowledged that using only primary diagnosis codes and excluding the ICD-10 codes I70.21 – 24 might lead to an underestimation of PAD hospitalisation. We found that the presence of secondary code E11.52 (diabetic foot infection) could also lead to misclassification. Individuals who have a diabetic foot infection as their primary concern might be classified as PAD cases due to the presence ICD-10 code I73.9 or ICD-9 code 443.9 as the primary diagnosis and ICD-10 code E11.52 as a secondary diagnosis. Using administrative data for creating a cohort is complex due to the hierarchy of diagnosis codes where primary and secondary codes are interrelated. Therefore, these findings should be interpreted with caution due to potential misclassification bias. Registries do not contain information about disease severity, smoking status, surgical intervention, or sex; thus, it was not possible to investigate their effect on the outcome of interest. Finally, due to the COVID-19 pandemic complete follow up information for the 2015 – 2018 cohort could not be gathered, particularly at the five-year timeline. As a result, this cohort was excluded from the five-year mortality analysis. However, 28-day and one year mortality data provide important insights into the short-term consequences of lower extremity PAD.

CONCLUSION

Mortality rates after first hospitalisation with lower extremity PAD remained stable at 28-day and one-year both for females and males. However, the five-year mortality rate has increased for both sexes, with males having a higher mortality risk than females.

Lower extremity PAD still carries unfavourable long-term consequences compared with the general population. Therefore, it is crucial to continue raising awareness among healthcare professionals and the public about the risks and potential outcomes associated with lower extremity PAD.

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SUPPLEMENTARY MATERIAL

Supplementary Table S1: *International Classification of Diseases (ICD) codes used to define comorbidities.*

	ICD-10	***ICD-9***
Lower extremity PAD	I73.9	443,9
CVD	I00-99	390-459
IHD	I20-25	410-414
AMI	I20, I21, I252†	410, 412
CHF	I43, I50, I099, I110, I130, I132, I255, I420, I425-429, P290	428
Stroke	I60-69, G45, G46, H340	430-438
DM	E10, E11, E13	250
Cancer	C00-96, D00-49	
Lung cancer	C34	
Respiratory disease	J00-99	
COPD	J41-44	

PAD: peripheral artery disease; CVD: cardiovascular disease; IHD: ischemic heart disease; AMI: acute myocardial infarction; CHF: cardiac heart failure; DM: diabetes mellitus.

Supplementary Table S2: *Causes of death at 28 days, 1 year, and 5 years for patients with a first hospitalisation for lower extremity peripheral arterial disease.*

	2007-2010 cohort								
	28-days			one-year			five-years		
	Males	Females		Males	Females		Males	Females	
n	117	113	p	522	415	p	1561	1008	p
Cause Of Death									
Cardiovascular Disease	62	77	.140	236	236	.012	637	470	.059
Ischemic Heart Disease	10	11	.754	47	40	.861	177	84	.017
Acute Myocardial Infarction				26	29	.218	91	57	.807
Congestive Heart Failure				24	22	.961	77	57	.653
Stroke				18	24	.128	60	75	<.001
Peripheral Arterial Disease		13		22	34	.037	41	50	.016
Other CVD	41	44	.707	125	116	.464	282	204	.613
Cancer	10			89	48	.202	376	187	.035
Lung Cancer				35	16	.245	160	65	.012
Respiratory System	11			65	24	<.001	172	81	.002
COPD				36	13	.014	97	48	.115
Complication From DM				10	10	.564	30	22	.465
Other	32	24	.512	122	97	.763	346	248	.156
	2011-2014 cohort								
	28-days			one-year			five-year		
	Males	Females		Males	Females		Males	Females	
N	153	124	p	635	497	p	2056	1353	p
Cause Of Death									
Cardiovascular Disease	92	83	.586	322	262	.649	822	584	.587
Ischemic Heart Disease	17			77	44	.074	206	114	.149
Acute Myocardial Infarction				40	27	.581	109	64	.504
Congestive Heart Failure	15			56	40	.307	158	116	.982
Stroke				26	29	.321	85	84	.025

Supplementary Table S2. *Continued*

	2011-2014 cohort								
Peripheral Arterial Disease	18	18	.605	38	35	.706	66	56	.290
Other CVD	41	42	.424	125	114	.546	307	214	.863
Cancer	15			100	63	.839	511	272	.15
Lung Cancer				41	20	.279	197	123	.500
Dis Of Respiratory System	11			48	33	.356	197	115	.107
COPD				24	19	.991	113	70	.670
Complications From DM				10	15	.085	25	29	.039
Other	31	24	.955	155	124	.785	501	353	.378
	2015-2018 cohort								
	28-days			one-year					
	Males	Females		Males	Females				
N	171	157	p	930	690	p			
Cause Of Death									
Cardiovascular Disease	94	85	.449	421	344	.536			
Ischemic Heart Disease	15	11	.649	99	39	<.001			
Acute Myocardial Infarction				42	18	.089			
Congestive Heart Failure	21			92	68	.312			
Stroke				26	34	.018			
Peripheral Arterial Disease	14	15	.868	38	51	.015			
Other CVD	41	41	.963	166	152	.221			
Cancer	14	15	.158	163	83	.139			
Lung Cancer				54	29	.720			
Dis Respiratory Sys	15	11	.523	85	50	.101			
COPD				45	28	.372			
Complications From Dm				29	16	.356			
Other	43	39	.969	232	197	.112			

p-value age adjusted sex difference.

Supplementary Table S3: *Mortality risk at 28 days, 1 year, and 5 years after a first hospitalisation for peripheral arterial disease.*

				2007-2010				
				Females		Males		*RR (95% CI) females vs males*
	No. males	*No. females*	*Age*	*No. deaths*	*% of death*	*No. deaths*	*% death*	
28-day mortality	194	179	<45					
	159	130	45-49					
	342	200	50-54					
	563	252	55-59					
	719	359	60-64	11	1,53			
	787	359	65-69	15	1,91			
	822	435	70-74	22	2,68			
	697	452	75-79	26	3,73	22	4,87	1.30 (0.74, 2.27)
	404	366	80-84	19	4,70	27	7,38	1.56 (0.88, 2.77)
	200	331	85+	15	7,50	45	13,60	1.81 (1.03, 3.16)
	4887	3063	all	117	2,39	113	3,69	1.54 (1.19, 1.98)
1-year mortality	194	179	<45					
	159	130	45-49					
	342	200	50-54					
	563	252	55-59	19	3,37			
	719	359	60-64	48	6,68	12	3,34	0.50 (0.26, 0.93)
	787	359	65-69	50	6,35	28	7,80	1.22 (0.78, 1.91)
	822	435	70-74	93	11,31	52	11,95	1.05 (0.76, 1.45)
	697	452	75-79	112	16,07	74	16,37	1.01 (0.77, 1.33)
	404	366	80-84	99	24,50	86	23,50	0.95 (0.74, 1.23)
	200	331	85+	88	44,00	142	42,90	0.97 (0.79, 1.19)
	4887	3063	all	522	10,68	415	13,55	1.26 (1.12, 1.43)
5-year mortality	194	179	<45					
	159	130	45-49					
	342	200	50-54	33	9,65	20	10,00	1.03 (0.61, 1.75)
	563	252	55-59	83	14,74	36	14,29	0.96 (0.67, 1.39)
	719	359	60-64	162	22,53	67	18,66	0.82 (0.64, 1.06)
	787	359	65-69	187	23,76	96	26,74	1.12 (0.91, 1.39)
	822	435	70-74	293	35,64	144	33,10	0.92 (0.78, 1.09)
	697	452	75-79	355	50,93	180	39,82	0.78 (0.68, 0.89)
	404	366	80-84	270	66,83	201	54,92	0.82 (0.73, 0.92)
	200	331	85+	160	80,00	250	75,53	0.94 (0.86, 1.03)
	4887	3063	all	1561	31,94	1008	32,91	1.03 (0.96, 1.09)

Supplementary Table S3: *Continued.*

				2011-2014				
				Females		Males		*RR (95% CI) females vs males*
	No. males	*No. females*	*Age*	*No. death*	*% of death*	*No. deaths*	*% death*	
28-day mortality	139	129	<45					
	149	152	45-49					
	381	246	50-54					
	590	278	55-59					
	803	415	60-64					
	1049	600	65-69	16	1,53			
	991	554	70-74	24	2,42			
	859	556	75-79	21	2,44	17	3,06	1.25 (0.66, 2.34)
	563	501	80-84	40	7,10	38	7,58	1.06 (0.69, 1.63)
	288	427	85+	36	12,50	53	12,41	0.99 (0.66, 1.47)
	5812	3858	all	153	2,63	124	3,21	1.22 (0.96, 1.54)
1-year mortality	139	129	<45					
	149	152	45-49					
	381	246	50-54	12	3,15			
	590	278	55-59	25	4,24	10	3,60	
	803	415	60-64	35	4,36	26	6,27	
	1049	600	65-69	68	6,48	37	6,17	
	991	554	70-74	100	10,09	41	7,40	0.73 (0.51, 1.03)
	859	556	75-79	125	14,55	75	13,49	0.92 (0.71, 1.20)
	563	501	80-84	153	27,18	118	23,55	0.86 (0.70, 1,06)
	288	427	85+	114	39,58	178	41,69	1.05 (0.87, 1.26)
	5812	3858	all	635	10,93	497	12,88	1.17 (1.05, 1.31)
5-year mortality	139	129	<45					
	149	152	45-49					
	381	246	50-54	51	13,39	28	11,38	0.85 (0.55, 1.31)
	590	278	55-59	109	18,47	41	14,75	0.79 (0.57, 1.10)
	803	415	60-64	160	19,93	96	23,13	1.16 (0.92, 1.45)
	1049	600	65-69	310	29,55	143	23,83	0.80 (0.67, 0.95)
	991	554	70-74	364	36,73	158	28,52	0.77 (0.66, 0.90)
	859	556	75-79	435	50,64	236	42,45	0.83 (0.74, 0.94)
	563	501	80-84	376	66,79	301	60,08	0.89(0.82, 0.98)
	288	427	85+	238	82,64	337	78,92	0.95 (0.88, 1.02)
	5812	3858	all	2056	35,38	1353	35,07	0.99 (0.93, 1.04)

Supplementary Table S3: *Continued.*

				2015-2018				
				Females		Males		*RR (95% CI) females vs males*
	No. males	*No. females*	*Age*	*No. deaths males*	*% death*	*No. deaths*	*% death*	
28-day mortality	129	130	<45					
	216	157	45-49					
	440	244	50-54					
	791	414	55-59					
	1141	537	60-64					
	1453	806	65-69	14	0,96			
	1494	890	70-74	26	1,74	16	1,80	1.03 (0.55, 1.91)
	1167	826	75-79	30	2,57	27	3,27	1.27 (0.76, 2.12)
	804	737	80-84	49	6,09	34	4,61	0.75 (0.49, 1.15)
	470	676	85+	34	7,23	64	9,47	1.30 (0.87, 1.95)
	8105	5417	all	171	2,11	157	2,90	1.37 (1.10, 1.70)
1-year mortality	129	130	<45					
	216	157	45-49					
	440	244	50-54	10	2,27			
	791	414	55-59	32	4,05	10		
	1141	537	60-64	65	5,70	23	4,28	
	1453	806	65-69	95	6,54	44	5,46	
	1494	890	70-74	155	10,37	78	8,76	0.84 (0.65, 1.09)
	1167	826	75-79	165	14,14	110	13,32	0.94 (0.75, 1.17)
	804	737	80-84	200	24,88	141	19,13	0.76 (0.63, 0.93)
	470	676	85+	197	41,91	271	40,09	0.95 (0.83, 1.10)
	8105	5417	all	930	11,47	690	12,74	1.11 (1.01, 1.21)

Supplementary Table S4: *Standardised mortality rates for patients with PAD compared with the general population – full data.*

	Standard population (01-01-2007)					***First hospitalisation for lower extremity PAD (2007-2010)***						
	No. males	*No. females*	Males *No. deaths*	Females *No. deaths*	*Age*	Males *No. deaths*	*Expected deaths*	*SMR males (95% CI)*	Females *No. deaths*	*Expected deaths*	*SMR females (95% CI)*	*SMR (95% CI*)*
28-day mortality	4849136	4716833	260	164	<45							
	623823	614592	120	100	45-49							
	570195	562847	176	131	50-54							
	559801	549370	335	215	55-59							
	468253	464359	393	282	60-64	11						
	346918	362286	520	310	65-69	15						
	271935	314654	737	482	70-74	22						
	201984	275476	901	691	75-79	26			22			
	124213	217041	975	1063	80-84	19			27			
	73520	193306	1289	2550	85+	15			45			
	8089778	8270764	5706	5988	all	117	14,18	8,25 (6.58, 9.85)	113	8,36	13.52 (11.2, 16.1)	1.63 (1.01, 2.54)
1-year mortality	4849136	4716833	2680	1804	<45							
	623823	614592	1438	1175	45-49							
	570195	562847	2194	1752	50-54							
	559801	549370	3764	2530	55-59	19						
	468253	464359	4994	3117	60-64	48			12			
	346918	362286	6292	3801	65-69	50			28			
	271935	314654	8348	5531	70-74	93			52			
	201984	275476	10940	8636	75-79	112	37,75	2.97 (2.45, 3.55	74	14,17	5.22 (4.13, 6.51)	1.75(0.94, 3.44)
	124213	217041	11476	12860	80-84	99	37,33	2.65 (2.16, 3.21)	86	21,69	3.96 (3.19, 4.87)	1.49 (0.61, 2.70)
	73520	193306	12933	27382	85+	88	34,47	2.55 (2.06, 3.13)	142	44,66	3.18 (2.68, 3.73)	1.24 (0.63, 2.83)
	8089778	8270764	65059	68588	all	522	162,36	3.21 (2.94, 3.50)	415	96,50	4.30 (3.90, 4.73)	1.33 (0.68, 2.72)

Supplementary Table S4: *Continued*

	Standard population (01-01-2007)					***First hospitalisation for lower extremity PAD (2007-2010)***						
			Males	Females		Males			Females			
	No. males	*No. females*	*No. deaths*	*No. deaths*	*Age*	*No. deaths*	*Expected deaths*	*SMR males (95% CI)*	*No. deaths*	*Expected deaths*	*SMR females (95% CI)*	*SMR (95% CI*)*
5-year mortality	4849136	4716833	14658	10219	<45							
	623823	614592	8508	6967	45-49							
	570195	562847	13318	10078	50-54	33			20			
	559801	549370	21174	14513	55-59	83			36			
	468253	464359	28453	17848	60-64	162	43,69	3.71 (3.16, 4.31)	67	13,80	4.86 (3.79, 6.12)	1.31 (0.59, 2.36)
	346918	362286	34289	21590	65-69	187	77,79	2.40 (2.07, 2.76)	96	21,39	4.49 (3.65, 5.45)	1.87 (0.67, 4.26)
	271935	314654	45700	31803	70-74	293	138,14	2.12 (1.88, 2.37)	144	43,97	3.28 (2.77, 3.84)	1.54 (0.76, 3.40)
	201984	275476	56220	50064	75-79	355	194,00	1.83 (1.64, 2.02)	180	82,14	2.19 (1.88, 2.53)	1.19 (0.59, 3.04)
	124213	217041	53769	69531	80-84	270	174,88	1.55 (1.37, 1.74)	201	117,25	1.71 (1.49, 1.96)	1.11 (0.40, 2.39)
	73520	193306	48489	114150	85+	160	130,58	1.22 (1.04, 1.42)	250	190,77	1.31 (1.15, 1.48)	1.06 (0.50, 2.99)
	8089778	8270764	324578	346763	all	1561	791,53	1.97 (1.87, 2.07)	1008	481,81	2.09 (1.96, 2.22)	1.06 (0.55, 2.28)

Supplementary Table S4: *Continued*

	Standard population (01-01-2007)				***First hospitalisation for lower extremity PAD (2011-2014)***							
			Males	Females		Males			Females			SMR (95% CI)
	No. males	*No. females*	*No. deaths*	*No. deaths*	*Age*	*No. deaths*	*Expected deaths*	*SMR males (95% CI)*	*No. deaths*	*Expected deaths*	*SMR females (95% CI)*	
28-day mortality	4849136	4716833	260	164	<45							
	623823	614592	120	100	45-49							
	570195	562847	176	131	50-54							
	559801	549370	335	215	55-59							
	468253	464359	393	282	60-64							
	346918	362286	520	310	65-69	16						
	271935	314654	737	482	70-74	24						
	201984	275476	901	691	75-79	21			17			
	124213	217041	975	1063	80-84	40			38			
	73520	193306	1289	2550	85+	36			53			
	8089778	8270764	5706	5988	all	153	18,43	8.30 (7.06, 9.69)	124	11,11	11.16 (9.3, 13.26)	1.34 (0.83, 2.21)
1-year mortality	4849136	4716833	2680	1804	<45							
	623823	614592	1438	1175	45-49							
	570195	562847	2194	1752	50-54	12						
	559801	549370	3764	2530	55-59	25			10			
	468253	464359	4994	3117	60-64	35			26			
	346918	362286	6292	3801	65-69	68			37			
	271935	314654	8348	5531	70-74	100			41			
	201984	275476	10940	8636	75-79	125	46,53	2.69 (2.24, 3.19)	75	17,43	4.30 (3.40, 5.36)	1.59 (0.81, 3.25)
	124213	217041	11476	12860	80-84	153	52,02	2.94 (2.50, 3.43)	118	29,68	3.98 (3.30, 4.74)	1.35 (0.55, 2.45)
	73520	193306	12933	27382	85+	114	48,62	2.34 (1.94, 2.80)	178	59,23	3.01 (2.58, 3.47)	1.28 (0.69, 3.08)
	8089778	8270764	65059	68588	all	635	211,10	3.01 (2.78, 3.25)	497	127,60	3.89 (3.56, 4.24)	1.29 (0.53, 2.40)

Supplementary Table S4: *Continued*

	Standard population (01-01-2007)				***First hospitalisation for lower extremity PAD (2011-2014)***							
			Males	Females		Males			Females			SMR (95% CI)
	No. males	*No. females*	*No. deaths*	*No. deaths*	*Age*	*No. deaths*	*Expected deaths*	*SMR males (95% CI)*	*No. deaths*	*Expected deaths*	*SMR females (95% CI)*	
5-year mortality	4849136	4716833	14658	10219	<45							
	623823	614592	8508	6967	45-49							
	570195	562847	13318	10078	50-54	51			28			
	559801	549370	21174	14513	55-59	109			41			
	468253	464359	28453	17848	60-64	160	48,79	3.28 (2.80, 3.81)	96	15,95	6.02 (4.90, 7.31)	1.83 (1.05, 3.55)
	346918	362286	34289	21590	65-69	310	103,68	2.99 (2.67, 3.33)	143	35,76	4.00 (3.38, 4.69)	1.33 (0.42, 3.22)
	271935	314654	45700	31803	70-74	364	166,54	2.19 (1.97, 2.41)	158	55,99	2.82 (2.40, 3.28)	1.28 (0.49, 2.54)
	201984	275476	56220	50064	75-79	435	239,09	1.82 (1.65, 1.99)	236	101,05	2.34 (2.05, 2.64)	1.28 (0.59, 3.06)
	124213	217041	53769	69531	80-84	376	243,71	1.54 (1.39, 1.71)	301	160,50	1.88 (1.67, 2.09)	1.22 (0.40, 2.39)
	73520	193306	48489	114150	85+	238	186,51	1.28 (1.12, 1.44)	337	249,65	1.35 (1.21, 1.50)	1.05 (0.48, 2.88)
	8089778	8270764	324578	346763	all	2056	1022,46	2.01 (1.92, 2.10)	1353	633,00	2.14 (2.02, 2.25)	1.06 (0.54, 2.77)

Supplementary Table S4: *Continued*

	Standard population (01-01-2007)				***First hospitalisation for lower extremity pad (2015-2018)***							
			Males	Females		Males			Females			SMR (95% CI)
	No. males	*No. females*	*No. deaths*	*No. deaths*	*Age*	*No. deaths*	*Expected deaths*	*SMR males (95% CI*	*No. deaths*	*Expected deaths*	*SMR females (95% CI)*	
28-day mortality	4849136	4716833	260	164	<45							
	623823	614592	120	100	45-49							
	570195	562847	17	131	50-54							
	559801	549370	335	215	55-59							
	468253	464359	393	282	60-64							
	346918	362286	520	310	65-69	14						
	271935	314654	737	482	70-74	26			16			
	201984	275476	901	691	75-79	30			27			
	124213	217041	975	1063	80-84	49			34			
	73520	193306	1289	2550	85+	34			64			
	8089778	8270764	5706	5988	all	171	27,56	6.21 (5.32, 7.18)	157	17,15	9.16 (7.80, 10.67)	1.47 (0.88, 2.53)
1-year mortality	4849136	4716833	2680	1804	<45							
	623823	614592	1438	1175	45-49							
	570195	562847	2194	1752	50-54	10						
	559801	549370	3764	2530	55-59	32			10			
	468253	464359	4994	3117	60-64	65	12,17	5.34 (4.15, 6.76)	23			
	346918	362286	6292	3801	65-69	95	26,35	3.60 (2.93, 4.38)	44			
	271935	314654	8348	5531	70-74	155	45,86	3.38 (2.87, 3.94)	78	15,64	4.99 (3.96, 6.19)	1.47 (0.65, 2.59)
	201984	275476	10940	8636	75-79	165	63,21	2.61 (2.23, 3.03)	110	25,89	4.25 (3.50, 5.10)	1.62 (0.84, 3.35)
	124213	217041	11476	12860	80-84	200	74,28	2.69 (2.33, 3.08)	141	43,67	3.23 (2.72, 3.79)	1.2 (0.60, 2.68)
	73520	193306	12933	27382	85+	197	82,45	2.39 (2.07, 2.74)	271	95,14	2.85 (2.52, 3.20)	1.19 (0.45, 2.33)
	8089778	8270764	65059	68588	all	930	311,97	2,98 (2,74, 3.17)	690	195,47	3.53 (3.28, 3.81)	1.18 (0.54, 2.42)

PART

III

Chapter

6

Left Ventricular Diastolic Dysfunction across Levels of Kidney Function

A Cross-Sectional Study Based on Routine Clinical Practice Data

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ABSTRACT

Background: Left ventricular diastolic dysfunction (LVDD) commonly coexists with kidney dysfunction. In this study, we investigated the presence of abnormalities in echocardiography parameters indicative of LVDD across stages of kidney function.

Methods: We selected patients who visited a university hospital and had a serum creatinine and echocardiography reported in their medical records. Participants were categorized based on their kidney function: normal (estimated glomerular filtration rate [eGFR] ≥ 90 mL/min/1.73 m2), mildly decreased (eGFR: 60–90), moderately decreased (eGFR: 30–60), and severely decreased (eGFR < 30). The relationship between kidney function and echocardiography parameters was examined using logistic and linear regressions.

Results: Among 4022 patients (age: 66.5 years [SD: 12.1], 41% women), 26%, 50%, 20%, and 4% had a normal, mildly, moderately, and severely decreased kidney function, respectively. Compared to patients with normal kidney function, patients with mildly decreased kidney function had higher odds for an abnormal E/e' ratio (OR: 1.51 [95% CI: 1.13, 2.02]). Patients with moderately decreased kidney function presented a higher risk of abnormal E/e' (OR: 2.90 [95% CI: 2.08, 4.04]), LAVI (OR: 1.62 [95% CI: 1.13, 2.33]), TR velocity (OR: 2.31 [95% CI: 1.49, 3.57]), and LVMI (OR: 1.70 [95% CI: 1.31, 2.20]), while patients with severely decreased kidney function had higher odds for abnormal E/e' (OR: 2.95 [95% CI: 1.68, 5.17]) and LVMI > 95 g/m2 in women or >115 g/m2 in men (OR: 2.07 [95% CI: 1.27, 3.38]). The linear regression showed a significant inverse association between eGFR and echocardiography parameters, meaning that with worse kidney function, the parameters for LVDD worsened as well.

Conclusions: Abnormal echocardiography parameters of LVDD were present even in patients with mildly decreased kidney function. As the kidney function worsened, there was a gradual increase in the risk of abnormal parameters of LVDD.

INTRODUCTION

Chronic kidney disease (CKD) is a significant public health concern, affecting over 10% of the global population.[1] CKD is associated with several systemic complications, among which cardiovascular disease (CVD) prevails,[2] as approximately 50% of the patients with CKD have some form of CVD.[3] One of the most prominent cardiovascular complications present in patients with CKD is left ventricle diastolic dysfunction (LVDD), i.e., an impaired relaxation, filling, and/or distensibility of the left ventricle during diastole.[4, 5] The coexistence of CKD and LVDD significantly increases the risk of heart failure, cardiovascular morbidity, and mortality, reflecting their impact on cardiovascular health.[6-8] LVDD is considered the preclinical stage of heart failure with preserved ejection fraction (HFpEF) and is commonly found in patients with CKD stages 4 and 5.[9-11] Despite these important implications for patient care, existing research has primarily focused on patients with severe kidney dysfunction, often overlooking those with milder kidney dysfunction, which is more prevalent than severe kidney dysfunction. Furthermore, previous studies have typically examined a limited set of echocardiographic parameters (e.g., E/e' ratio or E/A ratio),[8, 12] consisted of relatively small sample sizes, or were not representative of clinical practice.[13]

Traditionally, there were limited effective therapies specifically targeting LVDD and HFpEF, which might have diminished the perceived necessity of detailed diastolic function evaluation in clinical practice. In recent years, there have been significant developments in therapeutic options for HFpEF.[14, 15] These advancements have shifted the landscape of treatment, making the assessment of diastolic function increasingly important. We hypothesize that abnormal echocardiography parameters that reflect diastolic function are present in patients with kidney dysfunction, already at mild stages of kidney dysfunction. Therefore, this cross-sectional study aimed to investigate echocardiographic parameters of LVDD in a real-world clinical setting among patients with various stages of kidney dysfunction.

METHODS

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used to ensure transparent reporting (**Supplementary Material Table S1**).[16]

Study population

This cross-sectional study used electronic health records from the Utrecht Patient Oriented Database (UPOD), which comprises data of all patients treated at the University Medical Centre Utrecht (UMC Utrecht).[17] UPOD contains information on

clinical characteristics, medication, and laboratory measurements collected as part of routine care since 2000 and has been described in detail elsewhere.[18] The study population consisted of adults from the outpatient departments of nephrology, cardiology, urology, cardiothoracic surgery, vascular medicine, vascular surgery, and neurology, treated at the UMC Utrecht between 2012 and 2022 with a documented estimated kidney function (i.e., serum creatinine) performed 31 days around the index date and a first echocardiography performed (both for any indication) up to 180 days after the index date. The index date was defined as the first visit to the outpatient department listed above. We excluded patients aged below 18 years, those who had received renal replacement therapies (i.e., peritoneal dialysis, haemodialysis, or kidney transplantation), and patients with a history of atrial fibrillation and mitral stenosis prior to the index date.

Determinants and covariates

The patients' estimated kidney function was based on the measurement of serum creatinine levels. We calculated the estimated glomerular filtration rate (eGFR) for all patients included in this study using the latest CKD-EPI 2021 creatinine formula without ethnicity.[19]

Based on their eGFR, patients were categorized into four groups: normal kidney function (eGFR ≥ 90 mL/min/1.73 m2), mildly decreased kidney function (eGFR: 60–90), moderately decreased kidney function (eGFR: 30–60), and severely decreased kidney function (eGFR < 30). The normal kidney function group served as the reference group in all analyses.

We used data on history (i.e., blood pressure measurements), International Classification Disease (ICD) codes, diagnosis treatment combination (DBC) codes, medication (i.e., Anatomical Therapeutic Chemical Classification [ATC codes]), and laboratory measurements (e.g., glycated haemoglobin [HbA1c]) reported before the index date to define medical history. We defined hypertension as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, a history of use of blood-pressure-lowering medication, or a history of hypertension as in medical records based on ICD–DBC codes. Diabetes mellitus (DM) was defined as HbA1c ≥ 48 mmol/mL, a history of use of glucose-lowering medication, or a history of DM in medical records, without distinction between DM types 1 and 2. The prevalence of CVD was based on a history of myocardial infarction, stroke, or transient ischemic attack, peripheral artery disease, renal artery stenosis, or abdominal aortic aneurysm using ICD–DBC codes reported in medical records. History of autoimmune disease, malignancy, and chronic obstructive pulmonary disease or asthma was defined using the ICD–DBC codes and medication registered in the electronic health records (for details see **Supplementary Material Table S2**). For all analyses, in patients without ICD–DBC codes, medication

records, or laboratory measurements related to a history of comorbidities, we maintained a conservative approach and assumed that they did not have the comorbidities.

Outcome of interest

Information on echocardiography parameters was extracted from the different echocardiography reported in the electronic health records. We selected the parameters based on the guidelines for the assessment of LVDD from the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI).[20, 21] We focused on the early mitral inflow velocity and mitral annular early diastolic velocity (E/e' ratio), left atrial volume index (LAVI), tricuspid regurgitation (TR) velocity, relative wall thickness (RWT), left ventricle mass index (LVMI), and left ventricle posterior wall thickness (LVPWT). The cut-off values considered abnormal, based on the recommendation of the ASE and EACVI, were the following: E/e' > 14, LAVI > 34 mL/m2, TR velocity > 2.8 m/s, RWT > 0.42, LVMI > 95 g/m2 in women and >115 g/m2 in men, and LVPWT > 1.2 cm.

Statistical analysis

The baseline characteristics were stratified and presented by estimated kidney function stage. Descriptive statistics were used to summarize the characteristics of the study population, and data were presented as counts and percentages (%) for categorical variables and a mean with standard deviation (SD) or median with interquartile range (IQR) for continuous variables, depending on the distribution.

We assessed the relationship between estimated kidney function, as both continuous variables and categories (with normal kidney function as the reference group), and the presence of abnormal echocardiography parameters by using linear and logistic regression analyses, respectively. We estimated odds ratios (ORs), beta (β) estimates, and their 95% confidence intervals (95% CI). Three models were applied for all analyses, namely the crude model; Model 1, adjusted for age and sex; and Model 2, adjusted for age, sex, and history of DM, hypertension, CVD, and heart failure. To ensure accurate adjustment, we accounted for variables that may affect the relationship between eGFR and LVDD, as described by previous research on the topic (e.g., age, sex, hypertension, DM, CVD, and heart failure).[11, 22, 23] We tested for interaction between kidney function and sex.

If missing values in the outcome of interest (echocardiography parameters) were present, we performed 25 imputations using the Multivariate Imputation by Chained Equations (MICE) [21] method and additionally repeated the analyses in complete cases (which only utilizes data from observations with complete information on the outcome) and available cases (which uses all available data on the outcome).

Sensitivity analyses

To assess the robustness of our findings, we conducted sensitivity analyses, repeating the analyses in patients with preserved (≥50%) and reduced (<50%) ejection fractions separately. We conducted the analyses using the three methods: complete cases, available cases, and imputed data. The results from the regression analyses presented in this manuscript are from imputed datasets. All statistical analyses were performed using R Studio (R version 4.3.0 [023-04-21 ucrt]) and the MICE package.[24, 25]

RESULTS

Baseline characteristics

We included 4022 patients (41.4% women). A total of 26% had normal kidney function, 50% had mildly decreased kidney function, 20% had moderately decreased kidney function, and 4% had severely decreased kidney function. Kidney function worsened as age increased in patients with normal kidney function, presenting a mean age of 61.8 (SD: 11.5), while those with severely decreased kidney function had a mean age of 71.0 years (SD: 12.6). Similarly, the prevalence of hypertension increased as kidney function worsened: 63% in patients with normal kidney function versus 85% in those with severely decreased kidney function. Patients with moderately decreased kidney function exhibited the highest prevalence of history of CVD and heart failure, 84% and 25%, respectively (see **Table 1**).

Regarding medication used within the cohort, metoprolol was prescribed to 40–46% of the population. When medications were classified by ATC codes, the proportion of patients using antithrombotic medication (ATC codes: B01) increased from 65% in patients with normal kidney function to 83% and 72% in patients with moderately and severely decreased kidney function, respectively. Similarly, agents acting on the renin–angiotensin system (ATC codes: C09) and diuretics (ATC codes: C03) were used by 50% and 36% and 70% and 79% of patients with normal and severely decreased kidney function, respectively. **Supplementary Tables S3** and **S4** detail the ten most frequently used medications within the cohort.

Echocardiography Parameters

The percentage of patients with abnormal echocardiography parameters was significantly higher as kidney function deteriorated. Almost 5% of the patients with normal kidney function had an E/e' (>14), and this percentage increased to 16.4% (p-value <.001) and 15.0% (p-value <.001) for those with moderate and severely decreased kidney function, respectively. Similar trends were observed for other echocardiography parameters. For instance, LAVI > 34 mL/m^2 was present in 11.4% of participants with

normal kidney function but increased to 16.3% (p-value <.001) for those with moderately decreased kidney function.

The percentage of patients with TR velocity > 2.8 m/s increased from 4.4% in patients with normal kidney function to 7.6% (p-value = 0.001) in those with mildly decreased kidney function and 16.0% in those with moderately decreased kidney function. The proportion of individuals with RWT > 0.42 and LVMI (>95 g/m2 in women or >115 g/m2 in men) also progressively increased with declining kidney function. See **Table 2** and **Figure 1**.

Association between Kidney Function and LVDD

We observed a significant inverse association between eGFR and E/e' ratio (β: −0.85 [−1.1, −0.62), LAVI (β: −1.3 [−2.1, −0.56), TR velocity (β: −0.05 [−0.07, −0.03), and LVMI (β: −3.1 [−4.3, −1.8]) in the fully adjusted model. This indicates that as eGFR decreased by one standard deviation, LAVI, TR velocity, and LVMI increased and vice versa. We did not find an association between eGFR and RWT and LVPWT (see **Table 3**). When eGFR was analysed as clinical categories, we found that as eGFR decreased, distinct LVDD patterns became evident. Patients with a mildly decreased kidney function had higher odds of an abnormal E/e' ratio (OR: 1.51 [1.13, 2.02]) compared to patients with normal kidney function. Patients with moderately decreased kidney function exhibited higher odds of an abnormal E/e' ratio (OR: 2.90 [2.08, 4.04]), LAVI (OR: 1.62 [1.13, 2.33]), TR velocity (OR: 2.31 [1.49, 3.57]), and LVMI (OR: 1.70 [1.31, 2.20]). Patients with severely decreased kidney function presented higher odds of an abnormal E/e' ratio (OR: 2.95 [1.68, 5.17]) and LVMI (OR: 2.07 [1.27, 3.38]) compared to patients with normal kidney function. (see **Figure 2**). Analyses including the interaction between kidney function and sex were not statistically significant; hence, we did not present analyses stratified by sex.

Table 1. *Baseline characteristics stratified by kidney function.*

Kidney function	***Normal***	***Mildly Decreased***	***p ****	***Moderately Decreased***	***P *****	***Severely Decreased***	***p ******	***p *******
N (%)	1050 (26)	2007 (50)		818 (20%)		147 (4%)		
Age (mean (SD)	61.83 (11.50)	66.95 (11.84)	<.001	70.71 (11.43)	<.001	71.01 (12.64)	<.001	<.001
Women (%)	437 (41.6)	850 (42.4)	.726	310 (37.9)	.114	69 (46.9)	.257	.08
HT (%)	663 (63.1)	1271 (63.3)	.951	568 (69.4)	.005	125 (85.0)	<.001	<.001
DM (%)	91 (8.7)	122 (6.1)	.009	88 (10.8)	.149	26 (17.7)	.001	<0.001
CVD (%)	722 (68.8)	1525 (76.0)	<.001	693 (84.7)	<.001	117 (79.6)	.010	<.001
eGFR (ml/min/1.73 m²), median (IQR)	96.10 (92.92, 100.23)	77.30 (69.80, 84.13)	<.001	49.01 (41.20, 55.18)	<.001	22.36 (17.77, 27.27)	<.001	<.001
Potassium (mmol/L), mean (SD)	4.11 (0.32)	4.18 (0.34)	<.001	4.32 (0.40)	<.001	4.52 (0.43)	<.001	<.001
CRP (mg/L), median (IQR)	10.40 (2.30, 51.20)	8.30 (2.20, 48.50)	.556	18.05 (3.80, 70.75)	<.001	32.85 (6.78, 106.45)	<.001	<.001
Hba1c (mmol/mol), median (IQR)	39.00 (35.15, 47.25)	40.00 (36.00, 46.00)	.197	42.00 (38.00, 50.38)	<.001	48.50 (38.62, 61.75)	.001	<.001
Albumin (g/L), mean (SD)	36.84 (6.18)	37.23 (6.12)	.346	36.01 (6.97)	.102	33.65 (6.30)	<.001	<.001
Cholesterol (mmol/L), mean (SD)	4.99 (1.39)	4.83 (1.29)	.013	4.55 (1.34)	<.001	4.55 (1.34)	.016	<.001

*Normal kidney function: eGFR ≥ 90 mL/min/1.73 m2; mildly decreased kidney function: eGFR ≥60–<90 mL/min/1.73 m2; moderately decreased kidney function: eGFR ≥30—<60 mL/min/1.73 m2; severely decreased kidney function: eGFR < 30 mL/min/1.73 m2; SD: standard deviation; IQR: interquartile range; HT: hypertension; DM: diabetes mellitus; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; HbA1c: glycated haemoglobin; CRP: C-reactive protein; * p-value reporting the comparison between normal and mildly decreased kidney function; ** p-value reporting the comparison between normal and moderately decreased kidney function; *** p-value reporting the comparison between normal and severely decreased kidney function.*

Table 2. *Proportion of patients with abnormal echocardiography parameters.*

Kidney Function	*Normal*	*Mildly decreased*	*p **	*Moderately decreased*	*p ***	*Severely decreased*	*p ****	*p *****
N	1050	2007		818		147		
E/e' > 14	50 (4.8)	179 (8.9)	<.001	134 (16.4)	<.001	22 (15.0)	<.001	<.001
LAVI > 34 mL/m²	120 (11.4)	278 (13.9)	.011	133 (16.3)	<.001	16 (10.9)	.001	<.001
TR velocity > 2.8 m/s	46 (4.4)	153 (7.6)	.001	131 (16.0)	<.001	12 (8.2)	.128	<.001
RWT > 0.42	256 (24.4)	495 (24.7)	.985	190 (23.2)	.003	41 (27.9)	.205	.004
LMVI >95 or >115 g/m²	129 (12.3)	333 (16.6)	.002	169 (20.7)	<.001	32 (21.8)	<.001	<.001
LVPWT > 1.2	57 (5.4)	96 (4.8)	.725	46 (5.6)	.005	14 (9.5)	.054	.001

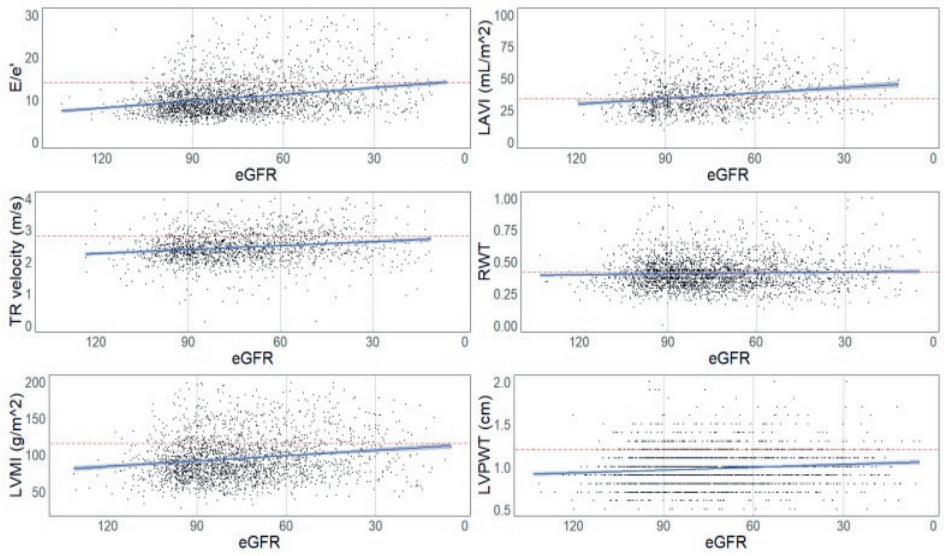
*Kidney function: Normal: eGFR ≥ 90 mL/min/1.73 m2; mildly decreased: eGFR ≥60–<90 mL/min/1.73 m2; moderately decreased: eGFR ≥30–<60 mL/min/1.73 m2; severely decreased: eGFR < 30 mL/min/1.73 m2; TR velocity: tricuspid regurgitation; LAVI: left atrial volume index; RWT: relative wall thickness; LVMI: left ventricle mass index; LVPWT: left ventricle posterior wall thickness. * p-value reporting the comparison between normal and mildly decreased kidney function; ** p-value reporting the comparison between normal and moderately decreased kidney function; *** p-value reporting the comparison between normal and severely decreased kidney function; **** p-value reporting the comparison across all categories.*

Table 3. *Association between eGFR and LVDD markers.*

eGFR	***E/e'***	***LAVI (mL/m²)***	***TR velocity (m/s)***	***RWT***	***LMVI (g/m²)***	***LVPWT (cm)***
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
	Crude					
eGFR	−1.3 (−1.5, −1.1)	−2.7 (−3.4, −1.9)	−0.08 (−0.11, −0.06)	−0.01 (−0.01, 0.00)	−5.6 (−6.9, −4.3)	−0.02 (−0.03, −0.01)
	Model 1					
eGFR	−1.1 (−1.3, −0.87)	−1.9 (−2.7, −1.1)	−0.06 (−0.09, −0.04)	0.00 (0.00, 0.01)	−4.8 (−6.1, −3.4)	−0.01 (−0.02, 0.00)
	Model 2					
eGFR	−0.85 (−1.1, −0.62)	−1.3 (−2.1, −0.56)	−0.05 (−0.07, −0.03)	0.00 (0.00, 0.01)	−3.1 (−4.3, −1.8)	−0.01 (−0.02, 0.00)

β*: estimates per changes in one standard deviation in eGFR; CI: 95% confidence interval; TR: tricuspid regurgitation; LAVI: left atrial volume index; RWT: relative wall thickness; LVMI: left ventricle mass index; LVPWT: left ventricle posterior wall thickness. Crude model; Model 1: adjusted for age and sex; Model 2: adjusted for Model 1 + history of diabetes, hypertension, cardiovascular disease, and heart failure.*

Figure 1. *Markers of LVDD at baseline scatter plot of eGFR against E/e', left atrial volume index (LAVI), tricuspid regurgitation (TR) velocity, relative wall thickness (RWT), left ventricular mass index (LVMI), and left ventricular posterior wall thickness (LVPWT).*



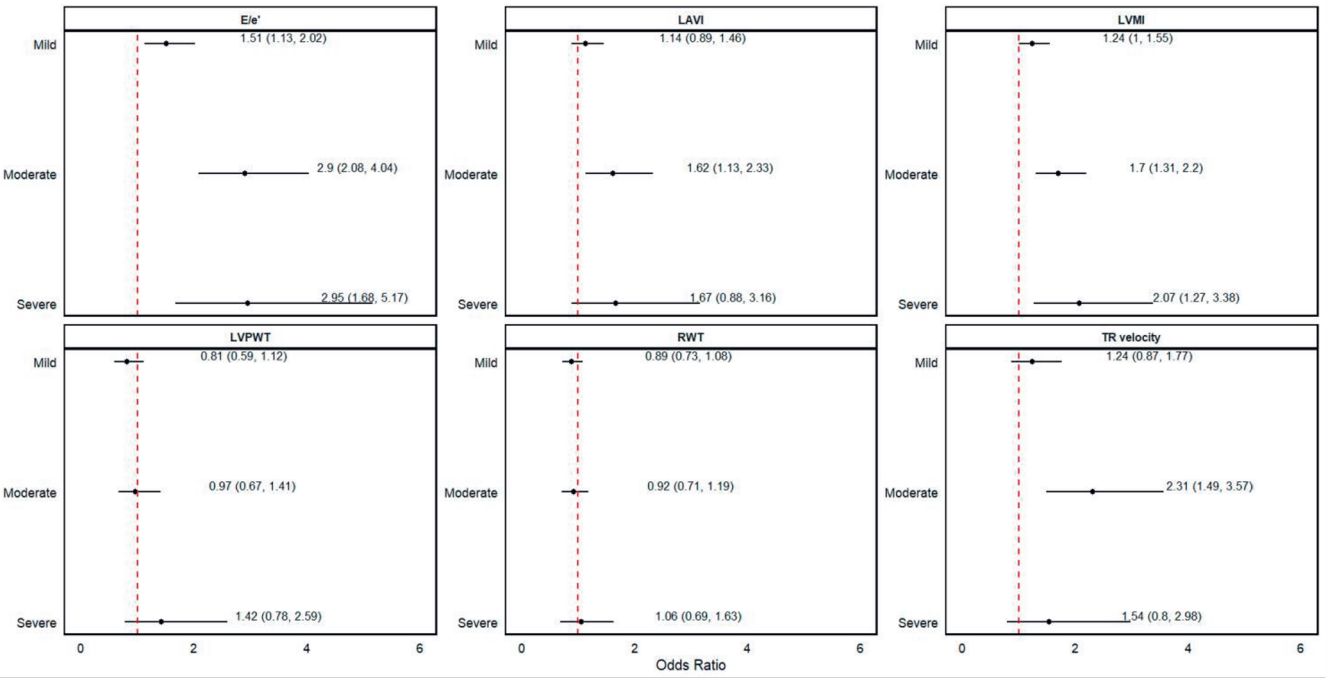
eGFR: estimated glomerular filtration rate. Blue lines: regression line. Red lines: cut-off of normal value for each parameter. Vertical lines identify the number of people in each kidney disease category: normal: eGFR ≥ 90 mL/min/1.73 m²; mildly decreased: eGFR ≥60–<90 mL/min/1.73 m²; moderately decreased: eGFR ≥30–<60 mL/min/1.73 m²; severely decreased: eGFR < 30 mL/min/1.73 m².

Sensitivity analysis

Sensitivity analysis performed in patients with preserved ejection fraction revealed an inverse association of eGFR with E/e', TR velocity, LVMI, and LVPWT, indicating that as kidney function increased, the E/e' ratio, TR velocity, LVMI, and LVPWT decreased. On the other hand, when eGFR was analysed as clinical categories, patients with moderately decreased kidney function showed a higher risk of an abnormal E/e' ratio, TR velocity, and LVMI. Similarly, patients with severely decreased kidney function showed a higher risk of an abnormal E/e' ratio and LVMI.

In patients with reduced ejection fraction, we found an inverse association of eGFR as a continuous variable with E/e' ratio, LAVI, TR velocity, and LVMI. For categories of kidney function, patients with moderately decreased kidney function presented a higher risk of an abnormal E/e', LAVI, and TR velocity, while those with severely decreased kidney function presented a higher risk of an abnormal E/e' ratio compared to patients with normal kidney function. **Supplementary Material Tables S5–S8**

Figure 2. *Reference group: normal kidney function: eGFR ≥ 90 mL/min/1.73 m^2; mild kidney function: eGFR ≥60–<90 mL/min/1.73 m^2; moderate kidney function: eGFR ≥30–<60 mL/min/1.73 m^2; severe kidney function: eGFR < 30 mL/min/1.73 m^2*



TR velocity: tricuspid regurgitation; LAVI: left atrial volume index; RWT: relative wall thickness; LVMI: left ventricle mass index; LVPWT: left ventricle posterior wall thickness. The results presented are from Model 2: adjusted for age + sex + history of diabetes mellitus, hypertension, cardiovascular disease, and heart failure. Forest plots represent the odds of E/e' > 14, LAVI > 34 mL/m2, TR velocity > 2.8 m/s, RWT > 0.42, LVMI > 95 g/m2 in women and >115 g/m2 in men, and LVPWT > 1.2 cm.

DISCUSSION

In this cross-sectional study of a large real-world data cohort of patients, we showed that as the kidney function worsened, there was a gradual increase in the presence of abnormal echocardiography parameters indicative of LVDD. Patients with mildly decreased kidney function were at a higher risk of having an abnormal E/e' ratio, while those with moderately and severely decreased kidney function had even higher risks. Furthermore, patients with moderately and severely decreased kidney function displayed a higher risk of having abnormalities in other echocardiography markers, such as LAVI, TR velocity, and LVMI, compared to those with normal kidney function. In addition, we found consistent inverse relations between eGFR and the echocardiography parameters of LVDD, indicating that as eGFR decreased, the echocardiography parameters worsened and vice versa.

Left ventricular diastolic dysfunction and kidney dysfunction commonly coexist. This has been attributed to factors such as increased left ventricle stiffness, left ventricular hypertrophy (LVH), fibrosis, and shared risk factors.[26] Additionally, as kidney function deteriorates, diastolic function further deteriorates.[10] This may be due to several factors, such as volume overload that can cause increased filling pressures, leading to cardiac remodelling and hypertrophy [9] and other factors related to kidney dysfunction, such as neurohumoral alterations, inflammation, anaemia, and mineral disorders, that are thought to lead to the development of LVDD. [10, 27] LVDD is typically more common in older individuals and those with medical conditions such as hypertension and DM.[23] These risk factors were quite prevalent in our population. We found that abnormal echocardiography parameters were significantly associated with varying stages of kidney dysfunction, even after accounting for age, sex, and comorbidities. This suggests that kidney dysfunction itself has an independent relationship with cardiac abnormalities.

In 2017, Jain et al. described a significant relationship between worsening eGFR and the degree of LVDD assessed by E/e' ratio, LVMI, and estimated right ventricular systolic pressure after adjustment for confounders in a retrospective cohort study in 2056 patients.[28] Additionally, our study showed that even in individuals with mildly decreased kidney function, there is a significantly higher risk of presenting abnormality in at least one echocardiography parameter. Furthermore, we aligned with previous research demonstrating a gradual development of abnormalities in echocardiography parameters of LVDD as kidney function deteriorates, with a more pronounced effect in patients with worse kidney function.[11, 28-31]

Kang et al. provided valuable insights into the bidirectional relationship between the heart and kidneys, demonstrating that a 1 unit increase in E/e' was associated with a 2.1% increased hazard of renal event development, suggesting that patients with LVDD

are at an increased risk of CKD progression.[22] Our study, however, highlights the reverse relationship, where reduced kidney function emerges as a significant risk factor for the development and progression of LVDD. These findings are not contradictory but rather illustrate the complex, bidirectional nature of the cardio-renal syndrome (CRS), where the heart and kidneys can both be initiators and targets of dysfunction.

We expanded on existing knowledge by assessing a wider range of echocardiographic parameters of LVDD, including TR velocity and RWT, which are useful to characterize cardiac function and structure, especially in the presence of elevated left ventricular filling pressures and hypertrophy.[20, 21] Additionally, we used a larger sample size compared to other observational studies [11, 32] and employed the new CKD-EPI 2021 formula without ethnicity, which is more accurate than the CKD-EPI 2009 and the modification of diet in renal disease (MDRD) equation, particularly for eGFR values greater than 60 mL/min/1.73 m^2.[33]

Clinical implications

The connection between LVDD and kidney dysfunction becomes more apparent as kidney disease progresses. This connection is linked to adverse cardiovascular outcomes and overall mortality, affecting around 50% of patients with an eGFR < 45 mL/min/1.73 m^2 over five years.[34, 35] Hence, assessment of diastolic function even in patients with mild kidney dysfunction is warranted. For years, the absence of specific therapies for LVDD and HFpEF might have reduced the perceived necessity for detailed diastolic function evaluation in clinical practice. The recent developments in therapeutic options for HFpEF, such as sodium–glucose cotransporters-2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists, have shifted the treatment landscape.[14,15] These agents have demonstrated substantial cardiovascular benefits, including reduction in body weight, heart failure hospitalisations, progression of kidney disease, and reduction in cardiovascular and all-cause mortality. These advancements make the evaluation of diastolic function in clinical practice increasingly important, as early identification of LVDD might serve as a first step to facilitate risk stratification for HFpEF and improve long-term prognosis. Yet, the decision to routinely assess diastolic function involves balancing clinical indications, symptoms, and the potential benefits against time and cost considerations. Future studies should explore the benefit of the early identification of LVDD in terms of impact on the prognosis.

Strengths and limitations

The main strength of this study includes its large sample size of routine care data, which provided the opportunity to evaluate multiple echocardiography parameters in a large cohort of patients at different kidney function stages. However, some limitations need to be acknowledged. Although we assessed multiple parameters, as the ASE and the

EACVI recommended, we focused on the abnormality of single echocardiography parameters. We acknowledge that a comprehensive multiparametric evaluation is ideal for a more accurate diagnostic of LVDD. However, the significant amount of missing data within the electronic health care records limited our ability to implement the algorithm proposed by Nagueh et al. [20] for the diagnostic of diastolic dysfunction. Consequently, while our findings provide valuable insights, they are limited by the inability to fully explore the broader multiparametric context of LVDD diagnosis. Second, there was a certain selection of patients who had at least a serum creatinine measurement and an echocardiography performed around the index date. Our cohort was derived from data collected in a university hospital, meaning that the findings may not be generalizable due to potential demographic differences. Third, due to the cross-sectional nature of the study, we cannot draw any conclusions about causality. Fourth, there may be potential unmeasured confounders that we have been unable to account for, such as body mass index (BMI) and smoking, which were not included in our analyses due to lack of data on BMI and smoking history in electronic care records. Finally, missing data posed a challenge, albeit mitigated through multiple imputation techniques, with no differences in the findings between complete case analysis and imputed data analysis.

CONCLUSIONS

Abnormal echocardiography parameters of LVDD are present in all patients with kidney dysfunction, even in those with mildly decreased kidney function. As kidney dysfunction worsened, more parameters were found to be abnormal, which aligns with the notion of the gradual development of LVDD in this population. Given new developments in therapeutic options for HFpEF, assessing diastolic function has become increasingly important. Therefore, clinicians should be aware that even mildly reduced kidney function is a risk factor for LVDD, and evaluation of diastolic function should be considered if patients are suspected of heart failure.

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SUPPLEMENTARY MATERIAL

Table S2: *Disease definition*

Disease	Definition
Diabetes type 1	Age of diabetes onset <40 years and Use of insulin (within 1 year of diagnosis?) ATC a10a (diabetes drugs)
Diabetes type 2	Hba1c ≥48 mmol/mol or Use of glucose-lowering medication or Atc_a10 History of diabetes in medical record (ICD-DBC codes e10-e14)
Hypertension	Blood pressure >140/90 mmHg or Use of blood-pressure lowering medication: ATC codes or Atc_c02 (antihypertensives) Atc_c03 (diuretics) Atc_c07 (beta-blockers) Atc_c08 (calcium channel blockers) Atc_c09 (Raas-inhibitors) History of hypertension in medical record (ICD_DBC codes i10-i13, i15)
Heart failure	History of heart failure in medical records ICD-DBC codes (i09.9, i25.5, i42.0, i42.5–i42.9, i43, i50)
Atherosclerotic cardiovascular disease	Medical history ICD-DBC codes: Myocardial infarction: i21-i22 Stroke/TIA: g45.0-g45.3, g45.8-g45.9, h34.1, i60, i61, i63, i64 Angina + Medication ATC code b01ac PAD: i70.2, i73.9 Carotid artery disease: i65.2 Renal artery stenosis: i70.1, q27.1 Vertebral artery stenosis AAA: i71.2 Use of antiplatelets. Atc_b01ac
Lung disease	COPD/asthma/other lung disease ICD-DBC codes: Astma: j45 COPD: i27.8, i27.9, j40–j44, j46-j47, j60–j67, j68.4, j70.1, j70.3 Use of SAMA/SABA/ICS/LABA/LAMA ATC R03 (drugs for asthma/COPD)

Table S3: *Top 10 most common medication by kidney function*

Medication	***Normal kidney function (n= 1050)***	***Mildly decreased kidney function (n= 2007)***	***Moderately decreased kidney function (n= 818)***	***Severely decreased kidney function (n= 147)***
Metoprolol (%)	40.7	42.6	45.8	45.9
Dalteparine (%)	28.3	24.8	28.0	37.8
Carbasalate calcium (%)	25.2	26.8	25.5	19.6
Furosemide (%)	24.2	29.8	49.0	67.6
Acetylsalicylic acid (%)	22.3	25.5	25.7	23.6
Perindopril (%)	18.6	20.2	24.5	22.6
Acenocoumarol (%)	18.4	22.8	34.5	27.7
Amlodipine (%)	16.3	16.5	19.6	33.8
Clopidogrel (%)	13.3	17.3	-	-
Metformine (%)	11.8	-	17.5	-
Spironolactone (%)	-	15.4	29.0	20.9
Insulin aspart (%)	-	-	-	25.7

Table S4: *Top 10 most common ATC categories by kidney function*

ATC codes	***Normal (n= 1050)***	***Mildly decreased (n= 2007)***	***Moderately decreased (n= 818)***	***Severely decreased (n= 147)***
B01: antithrombotic agents (%)	65.4	72.8	82.9	74.3
C09: agents acting on the renin-angiotensin system (%)	50.4	57.1	72.0	69.6
C03: diuretics (%)	35.7	45.5	69.4	79.1
C07: beta blocking agents (%)	50.6	56.0	62.5	59.5
C08: calcium channel blockers (%)	24.3	25.0	28.4	39.9
R03: drugs for obstructive airway diseases (%)	24.8	23.0	31.2	38.5
H02: corticoids for systemic use (%)	23.3	20.3	20.8	36.5
A10: drugs used in diabetes (%)	17.8	17.5	26.6	37.8
L04: immunosuppressants (%)	9.1	6.4	5.5	12.2
L01: antineoplastic agents (%)	5.7	3.9	3.1	6.1

Table S5: *Association between kidney function stages and LVDD markers patients with EF ≥ 50%*

	***E/e'* (> 14)**	***LAVI* (>34ml/m2)**	***TR velocity* (>2.8m/s)**	***RWT* (>0.42)**	***LMVI* (>95g/m2 or>115g/m2)***	***LVPWT* (>1.2cm)**
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Crude						
Normal	Ref	Ref	Ref	Ref	Ref	ref
Mildly decreased	1.79 (1.19, 2.69)	1.34 (1.04, 1.73)	1.41 (0.93, 2.12)	1.10 (0.90, 1.36)	1.37 (1.04, 1.80)	0.94 (0.66, 1.34)
Moderately decreased	3.78 (2.46, 5.83)	1.96 (1.35, 2.84)	3.12 (1.77, 5.50)	1.59 (1.19, 2.12)	2.08 (1.44, 3.00)	1.49 (0.97, 2.28)
Severely decreased	4.48 (2.13, 9.44)	1.62 (0.80, 3.28)	1.60 (0.59, 4.32)	1.93 (1.15, 3.25)	2.37 (1.33, 4.21)	2.42 (1.18, 4.97)
Model 1						
Normal	Ref	Ref	Ref	Ref	Ref	ref
Mildly decreased	1.34 (0.88, 2.05)	1.09 (0.83, 1.44)	1.14 (0.75, 1.71)	0.92 (0.74, 1.14)	1.16 (0.87, 1.54)	0.76 (0.52, 1.11)
Moderately decreased	2.42 (1.54, 3.81)	1.35 (0.88, 2.07)	2.20 (1.23, 3.93)	1.15 (0.85, 1.57)	1.61 (1.10, 2.35)	1.02 (0.65, 1.61)
Severely decreased	2.98 (1.34, 6.64)	1.19 (0.57, 2.51)	1.15 (0.43, 3.10)	1.50 (0.88, 2.55)	1.87 (1.02, 3.40)	1.80 (0.85, 3.80)
Model 2						
Normal	Ref	Ref	Ref	Ref	Ref	ref
Mildly decreased	1.32 (0.87, 2.03)	1.07 (0.81, 1.41)	1.13 (0.74, 1.70)	0.93 (0.75, 1.15)	1.15 (0.86, 1.53)	0.76 (0.51, 1.12)
Moderately decreased	2.22 (1.39, 3.52)	1.29 (0.83, 2.00)	2.12 (1.18, 3.78)	1.14 (0.83, 1.55)	1.49 (1.01, 2.20)	0.95 (0.60, 1.49)
Severely decreased	2.73 (1.20, 6.23)	1.23 (0.58, 2.61)	1.09 (0.39, 3.00)	1.36 (0.79, 2.32)	1.81 (0.98, 3.37)	1.61 (0.76, 3.43)

*Normal kidney function: eGFR ≥90 mL/min/1.73m^2. Mildly decreased kidney function: eGFR ≥60 - <90 mL/min/1.73m^2. Moderately decreased kidney function: eGFR ≥30 - <60 mL/min/1.73m^2. Severely decreased kidney function: eGFR<30 mL/min/1.73m^2. OR: odd ratio; CI: 95% confidence interval: TR velocity: tricuspid regurgitation; LAVI: left atrial volume index; RWT: relative wall thickness; *LVMI: left ventricle mass index > 95g/m^2 in females or >115g/m^2 in males ; LVPWT: left ventricle posterior wall thickness. F: female; M: male. Crude model. Model 1: adjusted for age and sex. Model 2: adjusted for Model 1 + history of diabetes mellitus, hypertension, cardiovascular disease, and heart failure.*

Table S6: *Association between eGFR and LVDD markers patients with EF >50%*

	E/e'	***LAVI (ml/m2)***	***TR velocity (m/s)***	***RWT***	***LVMI (g/m2)***	***LVPWT (cm)***
	B (95% ci)	B (95% ci)	B (95% ci)	B (95% ci)	B (95% ci)	B (95% ci)
Crude						
eGFR	-0.94 (-1.1, -0.74)	-1.5 (-2.3, -0.63)	-0.06 (-0.09, -0.03)	-0.02 (-0.02, -0.01)	-2.9 (-4.2, -1.7)	-0.03 (-0.04, -0.02)
Model 1						
eGFR	-0.63 (-0.83, -0.43)	-0.51 (-1.4, 0.41)	-0.03 (-0.06, 0.00)	-0.01 (-0.01, 0.00)	-1.7 (-3.0, -0.35)	-0.01 (-0.03, 0.00)
Model 2						
eGFR	-0.56 (-0.76, -0.35)	-0.44 (-1.3, 0.45)	-0.03 (-0.06, 0.00)	-0.01 (-0.01, 0.00)	-1.3 (-2.6, -0.07)	-0.01 (-0.02, 0.00)

β*: Beta estimates per changes in one-standard deviation in eGFR; CI: 95% confidence interval; eGFR mL/min/1.73m². TR velocity: tricuspid regurgitation; LAVI: left atrial volume index; RWT: relative wall thickness; LVMI: left ventricle mass index; LVPWT: left ventricle posterior wall thickness. Crude model; Model 1: adjusted for age and sex.; Model 2: adjusted for Model 1 + history of diabetes mellitus, hypertension, cardiovascular disease, and heart failure.*

Table S7: *Association between kidney function stages and LVDD markers patients with EF <50%*

	E/e' (> 14)	***LAVI (>34ml/m2)***	***TR vel (>2.8m/s)***	***RWT (>0.42)***	***LMVI (>95 or >115g/m2)****	***LVPWT (>1.2cm)***
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Crude						
Normal	Ref	Ref	Ref	Ref	Ref	ref
Mildly decreased	1.70 (1.11, 2.59)	1.41 (0.94, 2.11)	1.50 (0.89, 2.52)	0.97 (0.63, 1.47)	1.34 (0.94, 1.90)	1.02 (0.53, 1.94)
Moderately decreased	3.75 (2.42, 5.81)	2.64 (1.56, 4.47)	2.90 (1.71, 4.90)	0.91 (0.58, 1.45)	1.88 (1.25, 2.84)	1.22 (0.60, 2.50)
Severely decreased	3.08 (1.42, 6.66)	2.56 (0.94, 6.92)	2.23 (0.98, 5.09)	1.46 (0.72, 2.95)	1.95 (0.87, 4.37)	1.66 (0.54, 5.06)
Model 1						
Normal	Ref	Ref	Ref	Ref	Ref	ref
Mildly decreased	1.61 (1.05, 2.47)	1.25 (0.83, 1.89)	1.37 (0.82, 2.31)	0.82 (0.53, 1.28)	1.31 (0.92, 1.87)	0.94 (0.49, 1.82)
Moderately decreased	3.44 (2.19, 5.39)	2.17 (1.27, 3.70)	2.52 (1.48, 4.30)	0.70 (0.44, 1.12)	1.81 (1.18, 2.79)	1.08 (0.53, 2.23)
Severely decreased	2.65 (1.21, 5.82)	1.99 (0.73, 5.41)	1.87 (0.81, 4.33)	0.97 (0.47, 2.02)	1.75 (0.76, 4.03)	1.44 (0.47, 4.43)
Model 2						
Normal	Ref	Ref	Ref	Ref	Ref	ref
Mildly decreased	1.57 (1.02, 2.44)	1.18 (0.77, 1.82)	1.32 (0.78, 2.23)	0.86 (0.55, 1.36)	1.23 (0.85, 1.78)	0.95 (0.49, 1.86)
Moderately decreased	3.08 (1.93, 4.93)	1.90 (1.10, 3.29)	2.25 (1.29, 3.91)	0.80 (0.49, 1.30)	1.54 (0.98, 2.41)	1.11 (0.53, 2.32)
Severely decreased	2.52 (1.10, 5.80)	2.16 (0.76, 6.15)	1.82 (0.76, 4.36)	0.93 (0.44, 1.95)	1.81 (0.77, 4.27)	1.32 (0.43, 4.11)

*Normal kidney function: eGFR ≥90 mL/min/1.73m^2. Mildly decreased kidney function: eGFR ≥60 - <90 mL/min/1.73m^2. Moderately decreased kidney function: eGFR ≥30 - <60 mL/min/1.73m^2. Severely decreased kidney function: eGFR<30 mL/min/1.73m^2. OR: odd ratio; CI: 95% confidence interval: TR velocity: tricuspid regurgitation; LAVI: left atrial volume index; RWT: relative wall thickness; *LVMI: left ventricle mass index > 95g/m^2 in females or >115g/m^2 in males; LVPWT: left ventricle posterior wall thickness. F: female; M: male. Crude model. Model 1: adjusted for age and sex. Model 2: adjusted for Model 1 + history of diabetes mellitus, hypertension, cardiovascular disease, and heart failure.*

Table S8: *Association between eGFR and LVDD markers patients with EF <50%*

eGFR	*E/e'*	*LAVI (ml/m2)*	*TR velocity (m/s)*	*RWT*	*LMVI (g/m2)*	*LVPWT (cm)*
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Crude						
eGFR	-1.4 (-1.8, -0.92)	-2.7 (-4.0, -1.5)	-0.09 (-0.13, -0.06)	0.00 (-0.01, 0.01)	-4.8 (-7.7, -1.9)	-0.01 (-0.03, 0.00)
Model 1						
eGFR	-1.3 (-1.7, -0.77)	-2.1 (-3.4, -0.87)	-0.08 (-0.11, -0.04)	0.01 (0.00, 0.01)	-4.7 (-7.7, -1.6)	-0.01 (-0.02, 0.01)
Model 2						
eGFR	-1.1 (-1.5, -0.59)	-1.8 (-2.9, -0.57)	-0.07 (-0.11, -0.04)	0.00 (0.00, 0.01)	-3.5 (-6.4, -0.57)	-0.01 (-0.02, 0.01)

β: Beta estimates per changes in one-standard deviation in eGFR; CI: 95% confidence interval; eGFR mL/min/1.73m^2. TR velocity: tricuspid regurgitation; LAVI: left atrial volume index; RWT: relative wall thickness; LVMI: left ventricle mass index; LVPWT: left ventricle posterior wall thickness.

Crude model. Model 1: adjusted for age and sex. Model 2: adjusted for Model 1 + history of diabetes mellitus, hypertension, cardiovascular disease, and heart failure.

Chapter

7

Longitudinal Echocardiographic Parameters of Diastolic Dysfunction are Influenced by Kidney Function

A Study in Routine Clinical Practice

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ABSTRACT

Background: Left ventricular diastolic dysfunction (LVDD) is frequently observed in patients with chronic kidney disease (CKD). Nevertheless, the relationship between CKD and LVDD over time is poorly understood. This study aims to assess whether the association between CKD and LVDD varies over time.

Methods: We included outpatients from the Utrecht Patient Oriented Database, who underwent at least two echocardiographic assessments and had a measurement of kidney function. Linear-mixed effects models were used to estimate the associations of estimated glomerular filtration rate (eGFR) and echocardiography parameters.

Results: 1812 patients were included and stratified into three groups based on eGFR: >90 (491), 60–90 (923), and <60 (398). The mean age was 66.7 years, with 62.3% being male. At baseline patients with lower eGFR exhibited a higher prevalence of hypertension (62.3% vs. 55.2%) and diabetes (19.6% vs. 11.6%). Linear mixed-effects models showed that declining eGFR was significantly associated with increased E/e' ratio, left atrial volume index, tricuspid regurgitation velocity, and left ventricular mass index, with respective estimates of -0.03 ($p < .001$), -0.04 ($p = .005$), -0.00 ($p < .001$), and -0.16 ($p < .001$). The interaction between time and eGFR was not statistically significant ($p > 0.20$).

Conclusions: This study shows that declining eGFR was associated with abnormal echocardiographic parameters of LVDD that were evident early and showed relatively modest change over time, without differential trajectories across levels of kidney function.

INTRODUCTION

Left ventricular diastolic dysfunction (LVDD) characterized by impaired relaxation and stiffness of the left ventricle, represents an early and often asymptomatic stage of heart failure with preserved ejection fraction (HFpEF).[1] LVDD is commonly identified by measuring structural and functional echocardiographic parameters such as mitral annular early diastolic velocity (E/e' ratio) and left atrial volume index (LAVI) which serve to estimate left ventricular (LV) filling pressures. Additional parameters, namely tricuspid regurgitation (TR) velocity, left ventricle mass index (LVMI), and left ventricular posterior wall thickness (LVPWT) offer insight into pulmonary pressures and structural remodelling of the heart.[2-4] These parameters are integrated into diagnostic algorithms, which provide a standardized approach to identify the presence of LVDD based on a combination of threshold values and clinical context.[3]

In patients with chronic kidney disease (CKD), the prevalence of LVDD is notably high, with studies reporting the presence of LVDD any grade in more than 75% of the patient with CKD.[5,6] This coexistence is partly due to the shared pathophysiological mechanisms between kidney and cardiac dysfunction, such as volume overload, systemic inflammation, and vascular calcification, [7,8] as well as shared risk factors including cardiovascular disease (CVD), hypertension, diabetes mellitus (DM), higher age, and more common female sex.[9] With the growing prevalence of CKD and cardiovascular risk factors,[10] the global burden of cardiac and kidney dysfunction is expected to increase.[11]

Previous studies, including our own analyses, have consistently shown an elevated risk of LVDD in patients with CKD. This elevated risk is already apparent in the early stages of kidney dysfunction, and the association strengthens with more advanced kidney dysfunction.[12,13] However, most existing studies rely on cross-sectional data, which offer only a static snapshot and cannot determine whether these associations change over time. In particular, it remains unclear whether abnormalities echocardiographic parameters indicatives of LVDD in patients with CKD worsen with ongoing decline in kidney function or are established early and subsequently remain relatively stable. A few recent longitudinal studies have examined cardiac remodelling in CKD, but they often focus on specific subgroups (e.g., older adults or patients with diabetes or hypertension), rely on single echocardiographic parameters, or use dichotomous outcomes. [14-18]

To address this gap, we conducted a longitudinal study using real-world data from a large and diverse outpatient cohort. We aimed to assess whether the association between kidney function and echocardiographic parameters of LVDD changes over time. This study provides new insights into the timing and potential value of early cardiac monitoring in CKD and highlights the need to consider longitudinal patterns in risk stratification and clinical decision-making.

METHODS

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used to ensure transparent reporting (**Supplementary review material S1**).

Cohort selection

We conducted a cohort study using the Utrecht Patient Oriented Database (UPOD). The UPOD comprises prospectively collected data of all patients treated at University Medical Centre Utrecht (UMC Utrecht), including data on clinical characteristics, medication, and laboratory measurements collected as part of routine care since 2000.[19] We identified adult patients who received outpatient care at the UMC Utrecht between 2012 and 2022 and had undergone multiple echocardiographic assessments (ranging from two to ten). To minimize selection bias, we excluded patients with more than ten echocardiograms, as these likely reflect more severe disease status. Eligible patients had at least 90 days and no more than five years between successive echocardiograms, and serum creatinine measurements available within 31 days of each echocardiography. The first echocardiography was considered the index date (baseline). Patients were excluded if they had received renal replacement therapy (peritoneal dialysis, haemodialysis, or kidney transplantation) prior to enrolment or had a history of atrial fibrillation (n=41 as some parameters are not validated in this population[20]), prosthetic heart valves, or significant valvular abnormalities, including stenosis or regurgitation of the aortic (N = 280), mitral (N= 117), tricuspid (N=0), or pulmonary valves (N=1).

Study parameters

We collected data on demographics, history of hospitalisation (based on International Classification of Diseases [ICD-10] and Diagnosis Treatment Combination [DBC] codes), medication use (based on the Anatomical Therapeutic Chemical [ATC] classification system), laboratory measurements, and repeated measurements of serum creatinine and echocardiographic data. eGFR was calculated for all patients using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 creatinine formula without ethnicity,[21] and expressed in mL/min/1.73m^2. Patients were categorized into three groups: ≥90 mL/min/1.73 m^2, ≥60-<90 mL/min/1.73 m^2, and <60 mL/min/1.73 m^2. **Supplementary review material S2** contains baseline characteristics including individual with eGFR <30 mL/min/1.73 m^2.

Medical history at baseline was defined as follows: hypertension as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, documented history of antihypertensive medication use, or diagnosis of hypertension recorded in medical records. DM was defined as glycated haemoglobin (HbA1c) ≥48 mmol/mol (≥6.5%),

history of glucose-lowering medication use, or diagnosis of DM recorded in medical records, without distinction between type 1 and type 2 diabetes. The prevalence of CVD was determined based on a history of myocardial infarction (MI), stroke or transient ischemic attack (TIA), peripheral artery disease (PAD), renal artery stenosis (RAS), or abdominal aortic aneurysm (AAA), identified using ICD-10 codes recorded in medical records. History of malignancies, chronic obstructive pulmonary disease (COPD), and asthma were determined using ICD-10 codes and medication records. Heart failure (HF) was identified based on ICD-10 codes. Similarly, a history of cardiomyopathy was defined by the presence of any of the following ICD-10 codes: I42.0 (dilated cardiomyopathy), I42.1 (obstructive hypertrophic cardiomyopathy), I42.2 (other hypertrophic cardiomyopathy), I42.4 (endocardial fibroelastosis), I42.5 (other restrictive cardiomyopathy), I42.8 (other cardiomyopathies), or I42.9 (cardiomyopathy, unspecified). If no ICD codes, medication records, or relevant laboratory measurements were available for a given condition, the patient was assumed not to have the respective comorbidity. Details on the definitions of medical history can be found in **Supplementary review material S3**. Additionally, **supplementary review material S4** contains the prevalence of each cardiomyopathy categories in our cohort.

Outcome of interest

The primary outcomes were changes in echocardiographic parameters indicative of diastolic function over time. These included E/e' ratio, LAVI, TR velocity, LVMI, and LVPWT. These parameters were selected based on guideline recommendations and reflect both functional and structural aspects of LVDD. Longitudinal changes in these measures were used to evaluate the progression of LVDD and its association with kidney function across repeated echocardiographic assessments.

Statistical analysis

Continuous variables were summarized using means (± standard deviation [SD]) or medians (interquartile range [IQR]) depending on the distribution, and categorical variables as frequencies and percentages. To observe changes in echocardiographic parameters by eGFR groups, we calculated the change (Δ: delta) in mean or median values of each parameter relative to the first echocardiographic assessment. This analysis was restricted to the first five echocardiographic timepoints to ensure sufficient sample size and comparability across follow-up intervals.

To assess the longitudinal association between eGFR and echocardiographic parameters over time, we used linear mixed-effects regression models incorporating repeated measurements of E/e', LAVI, TR velocity, LVMI, and LVPWT from consecutive echocardiographic of the same individuals. We entered covariates assumed to have a potential prognostic impact into the model, including age, sex, history of hypertension,

DM, CVD, and history of any cardiomyopathy. Separate models were constructed for each echocardiographic parameter.

Time was modelled as a continuous variable in all analyses. We compared models with random intercepts only to models including both random intercepts and random slopes for time. The random intercept only model demonstrated best fit based on a lower Akaike Information Criterion (AIC) and was therefore selected. Random intercepts were specified for each participant to account for within-subject variability arising from repeated measurements. This approach accounts for correlation among repeated measurements, allowing observations from the same individual to share a common subject-specific intercept.

To evaluate whether longitudinal trajectories of echocardiographic parameters differed by kidney function, we included main effects of eGFR and interaction terms between eGFR and time. Subgroup analyses stratified by sex were performed to explore potential differences in associations between male and female patients.

We did not perform imputation for missing echocardiographic outcomes, as linear mixed-effects models are well-suited for handling unbalanced data and can accommodate missing values.[22] Additionally, there is evidence that multiple imputation of missing data before linear mixed effect model analysis does not increase precision in the estimates rated of change.[23]

Sensitivity analyses

To assess the robustness and consistency of our results, we conducted sensitivity analyses using both linear and logistic regression models. We conducted linear regression analyses to examine the relationship between kidney function and each parameter at multiple timepoints. These models used eGFR as continuous variable, with adjustment for the same covariates as in the primary analysis. Additionally, we calculate the change (Δ) between estimates at each echocardiography with respect to the baseline (1st echocardiography) to estimate temporal changes. To further explore potential effect modification, we repeated the longitudinal regression analyses, estimating changes in echocardiography across eGFR categories.

In addition, we conducted logistic regression analyses to evaluate the odds of clinically relevant echocardiographic abnormalities across eGFR categories. We applied the thresholds defined in the guidelines (E/e' ratio >14, LAVI >34 mL/m², TR velocity >2.8 m/s, LVMI >115 g/m² for men and >95 g/m² for women, and LVPWT >1.2 cm).[3,4] Odds ratios (ORs) and 95% confidence intervals were calculated for each eGFR category, with the >90 mL/min/1.73m² group serving as the reference.

Finally, as an additional sensitivity analysis, we fitted linear mixed-effects models with eGFR entered as a categorical variable (>90, 60–89, and <60 mL/min/1.73 m²) to assess

consistency with the primary mixed-effects analyses in which eGFR was modelled as a continuous variable.

All statistical analyses were performed using RStudio: R Core Team (2024). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.[24]

RESULTS

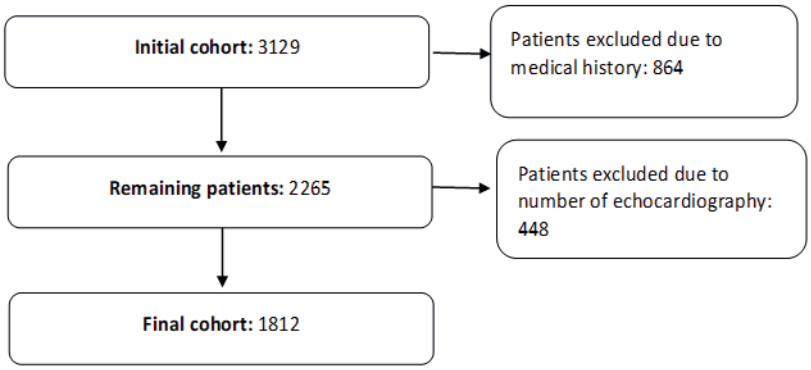
Baseline characteristics

The initial cohort consisted of 3129 patients. After excluding 1317 patients due to history of HF, atrial fibrillation, or valvular heart disease, or because had only one or more than 10 echocardiography assessments (**Figure 1**), our final cohort comprised 1812 patients (62.3% males) with a total of 5653 echocardiograms.

Patients were categorized according to eGFR into three groups: >90 (n=491), 60-90 (n=923), and <60 (n=398). Patients with lower eGFR were older (mean age 71.1 years in the <60 group vs. 62.7 years in the >90 group) and had a higher prevalence of hypertension (62.3% vs. 55.2%) and DM (19.6% vs. 11.6%). CVD was common across all groups, with a slightly lower prevalence in the lowest eGFR category (47.0%). Other comorbidities such as lung disease, autoimmune conditions, and malignancy were more frequent in patients with preserved kidney function.

Laboratory markers showed expected trends, patients with lower eGFR had higher C-reactive protein (PCR) and potassium levels, and lower haemoglobin levels. Baseline characteristics of the study population are presented in **Table 1**.

Figure 1. *cohort selection*



Medication use at baseline also varied by kidney function. Antithrombotic agents were the most prescribed across all groups, used by approximately one-third of patients. Diuretic use increased with declining kidney function, from 9.2% in the >90 group to 17.1% in the eGFR <60 group. Similarly, the use of renin-angiotensin system (RAS) agents was slightly more frequent in patients with reduced kidney function (12.1% in the <60 group vs. 10.8% in the >90 group). Beta-blockers and calcium channel blockers were used at similar rates across groups, while antihypertensive drugs were rarely prescribed overall. **Supplementary review material S5** present the cardiovascular medication at baseline.

Echocardiography parameters over time

The median number of echocardiography was 2 (IQR: 2). Echocardiographic parameters were not available for all examinations, reflecting routine clinical practice. Across all 5653 echocardiograms, the proportion of missing values varied by parameter, with missingness of 35.0% for E/e' ratio, 63.2% for LAVI, 56.3% for TR velocity, 39.4% for LVMI, and 32.9% for LVPWT.

At baseline, echocardiographic parameters indicative of LVDD were progressively worse with declining kidney function. The median E/e' ratio increased from 8.81 [IQR: 7.04 - 11.38] in the >90 group to 10.99 [8.53 - 15.43] in the <60 group. Similarly, LVMI rose from 87.04 [73.55 - 106.94] g/m² to 98.54 [82.65 - 128.24] g/m², and TR velocity increased from 2.36 ± 0.41 m/s to 2.63 ± 0.51 m/s.

Longitudinal changes in these parameters, across eGFR categories, were modest and variable. E/e' ratio fluctuated slightly across follow-up assessments, with no consistent trend. In the <60 eGFR group, E/e' increased by 2.76 units at the fifth echocardiogram compared to baseline, but intermediate timepoints showed mixed changes. For LAVI, while patients with lower eGFR had higher baseline values, the most pronounced increase over time was observed in the >90 eGFR group at the third and fourth assessments. LVMI tended to decrease over time in the >90 and 60-89 groups, while remaining relatively stable or increasing slightly in the <60 group. TR velocity and LVPWT showed minimal changes across timepoints. **Table 2** present complete results of echocardiographic parameters at baseline and the changes in the subsequent measurements.

Figure 2 illustrates the crude trajectories of echocardiographic parameters over the 10-year follow-up. Patients with lower eGFR exhibited worse diastolic function already at baseline compared with those with preserved kidney function. Importantly, the magnitude of change over time was small, and trajectories across eGFR categories were parallel, indicating that echocardiographic abnormalities are established early and subsequently show a plateauing pattern. Shaded areas represent 95% confidence intervals.

Linear Mixed Model analysis

Linear mixed effect models showed that declining eGFR was significantly associated with increased E/e' ratio, LAVI, TR velocity, and LVMI, with estimates of -0.03 (p<.001), -0.04 (p=.005), -0.00 (p<.001), and -0.16 (p<.001) respectively, meaning that as eGFR was lower the parameter increased.

These associations although small, remained after adjusting for age, sex, DM, hypertension, CVD, and cardiomyopathy. Importantly, the interaction term between time and eGFR was not statistically significant for any of the echocardiographic parameters, indicating that the association of kidney function on LVDD markers remained consistent throughout the follow-up period. **Table 3**.

Other covariates also showed independent associations. Age was consistently associated with worsening echocardiographic parameters. Each additional year of age was linked to higher E/e' (0.09, p<.001), LAVI (0.28, p<.001), TR velocity (0.01, p<.001), LVMI (0.45, p<.001), and LVPWT (0.00, p<.001). Male sex was associated with lower E/e' ratio (-1.38, p<.001), but higher LVMI (9.90, p<.001) and LVPWT (0.06, p<.001).

Furthermore, the presence of DM was significantly associated with higher E/e' ratio (1.53, p<.001) and LVPWT (0.04, p<.001), but with lower LAVI (-2.39, p=.019). Lastly, cardiomyopathy showed the most pronounced associations, with significantly elevated E/e' ratio (2.43, p<.001), LAVI (3.86, p=.010), LVMI (22.36, p<.001), and LVPWT (0.11, p<.001). **Table 3**.

Sex-stratified analyses showed consistent directions of association for both women and men (**Supplementary review material S6 and S7**).

Table 1. *Baseline characteristics.*

	Overall	***eGFR >90***	***eGFR 60-89***	***eGFR <60***
N (%)	1812	491 (27.1%)	923 (50.9%)	398 (22%)
Age (mean (SD))	66.79 (11.62)	62.70 (11.91)	67.09 (11.00)	71.11 (10.96)
Male (%)	1128 (62.3)	301 (61.3)	571 (61.9)	256 (64.3)
Hypertension (%)	1076 (59.4)	271 (55.2)	557 (60.3)	248 (62.3)
Diabetes (%)	271 (15.0)	57 (11.6)	136 (14.7)	78 (19.6)
CVD (%)	903 (49.8)	248 (50.5)	468 (50.7)	187 (47.0)
Lung disease (%)	187 (10.3)	65 (13.2)	88 (9.5)	34 (8.5)
Cardiomyopathy (%)	86 (4.7)	26 (5.3)	42 (4.6)	18 (4.5)
Autoimmune disease	143 (7.9)	47 (9.6)	72 (7.8)	24 (6.0)
Malignancy (%)	93 (5.1)	28 (5.7)	48 (5.2)	17 (4.3)
eGFR (ml/min/1.73/m^2), (median [IQR])	79.13 [63.27, 91.02]	95.69 [92.75, 99.88]	77.78 [69.80, 83.94]	47.40 [36.89, 55.35]
Potassium (mmol/L), (mean (SD))	4.20 (0.33)	4.14 (0.31)	4.18 (0.31)	4.33 (0.36)
CRP (mg/L), (median [IQR])	14.70 [2.50, 60.00]	12.00 [2.60, 59.60]	12.80 [2.10, 56.05]	22.20 [4.70, 70.35]
Hb (mmol/L), (mean (SD))	8.14 (1.22)	8.28 (1.19)	8.26 (1.20)	7.70 (1.20)
HbA1c (mmol/mol), (median [IQR])	41.00 [37.00, 50.00]	39.00 [36.00, 45.00]	41.00 [37.00, 51.00]	43.00 [39.00, 54.60]
Cholesterol (mmol/L), (mean (SD))	4.67 (1.29)	4.73 (1.33)	4.72 (1.26)	4.47 (1.28)
HDL (mmol/L), (median [IQR])	1.20 [1.00, 1.50]	1.20 [1.00, 1.50]	1.20 [1.00, 1.50]	1.10 [0.90, 1.40]
LDL (mmol/L), (median [IQR])	2.40 [1.80, 3.20]	2.40 [1.80, 3.30]	2.50 [1.90, 3.20]	2.20 [1.60, 2.80]
Triglycerides (mmol/L), (median [IQR])	1.60 [1.20, 2.20]	1.50 [1.10, 2.10]	1.60 [1.20, 2.30]	1.70 [1.20, 2.40]

CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; Hb: haemoglobin; HbA1c: glycated haemoglobin; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein.

Sensitivity analyses

In fully adjusted linear regression, eGFR was significantly associated with higher E/e' at baseline, but the association weakened over time, with no significant differences observed at later echocardiograms. For LAVI, a significant increase was observed at the third echocardiogram, but the direction and magnitude of association varied across time points. LVMI showed a significant inverse association with eGFR at baseline but at the third follow-up, the association became positive. When analyses were stratified by kidney function categories, the group with eGFR <60 exhibited more pronounced and persistent adverse changes in echocardiographic measures.

Logistic regression analyses further supported these findings.

In fully adjusted models, participants with eGFR <60 had significantly higher odds of abnormal E/e' ratio, LAVI and TR velocity. The likelihood of having an elevated LVMI was highest at baseline and the second echocardiogram in the eGFR <60. No significant associations were observed for increased LVPWT over time.

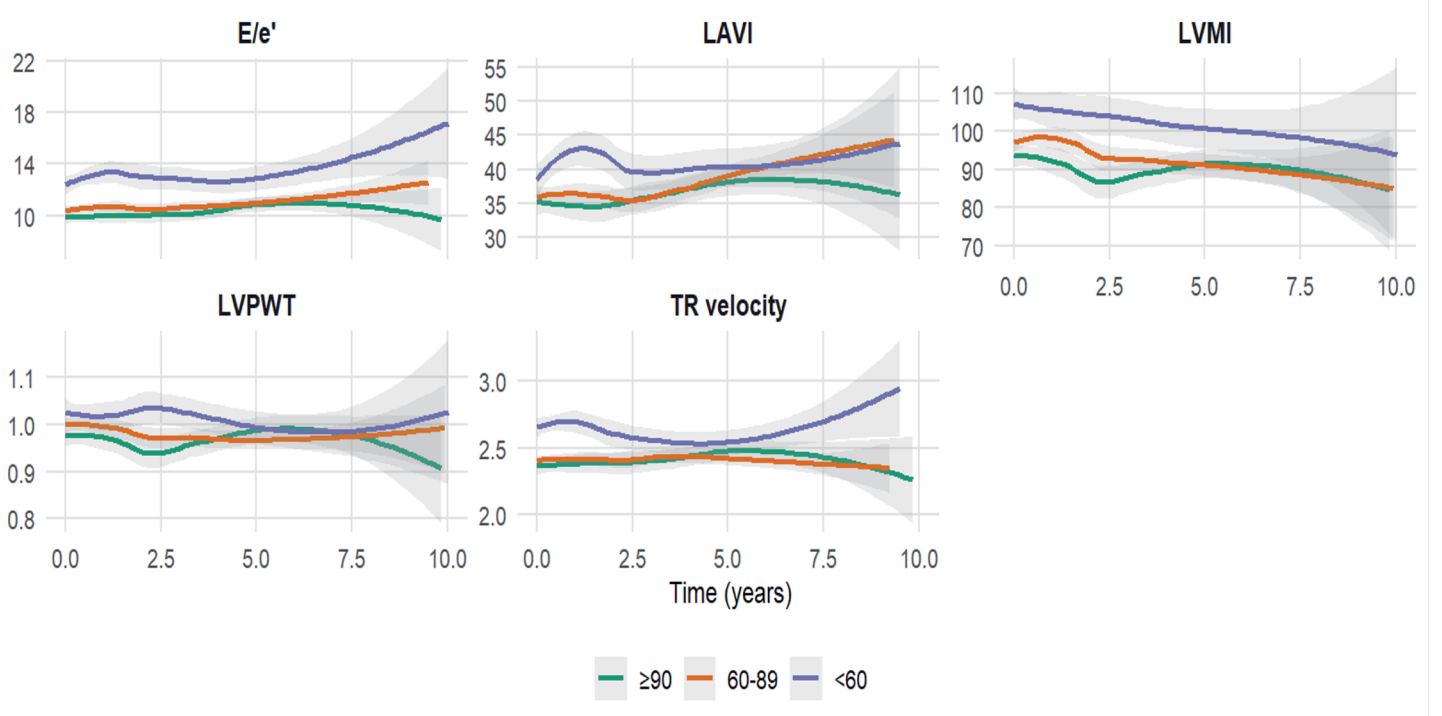
Mixed-effects models using categorical eGFR yielded results consistent with the primary analyses, with worse echocardiographic parameters observed in lower eGFR categories and no significant interaction between time and eGFR category. See complete results in **Supplementary review material S8-S11**.

Table 2. *Change in mean or median values of each parameter relative to the first echocardiographic assessment.*

eGFR	*Mean/median 1st echo*	*Δ 2nd echo*	*Δ 3rd echo*	*Δ 4th echo*	*Δ 5th echo*
	E/e' (change in median and IQR)				
>90	8.81 [7.04-11.38]	-0.05 [-1.65-1.68]	0.83 [-1.45-2.65]	0.39 [-0.99-2.26]	-0.61 [-1.86-0.89]
60-90	9.44 [7.55-12.19]	0.14 [-1.65-2.15]	0.46 [-1.19-2.29]	0.44 [-2.23-2.43]	1.16 [-0.88-3.97]
<60	10.99 [8.53-15.43]	0.06 [-2.07-2.76]	-0.95 [-2.80-2.35]	-0.09 [-2.66-3.42]	2.76 [-0.54-5.70]
	LAVI (change in mean and SD)				
>90	34.78 ± 12.99	1.50 ± 9.69	6.94 ± 10.12	7.47 ± 14.33	2.03 ± 12.52
60-90	35.52 ± 11.81	1.08 ± 10.75	1.97 ± 13.51	4.55 ± 12.37	3.04 ± 9.81
<60	38.65 ± 12.57	1.41 ± 12.70	2.23 ± 14.07	2.08 ± 16.42	-3.38 ± 10.83
	TR velocity (change in mean and SD)				
>90	2.36 ± 0.41	0.03 ± 0.48	0.05 ± 0.40	0.10 ± 0.50	0.02 ± 0.60
60-90	2.41 ± 0.40	0.01 ± 0.41	0.05 ± 0.44	0.05 ± 0.49	-0.00 ± 0.40
<60	2.63 ± 0.51	0.02 ± 0.50	0.02 ± 0.52	0.02 ± 0.43	-0.12 ± 0.53
	LVMI (change in median and IQR)				
>90	87.04 [73.55-106.94]	-0.23 [-14.07-12.93]	-1.17 [-22.09-9.90]	-2.04 [-20.56-7.51]	-7.95 [-20.00-11.86]
60-90	93.40 [77.15-109.80]	-4.10 [-17.33-11.26]	-3.50 [-14.98-13.12]	-7.80 [-20.91-11.23]	-10.07 [-28.58-5.58]
<60	98.54 [82.65-128.24]	-2.70 [-18.32-18.37]	-1.06 [-17.77-16.55]	-11.04 [-24.59-8.17]	4.24 [-25.22-11.03]
>90	0.98 ± 0.22	0.00 ± 0.22	-0.04 ± 0.21	-0.05 ± 0.23	0.03 ± 0.26
60-90	1.00 ± 0.20	-0.00 ± 0.22	-0.01 ± 0.22	-0.04 ± 0.20	-0.01 ± 0.23
<60	1.03 ± 0.23	-0.03 ± 0.23	-0.05 ± 0.23	-0.01 ± 0.29	-0.02 ± 0.25

eGFR: estimate glomerular filtration rate; Δ delta: change with respect to first echocardiography; IQR: interquartile range; SD: standard deviation; LAVI: left atrial volume index; TR velocity: tricuspid regurgitation velocity; LVMI: left ventricle mass index; LVPWT: left ventricle posterior wall thickness

Figure 2. *Trajectories of echocardiographic parameters over 10 years by eGFR category.*



Patients with eGFR <60 mL/min/1.73 m² (purple line) consistently showed worse diastolic function compared to those with preserved kidney function (green line). The trajectories for each eGFR category were nearly parallel, suggesting that the relationship between kidney function and LVDD markers did not change over time.

Table 3. *Linear mixed-effect models*

	E/e'		***LAVI***		***TR velocity***		***LVMI***		***LVPWT***	
Variable	*Estimates (CI)*	*p*	*Estimates (CI)*	*p*	*Estimates (CI)*	*p*	*Estimates (CI)*	*p*	*Estimates (CI)*	*p*
Intercept	7.84 (6.16, 9.52)	<.001	20.53 (14.47, 26.58)	<.001	2.23 (2.03, 2.42)	<.001	74.04 (63.64, 84.43)	<.001	0.75 (0.68, 0.82)	<.001
Time-y	0.00 (-0.01, 0.02)	.488	0.02 (-0.04, 0.07)	.553	-0.00 (-0.00, 0.00)	.439	-0.13 (-0.22, -0.04)	.004	-0.01 (-0.00, 0.00)	.185
eGFR	-0.03 (-0.04, -0.02)	<.001	-0.04 (-0.08, -0.01)	.050	-0.00 (0.00, -0.00)	<.001	-0.16 (-0.23, -0.09)	<.001	-0.00 (-0.00, 0.00)	.395
Age-y	0.09 (0.07, 0.11)	<.001	0.28 (0.21, 0.35)	<.001	0.01 (0.00, 0.01)	<.001	0.45 (0.33, 0.57)	<.001	0.00 (0.00, 0.00)	<.001
Males	-1.38 (-1.81, -0.95)	<.001	1.43 (-0.01, 2.86)	.052	-0.05 (-0.09, 0.00)	.055	9.90 (7.20, 12.60)	<.001	0.06 (0.04, 0.08)	<.001
DM	1.53 (0.96, 2.11)	<.001	-2.38 (-4.38, -0.38)	.019	0.04 (-0.03, 0.11)	.290	0.92 (-2.79, 4.64)	.626	0.04 (0.02, 0.07)	<.001
HT	0.12 (-0.22, 0.46)	.482	-0.85 (-2.06, 0.36)	.167	-0.00 (-0.04, 0.04)	.881	0.76 (-1.37, 2.88)	.486	0.02 (0.01 – 0.04)	.003
CVD	-0.31 (-0.68, 0.06)	.104	-0.81 (-2.13, 0.50)	.226	-0.02 (-0.07, 0.02)	.314	-3.14 (-5.49, -0.78)	.009	-0.01 (-0.03, 0.00)	.166
CMP	2.43 (1.44, 3.41)	<.001	3.86 (0.92, 6.80)	.010	-0.01 (-0.12, 0.09)	.782	22.36 (16.52, 28.21)	<.001	0.11 (0.08, 0.15)	<.001
*Time*eGFR*	-0.00 (-0.01, 0.00)	.794	-0.00 (-0.02, 0.02)	.668	0.00 (-0.00, 0.00)	.208	0.00 (-0.00, 0.06)	.203	0.00 (-0.00, 0.00)	0.359

eGFR: *estimate glomerular filtration rate (mL/min/1.73/m2); Δ delta: change with respect to first echocardiography; IQR: interquartile range; SD: standard deviation; LAVI: left atrial volume index; TR velocity: tricuspid regurgitation velocity; LVMI: left ventricle mass index; LVPWT: left ventricle posterior wall thickness; DM: diabetes mellitus, CVD: cardiovascular disease; CMP: cardiomyopathy; HT: hypertension.*

DISCUSSION

In this longitudinal study, including data over a 10-year time span of 1812 patients, we showed that a lower eGFR was associated with higher E/e' ratio, LAVI, TR velocity, LVMI values. Notably, the interaction between time and eGFR was not statistically significant, suggesting that in patients with CKD, abnormalities in echocardiographic parameters indicative of LVDD is established early and subsequently follow a relatively stable trajectory.

Diastolic function is typically assessed using a combination of echocardiographic parameters. In this study, we examined these parameters individually and found that, for example, the E/e' ratio was a consistent marker of impaired diastolic function in patients with declining kidney function. Specifically, for every 10 mL/min/1.73 m² decrease in eGFR, E/e' increases by approximately 0.3 units. While this change may appear modest, it reflects a measurable shift in cardiac function. For example, in a 56-year-old female patient with diabetes and hypertension, the predicted E/e' increases from 12.73 to 13.03 when eGFR declines from 60 to 50 mL/min/1.73 m². Although this change alone may not be clinically decisive, it contributes to a broader pattern of cardiac remodelling. Other parameters, such as LAVI and TR velocity, also showed robust associations with lower eGFR, suggesting early atrial remodelling and increased pulmonary pressures. In contrast, LVMI increased more modest and LVPWT showed minimal change. Together, these trends indicate that E/e', LAVI, and TR velocity may serve as sensitive indicators of early cardiac remodelling in CKD, and their combined interpretation may offer clinical value in identifying patients at risk.

Several pathophysiological mechanisms may explain these observations. Hemodynamic factors likely play a central role, including hypertension, chronic volume overload, and increased arterial stiffness, which are common in CKD and contribute to elevated filling pressures, left atrial enlargement, and pulmonary hypertension.[32] In addition, activation of the renin-angiotensin-aldosterone system (RAAS) promotes myocardial fibrosis and impaired relaxation, even in earlier stages of kidney dysfunction. Beyond hemodynamic stressors, metabolic and systemic factors characteristic of CKD, such as anaemia, inflammation, oxidative stress, and accumulation of uremic toxins, may further impair myocardial relaxation and increase ventricular stiffness. The combined influence of these mechanisms may contribute to the early development of LVDD-related abnormalities, after which additional progression becomes less pronounced.

Our findings are consistent with previous follow-up studies showing that reduced eGFR contributes to the risk of HF, kidney events, cardiovascular and all-cause mortality.[19,25,26] However, this study differs in several important aspects. First, the study population reflects real-world clinical practice and consisted of patients drawn from routine outpatient care. Thus, we analysed a more heterogeneous population than prior studies

such as Buckley et al.[25] and Hallan et al.,[26] which focused on older adults or patients with DM and hypertension. Another key distinction of our study is the inclusion of multiple echocardiographic parameters of LVDD as continuous measures rather than looking at dichotomous events, which provide a better view of cardiac remodelling. The use of hospital data, which provide access to detailed and accurate medical records, contrasts with community-based studies that often rely on self-reported data. This allows the external validity of our findings, making them applicable to everyday clinical settings. However, it also introduces challenges inherent to real-world data, such as variability in measurement timing, missing data, and indication bias.[27] For example, patients undergoing repeated echocardiography may represent a higher-risk subgroup with more severe disease or more intensive monitoring. We attempted to mitigate this by excluding patients with HF, significant valvular disease, and those receiving renal replacement therapy, but residual bias may remain.

A key novel finding of our study is the temporal stability of the association between kidney function and LVDD. Specifically, the absence of a statistically significant interaction between time and eGFR indicates that patients with impaired kidney function exhibit echocardiographic abnormalities early, which persist with relatively modest change over the duration of follow-up.

These findings highlight the potential value of early monitoring of diastolic function in patients with CKD, as the association between kidney function and echocardiographic markers of LVDD remains largely consistent over time. This temporal stability suggests that myocardial remodelling associated with CKD may follow a plateau trajectory, where early structural and functional alterations persist without proportional worsening as kidney function further declines.[28,29]

Potential explanations include compensatory physiological mechanisms and the stabilizing effects of standard treatments, such as antihypertensive therapy, RAAS inhibitors, glucose-lowering agents, and lifestyle interventions. However, in this study we did not account for treatment effects, and we acknowledge that medication use and adherence may play a role in modulating cardiac outcomes. Future studies incorporating time-varying pharmacological data are needed to understand how therapeutic strategies influence the trajectory of LVDD in CKD populations.

Strengths and limitations

This study has several strengths. First, the use of real-world data allowed a long follow-up period of approximately 10 years and the inclusion of a large, clinically diverse patient population. This resulted in over 5000 echocardiographic assessments, providing a rich dataset for longitudinal assessment. Second, unlike previous studies that focussed primarily on the E/e', we examined multiple parameters, including LAVI, TR velocity, LVMI and LVPWT, offering a better understanding of the structural and functional

changes associated with declining kidney function. Third, although the diagnosis of LVDD typically relies on a combination of echocardiographic abnormalities, we deliberately analysed each parameter individually. This approach allowed us to identify which specific aspects of diastolic structure and function were most sensitive to changes in kidney function over time.

Nonetheless, some limitations must be acknowledged. First, echocardiographic parameters, particularly LAVI and TR velocity, had a substantial proportion of missing values. This reflects variability in routine echocardiographic acquisition rather than selective exclusion. While linear mixed-effects models are robust to unbalanced data, missingness may still have reduced precision for some estimates. Second, the small number of patients with advanced CKD (eGFR <30 mL/min/1.73m²) limits our ability to draw conclusions about this group of patients. Third, the definition of cardiomyopathy in our study was based on ICD-10 codes within category I42, except for subtypes I42.3 (endomyocardial disease, eosinophilic) and I42.7 (cardiomyopathy due to alcohol). Due to small sample size, we could not test the impact of each specific cardiomyopathy subtypes in our outcomes. Thus, we group all patients with any ICD-10 code I42 to adjust for the presence or absence of cardiomyopathy in our analyses. While this approach ensured consistency and statistical feasibility, it may have masked subtype specific effects.

Fourth, defining an 'index date' in observational data remains challenging, as disease progression cannot be precisely determined. For example, medication use was described at baseline, and we did not adjust for individual drug classes in the regression models. Medication exposure was incorporated into the definition of key comorbidities such as hypertension, diabetes, and cardiovascular disease. Additional adjustment for medication may therefore result in overadjustment or collinearity, particularly given the absence of longitudinal treatment data.

Finally, indication and survivor bias should be considered. Patients who undergo repeated echocardiography assessment may represent a subgroup at higher risk and may receive more frequent and detailed evaluation that could influence observed associations. At the same time, patients with more advanced CKD or more severe cardiovascular disease may have been less likely to survive, which could lead to an underestimation of longitudinal progression in LVDD.

We attempted to mitigate these sources of bias by excluding patients with established HF, valvular disease, and those with history renal replacement therapy. Future studies incorporating information on the indications for echocardiography and survival status could help to understand the impact of these biases on longitudinal echocardiographic assessment in CKD populations.

CONCLUSION

LVDD is a well-established predictor of major adverse cardiac events and mortality, particularly among individuals with CKD. In this longitudinal study, lower kidney function was associated with worse echocardiographic parameters indicative of LVDD, with these abnormalities already evident at earlier stages of CKD and exhibiting relatively modest change over time. The absence of differential trajectories across kidney function groups suggests a pattern of early myocardial remodelling followed by relative stability during follow-up.

These findings highlight the potential value of early echocardiographic assessment in patients with impaired kidney function to identify subclinical cardiac remodelling and support cardiovascular risk stratification. While current CKD guidelines do not recommend routine screening for LVDD, future studies evaluating the prognostic and therapeutic implications of early LVDD detection are needed to determine whether systematic cardiac evaluation should be considered in this population.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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SUPPLEMENTARY MATERIAL

Table S1: *Disease definition*

Disease	Definition
Diabetes type 1	Age of diabetes onset <40 years AND Use of insulin (within 1 year of diagnosis?) ATC A10A (Diabetes drugs)
Diabetes type 2	HbA1C ≥48 mmol/mol OR Use of glucose-lowering medication OR ATC_A10 History of diabetes in medical record (ICD-DBC codes E10-E14)
Hypertension	Blood pressure >140/90 mmHg OR Use of blood-pressure lowering medication: ATC codes OR ATC C02 (antihypertensives) ATC C03 (diuretics) ATC C07 (beta-blockers) ATC C08 (calcium channel blockers) ATC C09 (RAAS-inhibitors) History of hypertension in medical record (ICD-DBC codes I10-I13, I15)
Heart failure	History of heart failure in medical records ICD-DBC codes (I50)
Cardiomyopathy	History of cardiomyopathy in medical records ICD-DBC codes (I42)
Atherosclerotic cardiovascular disease	Medical history ICD-DBC codes: Myocardial infarction: I21-I22 Stroke/TIA: G45.0-G45.3, G45.8-G45.9, H34.1, I60, I61, I63, I64 Angina + medication ATC_B01AC PAD: I70.2, I73.9 Carotid artery disease: I65.2 Renal artery stenosis: I70.1, Q27.1 Vertebral artery stenosis AAA: I71.2 Use of antiplatelets ATC_B01AC
Lung disease	COPD/asthma/other lung disease ICD-DBC codes: Astma: J45 COPD: I27.8, I27.9, J40–J44, J46-J47, J60–J67, J68.4, J70.1, J70.3 Use of SAMA/SABA/ICS/LABA/LAMA ATC R03 (drugs for asthma/COPD)

Table S2: *Linear mixed effect model results in women (n=684)*

Variable	*E/e' , B (95% CI)*	*p*	*LAVI, B (95% CI)*	*p*	*TR, B (95% CI)*	*p*	*LVMI, B (95% CI)*	*p*	*LVPWT, B (95% CI)*	*p*
Interc	6.61 (3.92 – 9.29)	<.001	21.58 (12.50 – 30.67)	<.001	2.33 (2.05 – 2.62)	<.001	69.70 (54.35 – 85.06)	<.001	0.72 (0.63 – 0.82)	<.001
Time (y)	-0.01 (-0.03 – 0.01)	.267	-0.02 (-0.11 – 0.06)	.606	0.00 (-0.00 – 0.00)	.562	-0.09 (-0.24 – 0.05)	.213	-0.00 (-0.00 – 0.00)	.712
eGFR	-0.03 (-0.05 – -0.01)	.001	-0.06 (-0.12 – 0.01)	.103	-0.00 (-0.01 – -0.00)	<.001	-0.10 (-0.21 – 0.01)	.076	-0.00 (-0.00 – -0.00)	.602
Age (y)	0.11 (0.08 – 0.14)	<.001	0.29 (0.19 – 0.39)	<.001	0.01 (0.00 – 0.01)	<.001	0.45 (0.28 – 0.61)	<.001	0.00 (0.00 – 0.00)	<.001
DM	1.69 (0.63 – 2.75)	.002	-2.47 (-5.92 – 0.99)	.162	0.13 (0.01 – 0.25)	.039	0.23 (-6.18 – 6.64)	.944	0.06 (0.02 – 0.10)	.003
HT	0.48 (-0.10 – 1.05)	.105	-0.93 (-2.87 – 1.01)	.346	0.03 (-0.09 – 0.04)	.397	1.25 (-2.08 – 4.58)	.462	0.04 (0.02 – 0.06)	.001
CVD	-0.45 (-1.09 – 0.19)	.166	-1.03 (-3.21 – 1.16)	.356	-0.01 (-0.08 – 0.06)	.724	-1.84 (-5.69 – 2.01)	.349	0.00 (-0.02 – 0.03)	.724
CMP	2.72 (1.06 – 4.39)	.001	0.13 (-4.43 – 4.70)	.954	-0.01 (-0.17 – 0.15)	.939	14.57 (5.54 – 23.60)	.002	0.07 (0.02 – 0.13)	.008
T ×eGFR	0.00 (-0.00 – 0.00)	.137	0.00 (-0.00 – 0.00)	.672	0.00 (-0.00 – 0.00)	.361	0.00 (-0.00 – 0.00)	.853	0.00 (-0.00 – 0.00)	.844

Table S3: *Linear mixed effect results model in men (n=1128)*

Variable	*E/e', B (95% CI)*	*p*	*LAVI B (95% CI)*	*p*	*TR B (95% CI)*	*p*	*LVMI B (95% CI)*	*p*	*LVPWT B (95% CI)*	*p*
Interc	7.57 (5.41 – 9.74)	<.001	21.33 (13.17 – 29.49)	<.001	2.09 (1.83 – 2.36)	<.001	86.39 (72.17 – 100.61)	<.001	0.85 (0.75 – 0.95)	<.001
Time (y)	0.01 (-0.00 – 0.03)	.071	0.04 (-0.03 – 0.10)	.266	-0.00 (-0.00 – 0.00)	.534	-0.15 (-0.26 – -0.04)	.008	-0.00 (-0.00 – 0.00)	.151
eGFR	-0.03 (-0.04 – -0.02)	<.001	-0.03 (-0.08 – 0.02)	.236	-0.00 (-0.00 – -0.00)	.002	-0.19 (-0.28 – -0.11)	<.001	-0.00 (-0.00 – 0.00)	.439
Age (y)	0.08 (0.05 – 0.10)	<.001	0.27 (0.18 – 0.36)	<.001	0.01 (0.00 – 0.01)	<.001	0.45 (0.28 – 0.62)	<.001	0.00 (0.00 – 0.00)	<.001
DM	1.46 (0.79 – 2.14)	<.001	-2.27 (-4.74 – 0.19)	.071	-0.01 (-0.10 – 0.08)	.819	1.25 (-3.32 – 5.83)	.591	0.04 (0.01 – 0.07)	.017
HT	-0.10 (-0.51 – 0.31)	.624	-0.78 (-2.33 – 0.77)	.326	0.01 (-0.04 – 0.07)	.650	0.33 (-2.45 – 3.10)	.817	0.01 (-0.01 – 0.03)	.276
CVD	-0.25 (-0.70 – 0.20)	.276	-0.73 (-2.39 – 0.94)	.393	-0.03 (-0.09 – 0.03)	.349	-3.80 (-6.79 – -0.82)	.013	-0.02 (-0.04 – 0.00)	.073
CMP	2.22 (1.00 – 3.43)	<.001	6.38 (2.52 – 10.24)	.001	-0.01 (-0.16 – 0.13)	.834	27.46 (19.78 – 35.15)	<.001	0.14 (0.09 – 0.19)	<.001
T× eGFR	-0.00 (-0.00 – 0.00)	.111	-0.00 (-0.00 – 0.00)	.425	0.00 (-0.00 – 0.00)	.313	0.00 (-0.00 – 0.00)	.131	0.00 (-0.00 – 0.00)	.293

Chapter

8

The Hidden Barrier for Heart Failure Risk Prediction Models:

Missing Data and Variation in Predictions Resulting from Imputation Methods

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ABSTRACT

Aim: Prognostic models are typically developed using well-protocolised research data with limited missingness. When applied in routine clinical practice, these models often rely on electronic health record (EHR) data, where missingness in predictors is common. We set out to assess how different approaches to handling missing data affect the applicability of risk predictions in EHRs.

***Methods*:** We identified published prognostic models for heart failure (HF) risk and assessed their applicability in a large EHR dataset. For each model, we constructed model-specific cohorts reflecting original eligibility criteria of the development cohort. We examined the possibility of running the model using a complete-case approach and assessed the impact of single-value imputation (means or clinically defined normal value) and flexible methods such as k-nearest neighbours (kNN) imputation, multiple imputation by chained equations (MICE), and random forest imputation on predicted risk estimates.

Results: We evaluated eight models across eight sub-cohorts including between 3,209 to 28,429 individuals. Across all models, the proportion of patients with complete data for all required predictors was low. Complete-case application was possible for less than 8% of the included population in five models and for the other three models in less than 1% of the population. When missing data were handled through imputation, predicted HF risk estimates changed substantially compared with non-imputed analyses and varied notably across imputation techniques. The model from Khan et al. showed relatively stable 10-year risk estimates (0.74%–0.85% vs. 0.75% in complete cases), whereas the model from Nambi et al. was highly sensitive to missing data handling, with mean risk ranging from 14.20% to 58.88%. In risk category models, the proportion of patients classified as high risk varied widely, from 0% in non-imputed data to 73.5% with kNN imputation in the model from Said et al.

Conclusions: Missing data represent a major barrier to the use of prognostic models for HF risk in routine clinical practice, as complete-case application is rarely feasible. While imputation methods allow model use, predicted risks may vary substantially depending on how missing data are handled, further hampering the implementation of prognostic models in clinical practice.

INTRODUCTION

Prognostic models are designed to estimate a future outcome (often a probability) for an individual based on information available at a specific point in time.[1] In the last decades, a plethora of prognostic models have been developed or validated across various clinical settings.[2] These models are typically derived using cohort or trial data where the data collection of predictors is commonly well-protocolised, leading to limited missing data, with limited generalisability to other settings.

If prognostic models are applied in routine clinical practice, they commonly use clinical data stored in electronic health records (EHRs). EHRs offer a rich source of longitudinal data, capturing diverse patient information including demographics, diagnoses, medications, procedures, and laboratory results over time. However, EHR data can be unstructured and missingness is common as information is based on patient and physician's need and not on research's need.[3]

Missing data may limit the use of prognostic models in clinical practice in several ways. For example, when predictors are missing, models may not be directly applicable without additional data processing. Several strategies exist for addressing missing data, from simple dropping out incomplete cases and work only with complete-case or single-value imputation using means or clinically defined normal values to more sophisticated and flexible methods such as k-nearest neighbours (kNN) imputation, multiple imputation by chained equations (MICE), and random forest imputation.[4] The suitability of each approach depends on assumptions about the mixture of missing data mechanism: i.e., missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR).4 This is particularly relevant in EHR data, where missingness often has a clinical meaning, as clinical measurements are more likely to be recorded when abnormalities are suspected.[5,6] When imputation is used to address missingness in prediction models, the resulting risk estimates may depend on the chosen method and its underlying assumptions. In this study, we set out to assess how different approaches to handling missing data affect the applicability and stability of heart failure (HF) risk predictions models in EHR settings.

METHODS

Data source

This study used data from the Utrecht Patient Oriented Database (UPOD) comprising data on patient characteristics, hospital discharge diagnoses, medical procedures, medication orders and laboratory tests for all patients treated at the University Medical Centre Utrecht (UMC Utrecht) since 2004. UPOD data acquisition and management are in accordance with current regulations concerning privacy and ethics. The structure and content of UPOD have been described in more detail elsewhere.[7]

Study population

The study cohort consisted of adult patients referred to outpatient departments, including nephrology and hypertension, cardiology, vascular medicine, neurology, endocrinology, urology, vascular surgery, cardiothoracic surgery, and geriatrics, between January 2012 and December 2023. Patients were eligible if they were aged ≥18 years, had visited one of the outpatient departments and had at least one echocardiographic assessment within 180 days before or after the first visit.

Identification and selection of prognostic models

Prognostic models for predicting the risk of HF were identified through a systematic review using PubMed and EMBASE, covering studies from January 2015 to November 2025. The search strategy combined terms related to HF, prognosis, and prediction modelling. Titles and abstracts were screened by two reviewers (CP and GV) for relevance, followed by independent full-text assessment by the same reviewers. Models were included if they met the following criteria: (i) applicability to an adult, outpatient population, comparable to the UPOD cohort, (ii) included predictors available in UPOD or that can be derived using proxies, (ii) availability of sufficient information to calculate individual risk estimates (e.g. regression coefficients, nomograms, or explicit algorithms), and (iii) evidence of at least internal or external validation.

Risk of bias was assessed independently by two reviewers (CP and GV) for each included study using the Prediction model Risk Of Bias ASsessment Tool (PROBAST).[8]

Predictors extraction and harmonisation

Predictor variables extracted from UPOD were based on the predictors specified in each included prognostic model. When direct extraction was not possible, proxy or derived variables were used. For example, left ventricular hypertrophy was derived from echocardiography-based LV mass index above guideline thresholds. All variables were harmonised across models to ensure consistency in definitions, coding, and measurement units.

Model-specific study populations

To approximate the populations in which the prognostic models were originally developed, we constructed model-specific sub cohorts within UPOD using the published eligibility criteria where possible. The inclusion and exclusion criteria, as well as the assumptions used for each model, are detailed in Supplementary Table S0. In brief, the model from Jacobs et al. (2017) was applied to individuals aged ≥70 years.[9] Models from Said et al. (2024) and Pfister et al. (2013) were applied to individuals with type 2 diabetes.[10,11] The model from Khan et al. (2019) was applied to adults without established cardiovascular disease.[12] Ergatoudes et al. (2018) was restricted to men,[13]

while the model from Chahal 2024, Kannel et al. (1999), and Nambi et al. (2013) were applied to the broader eligible UPOD cohort.[14-16] This resulted in eight datasets, each intended to approximate the target population of the original development study as closely as possible.

Assessment of missing data

For each model-specific dataset, we quantified the proportion of missing data for each predictor at baseline. Baseline was defined as the index date, corresponding to the patient's first outpatient department visit during the study period. Predictor values were extracted from measurements recorded on the index date or within a ±31-day window around that date, except for echocardiographic variables, for which measurements within ±180 days of the index date were allowed. Patterns of missingness were explored both in the overall UPOD cohort and within each model-specific dataset and were assessed for each predictor individually.

Handling of missing data

For each prognostic model, missing data were handled using six approaches. These included a complete-case analysis and different imputation strategies. Five imputation strategies were used to address missing predictor information: 1) Mean imputation replacing missing values with the mean or median of the corresponding predictor in the model-specific derivation population; 2) Normal-value imputation replacing missing values with clinically defined normal values, for dichotomous variables, the absence of the condition was considered the normal value and coded as 0; 3) kNN imputation using information from the 10 most similar individuals, based on Euclidean distance; 4) MICE imputation generating 20 imputed datasets, with 50 iterations per imputation; and 5) Random forest imputation using ensemble learning with 500 trees. Missing data handling was performed separately for each prognostic model and its corresponding dataset.

Application of prognostic models

After handling missing data, each prognostic model was applied separately within its corresponding dataset. Models were first run using complete-case data, then each model was re-applied on each imputed dataset using the original model specifications, including the published regression coefficients, baseline hazards, or risk equations, as provided in the original model development studies.

RESULTS

A total of 2,489 articles were identified through PubMed and EMBASE databases. After discarding duplicates, the titles and abstracts of 2,308 articles were screened. Then, the full texts of 37 articles were reviewed. Of these, eight studies describing eight prognostic models for predicting risk of HF met the inclusion criteria and were included in the analysis.[9-16] The remaining studies were excluded primarily because outcome of interest did not concern HF risk or because they relied on predictors not routinely collected in UPOD, e.g., genetic information or specific socioeconomic indicators (e.g., poverty income ratio).

The included models aimed to estimated HF risk across a range of time horizons, from 1-year risk to 21-year predictions. Five models provided absolute risk estimates expressed as percentages, whereas three models stratified individuals into qualitative risk categories using point-based systems or percentage thresholds (e.g., low to very high risk). Characteristics of the included models are summarised in **Table 1**. **Supplementary Table S1** contains the description of the studies excluded after full-text assessment.

Risk of bias was assessed for all included studies using PROBAST. Seven models were judged to be at high risk of bias, while the model by Chahal et al., was classified as having unclear risk of bias based on the overall judgement. High risk of bias was primarily due to concerns in the analysis domain, particularly related to handling of missing data and predictor selection. Summary risk of bias is provided in **Figure 2** and details of the assessment for each model is provided in **Supplementary Table S2**.

Baseline characteristics

The total UPOD cohort comprised 28,429 individuals, with a mean age of 59.2 years (SD 16.7). Women represented 43.1% of the population. Hypertension was present in 62.1% of individuals, diabetes mellitus in 11.3 %, and a history of cardiovascular disease in 26.5%. The baseline characteristics of the UPOD and comparison with the characteristics of derivation populations are described in **Table 2**.

Model-specific datasets

The number of eligible individuals in each varied across each model-specific dataset, from 3,209 patients for models including only patients with type 2 diabetes to 28,429 patients for models developed in the outpatient population. The prognostic models also differed substantially in the number and type of predictors included, spanning from demographic characteristics, cardiovascular risk factors, comorbid conditions, medication use, laboratory measurements to electrocardiographic parameters, and

echocardiographic findings. An overview of predictors used in each model is provided in **Table 3**.

Figure 1: *PRISMA flowchart*

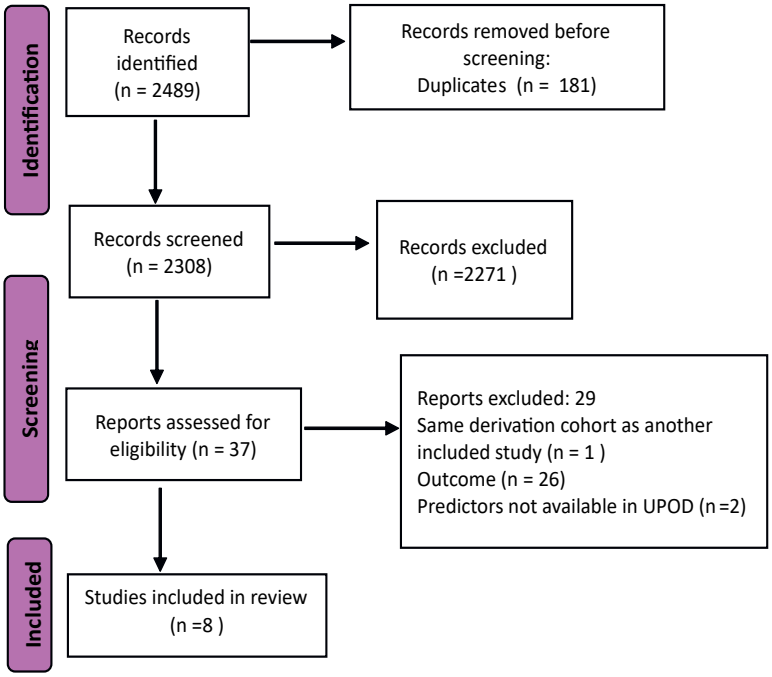


***Table 1**: Included prognostic models*

Author (year)	*Domain*	*Statistical method*	*Variables in the final model*
Jacobs et al. (2017)[9]	Elderly people	Cox regression model	Sex, Age, BMI, Smoking, DM, CAD, antihypertensive medication use, SBP, HR, Serum Creatinine
Said et al. (2024)[11]	Patients with T2D	Cox regression model	Age, BMI, Calcium channel blocker use, HbA1c, NT-proBNP, UACR, Haematocrit, hsTnT
Khan et al. (2019)[12]	Adults free of CVD at baseline	Cox regression model	Age, SBP, Smoking, Glucose, Total Cholesterol, HDL cholesterol, BMI, QRS duration
Chahal et al. (2014)[14]	Participants from the Multi-Ethnic Study of Atherosclerosis (USA)	Cox proportional hazard models	Age, Gender, Smoking, BMI, SBP, HR, DM, NT pro-BNP
Ergatoudes et al. (2018)[13]	Population-based cohort (Sweden)	Multivariable logistic regression	NT-proBNP, hs-CRP, BMI, IL-6, Hypertension
Kannel et al. (1999)[15]	Individual from Framingham study (USA)	Logistic regression	Age, Hypertension, HR, LVH, CHD, Valve disease, DM
Nambi et al. (2013)[16]	Black or White individuals (USA)	Cox proportional hazard models	Race, Antihypertensive medication, smoking, DM, BMI, CHD, HR, NT-proBNP, cTnT
Pfister et al. (2013)[10]	T2 DM (Europe)	Multivariable logistic regression	Age, Serum Creatinine, Diuretic use, HbA1c, DM duration, LDL cholesterol, HR, Right and left bundle branch block, Microalbuminuria +, previous MI, Pioglitazone treatment

BMI: body mass index; DM: diabetes mellitus; SBP: systolic blood pressure; HR: heart rate; HbA1c: Glycated haemoglobin; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; UACR: urine albumin-creatinine ratio; hsTnT: High-sensitivity cardiac troponin T; HDL: High-density lipoprotein cholesterol; LDL: Low-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; IL-6: Interleukin-6; CVD: cardiovascular disease; CAD: coronary artery disease; LVH: left ventricular hypertrophy; CHD: coronary heart disease.

***Table 2**: Baseline characteristics: UPOD and derivation population from each model*

	UPOD cohort	***Jacob (2017)[10]***	***Sai (2024)[12]***	***Khan (2019)[13]***	***Chaha (2014)[15]***	***Ergatoudes (2018)[14]***	***Kannel (1999)[16]***	***Nambi (2013)[17]***	***Pfister (2013)[11]***
Domain		*Elderly (70+)*	*T2D*	*Free of CVD*	*General population*	*Men*	*General population*	*General population*	*T2D*
N of patients	28429	10236	5081	6699	6814	747	15267	9868	4951
Age, y	59.23 ±16.65	74.5±3.7	64±9.8	49.3± 12.2	62.1 ± 10	50	62.9	62.7 ± 5.65	61.7 ±7.7
Women	12237 (43.1)	5248 (51.3)	1577 (31)	3493 (52)	3604 (52.9)			5496 (55.7)	1674 (33.8)
BMI, kg/m2	26.26 ± 4.83	26.9±4.4	29.45 ± 5.75	26.1 ± 4.2	28.3±5.5	26.22 ± 3.38		28.6 ± 5.44	30.9 ±4.8
SBP, mm Hg	134.1 ± 23.0	146.9±22.7	137.4±9.6	129 ± 20	126.6±21.5	128.8 ± 17.0	152.1	127.3 ±18.91	144 ±18
DBP, mm Hg	77.4 ± 13.2	79.9±12.3	74.4 ± 9.6		71.9±10.3	84.3 ± 10.6		71.0 ± 10.2	83 ±10
Heart rate, bpm	74 ± 16	66±11			63±10	67 ± 12	76		72 ±14
Smokers (%)	1963 (6.9)	2052 (20.1)	737 (14.5)	2552 (38)	886 (13.0)	228 (30.5)		1450 (14.7)	
Hypertension (%)	17665 (62.1)	6577 (64.3)		933 (14)	3059 (44.9)	294 (39.4)		4509 (45.7)	
Diabetes (%)	3209 (11.3)	1299 (12.7)	5081 (100)	232 (4)	858 (12.6)	27 (3.6)		1539 (15.6)	4951 (100)
CVD (%)	7534 (26.5)	3701 (36.2)	1748 (34.4)						4690(94.7)
CAD (%)	2923 (10.3)	2606 (25.5)					15.7		668 (13.5)
MI (%)	505 (1.8)					10 (1.3)			2319 (46.8)
PAD (%)	276 (1.0)	257 (2.5)							1225 (24.7)
CeVD (5)	735 (2.6)	856 (8.4)				2 (0.3)			
HbA1c (%)	5.6 [5.4, 6.2]								8.1 ±1.4
Cholesterol, mmol/L	4.81 ± 1.25	5.50±0.97		5.69 ±1.14	5.02± 0.92	5.87 ± 1.03		5.21 ± 0.95	
Creatinine, mmol/L	78.0[65.0,92.0]	96.2±27.7			0.96±0.3				
GFR mL/min/1.73 m^2	90.3 [72.2, 104.1]							82.3 ± 18.96	
antiHT drug (%)	15018 (52.8)	6596 (64.4)						3384 (34.3)	

BMI: body mass index; DM: diabetes mellitus; SBP: systolic blood pressure; HbA1c: Glycated haemoglobin; eGFR: estimate glomerular filtration rate; CVD: cardiovascular disease; CAD: coronary artery disease; PAD: peripheral artery disease; CeVD: cerebrovascular disease.

***Table 3**: Overview of variables in the models*

Predictor	*Definition in UPOD*	*Proxy / derived*[1]	*Jacobs (2017)*[10]	*Said (2024)*[12]	*Khan (2019)*[13]	*Chahal (2014)*[15]	*Ergatoudes (2018)*[14]	*Kannel (1999)*[16]	*Nambi (2013)*[17]	*Pfister (2013)*[11]
Age	Age in years at index date	No	*	*	*	*		*		*
Sex	Biological sex	No	*			*				
Race	Not available	N/A					*			
Body mass index	Weight (kg) / height² (m)	Derived	*	*	*	*	*		*	
Smoking	Ever vs never smoker	Proxy	*		*	*			*	
Systolic blood pressure	Outpatient SBP	No	*		*	*		*		
Heart rate	Outpatient heart rate	No	*			*		*	*	*
Diabetes mellitus	Diagnosis code, HbA1c, and/or glucose-lowering medication	Proxy	*	*		*		*	*	*
Coronary heart disease	History of MI or coronary revascularisation	Proxy	*					*	*	*
Antihypertensive medication	Any antihypertensive prescription	No	*						*	
Diuretic use	Prescription of loop or thiazide diuretics	No								*
HbA1c	Closest value to index date	No		*						*
Glucose	Closest plasma glucose to index date	No			*					
Total cholesterol	Closest measurement to index date	No			*					
HDL cholesterol	Closest measurement to index date	No			*					
LDL cholesterol	Closest measurement to index date	No								*

***Table 3**: Continued.*

Predictor	*Definition in UPOD*	*Proxy / derived*[1]	*Jacobs (2017)*[10]	*Said (2024)*[12]	*Khan (2019)*[13]	*Chahal (2014)*[15]	*Ergatoudes (2018)*[14]	*Kannel (1999)*[16]	*Nambi (2013)*[17]	*Pfister (2013)*[11]
NT-proBNP	Closest measurement to index date	No		*		*	*		*	
Cardiac troponin (hs-TnT / cTnT)	Closest value to index date	No		*						*
Serum creatinine	Closest measurement to index date	No	*							*
UACR / microalbuminuria	UACR or microalbuminuria measurement	No		*						
QRS duration / RBBB / LBBB	ECG-based conduction abnormalities	No			*					*
Inflammatory markers (hs-CRP, IL-6)	Closest available measurement	No					*			
Left ventricular hypertrophy	Echo-based LV mass index above guideline thresholds	Derived						*		
Valvular heart disease	Diagnostic codes	No						*		
Previous myocardial infarction	Prior MI, diagnostic code	Proxy								*
Pioglitazone treatment	Active prescription	No								*

*1 Variables marked as derived were calculated from observed data using predefined algorithms; variables marked as proxies were used as indirect measures of underlying clinical constructs not directly observed in the EHR. * Indicates that the model includes the variable. BMI: body mass index; DM: diabetes mellitus; SBP: systolic blood pressure; HR: heart rate; HbA1c: Glycated haemoglobin; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; UACR: urine albumin-creatinine ratio; hsTnT: High-sensitivity cardiac troponin T; HDL: High-density lipoprotein cholesterol; LDL: Low-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; IL-6: Interleukin-6; CVD: cardiovascular disease; CAD: coronary artery disease; LVH: left ventricular hypertrophy; CHD: coronary heart disease.*

***Figure 2**: Summary PROBAST risk of bias*

Author (year)	*Participants*	*Predictors*	*Outcomes*	*Analysis*	*Overall*
Jacobs et al. (2017)	Low	Low	High	Low	High
Said et al. (2024)	Low	Low	Low	High	High
Khan et al. (2019)	Low	Low	Low	High	High
Chahal et al. (2014)	Low	Low	Unclear	Unclear	Unclear
Ergatoudes et al. (2018)	Low	Low	Low	High	High
Kannel et al. (1999)	Low	Low	Low	High	High
Nambi et al. (2013)	Low	Low	Low	High	High
Pfister et al. (2013)	Low	Low	Low	High	High

Risk of bias was assessed using the Prediction model Risk Of Bias ASsessment Tool (PROBAST). Overall risk of bias was judged as high if at least one domain was rated as high risk. Detailed signalling questions and rationales are provided in Supplementary Table S2.

Missing data

In the UPOD cohort, the extent of missing data varied widely across predictors. Age and sex were complete for all individuals. In contrast, laboratory and biomarker variables were subject to substantial missingness, including NT-proBNP (94.6%), HbA1c (75.8%), lipid measurements (±50%), and inflammatory markers such as IL-6 (99.9%). Clinical variables such as systolic blood pressure (41.7%) and smoking status (76.6%) also showed considerable missingness (**Supplementary Table S3**).

Across model-specific datasets, missingness patterns differed depending on predictor requirements. The application of prognostic models without imputation was possible for less than 8% of the included patients in all models. Models requiring biomarkers or specialised laboratory measurements, such as the cases of the models from Nambi et al. (2013) and Said et al. (2024) that included Troponin T and NT-proBNP as predictors, were particularly affected. For these models, complete case application without imputation was feasible in only 0.07% and 0.12% of the population, respectively. Missing data patterns for each model-specific dataset are shown in **Supplementary Figures S1.**

Heart failure risk across models

Estimated HF risk varied across both prognostic models and imputation strategies (**Table 4**). Differences in the distributions of predicted individual risks across imputation strategies are presented in **Supplementary Figure S2**. Some models showed relatively similar distributions of predicted risks regardless of the imputation method used when compared with the risk estimated in complete cases analyses. For instance, the model from Khan et al. (2019), which estimate the 10-year HF risk in individuals free of cardiovascular disease, yielded to a mean HF risk of 0.75% when applied to patients with

complete cases and without imputation. When applied to imputed datasets, the estimated risk ranged from 0.74% with normal value imputation to 0.85% with mean imputation.

In contrast, other models demonstrated substantial sensitivity to the choice of imputation method. The model from Nambi et al. (2013) showed important variability in estimated 10-year HF risk, with a mean risk of 58.88% in complete case analysis compared with 14.20% when mean imputation was applied. Models that classify individuals into risk categories also exhibited considerable shifts depending on the imputation strategy. In the model from Said et al. (2024), 0% of patients were classified as high risk when using non imputed data. After applying imputation, this proportion ranged from 3.77% with normal value imputation to 73.5% with kNN imputation. Similar shifts were observed for the models from Pfister et al. (2013) and Chahal et al. (2024).

DISCUSSION

In this study, we evaluated the missingness of the predictors underlying the prognostic models used to predict HF risk using data from EHR and assessed the impact of different imputation strategies on the predicted risk estimates. We found that, across models, the availability of all required predictors was rare, and HF risk estimates varied depending on how missing data were handled, with substantial variability observed for some models at the population level. Our findings suggest that the direct application of prediction models in routine EHR data is challenging and possible in only a few patients. While these models can generate risk estimates when missing data are addressed through imputation, the resulting predictions varied considerably with respect to results from non-imputed data and there is also important variation across imputation strategies.

The practical usefulness of prognostic models depends not only on their statistical methods, but also on predictor availability. Without careful consideration of these issues, the application of prognostic models in EHR data risks creating an illusion of usefulness rather than providing reliable tool to estimated individual risk. In routine care, clinicians are unlikely to have access to, or the time to run, complex imputations such as MICE or random forest imputation in real time. Simpler approaches, like mean imputation or assuming clinically normal values, may seem pragmatic. However, mean imputation, for example, requires knowledge of the derivation population's predictor distribution, which is rarely available during consultation. Consequently, clinicians must often rely on imperfect strategies when applying prognostic models to patients with incomplete data, undermining the reliability of the resulting risk estimates.

Imputation offers a way to address the issue of missing data by using information from observed variables to approximate missing values and thereby avoid the loss of

information. This is particularly appealing in EHR data, where excluding large numbers of patients is neither practical nor desirable. Simple approaches, such as assuming clinically normal values or using single-value imputation, rely on often implausible assumptions and may introduce systematic bias. More flexible methods, including k-NN and MICE, may better preserve relationships between predictors, although their validity depends on assumptions about the missing mechanism.[17,18] In routine EHR data, where missingness is heterogeneous and clinically driven, these assumptions are frequently difficult to justify. Consequently, different imputation approaches may result in different risk estimates that cannot be readily adjudicated.

Our findings align with broader methodological concerns regarding the alignment between model development and implementation. Prognostic models are typically developed under specific assumptions about predictor availability and missing data mechanisms that are frequently violated in routine EHR data. Prior methodological work has showed that such misalignment can result in unstable or misleading predictions.[19] In this context, our results provide empirical evidence from real-world data, quantifying how different imputation strategies influence predicted HF risk across multiple established prognostic models, at both the population and individual patient level. Thus, even when models can be used with imputed data, predicted estimates may depend strongly on how missing data are handled.

Improving the usability of prognostic models does not necessarily require the development of new models, but the adaptation of existing ones so they can be used in real world clinical scenarios.[20] This may involve prioritising predictors that are routinely and consistently captured in EHR systems, incorporating missing data handling directly into the model structure, or developing simplified versions of current models that preserve acceptable performance while reducing dependence on sparsely recorded variables. In addition, transparent reporting of predictor availability and missing data strategies during model development would enable clinicians to assess whether a model is suitable for their context.

This study has several strengths. Rather than using a single imputation approach, we evaluated multiple imputation strategies across several prognostic models. This allowed us to examine not only whether imputation makes model application possible, but also how sensitive, predicted risk estimates are to different assumptions about missing data. The use of EHR data represents a key strength of this work. Unlike simulation studies, our study captures the complexity, selectivity, and informativeness of missingness as it occurs in clinical practice.

Table 4: *Risk estimation in complete cases and in imputed data*

Model characteristics			***Cohorts from UPOD***	***Complete cases***		***Risk calculation by imputation method***				
Model	*Domain*	*Risk type*	*N*	*n (%)*	*Risk without imputation*	*Normal value*	*Mean*	*KNN*	*MICE*	*Random Forest*
Jacobs et al. (2017)	Elderly (70+)	5-year	8732	444 (5.08)	5.19%	3.53%	4.55%	4.38%	4.79%	4.07%
Khan et al. (2019)	Free of CVD	10-year	8545	651 (7.6)	0.75%	0.74%	0.85%	0.78%	0.84%	0.72%
Ergatoudes et al. (2018)	Men	21-year	16192	256 (1.58)	83.64%	79.27%	80.71%	82.87%	83.33%	85.77%
Kannel et al. (1999)	General population	4-year	28429	429 (1.50)	0.06%	0.03%	0.04%	0.04%	0.05%	0.04%
Nambi et al. (2013)	General population	10-year	28429	21 (0.07)	50.88%	18.67%	14.20%	31.70%	32.89%	36.05%
Said et al. (2024)	T2D	1-year	3209	4 (0.12)	HR: 0.0%	HR: 3.77%	HR: 77.50%	HR: 73.57%	HR: 58.95%	HR: 73.38%
Pfister et al. (2013)	T2D	3.3-year	3209	138 (4.3)	52.89 (LR) 33.33 (MR) 13.76 (HR	61.23% (LR) 29.94% (MR) 8.81% (HR)	45.12% (LR) 37.08% (MR) 17.79% (HR)	54.34% (LR) 32.37% (MR) 13.27% (HR)	51.32% (LR) 34.20% (MR) 14.47% (HR)	54.22% (LR) 29.82% (MR) 15.95% (HR)
Chahal et al. (2024)	General population	5-year	28429	45 (0.15)	28.8% (LR) 20% (AR) 6.6% (HR) 44.4% (VHR)	81.52% (LR) 14.09% (AR) 2.68% (HR) 1.70% (VHR)	79.30% (LR) 15.14% (AR) 3.43% (HR) 2.11% (VHR)	42.31% (LR) 20.92% (AR) 11.15% (HR) 25.60% (VHR)	41.20% (LR) 15.43% (AR) 8.98% (HR) 34.37% (VHR)	36.51% (LR) 14.08% (AR) 7.76% (HR) 41.63% (VHR

LR: low risk <5% probability; AR: average risk 5%-10% probability; HR: high risk 10%-20% probability; VHR: very high risk >20% probability.

Some limitations should also be acknowledged. First, this study focused on variation in predicted risk rather than on model performance, and we did not assess discrimination, calibration, or clinical outcomes associated with different risk estimates. This was a deliberate methodological choice, as the included prognostic models differed substantially in their target populations, predictor sets, risk horizons, and statistical approaches. Under these circumstances, identifying a single reference standard for performance comparison across models would not only be impractical but would also fail to address the central question of this study. Second, risk estimation was restricted to baseline information. In routine care, additional diagnostic tests are often ordered after the initial visit, which may reduce missingness and enable more complete risk estimation over time. However, the first outpatient visit is commonly the moment when initial risk assessment and shared decision-making regarding further diagnostic work-up or management occur. Our analysis therefore reflects the clinical reality in which prognostic information is most needed but often least complete. We did not evaluate how predicted HF risk might change when incorporating longitudinally updated clinical data over time. Finally, our findings are based on data from a single academic medical centre in the Netherlands. Patterns of data availability and missingness are shaped by local clinical practice and may therefore differ from other places. To mitigate this limitation, we focused on widely used predictors and models derived in diverse populations. Nevertheless, our findings may not be directly generalisable to settings where certain laboratory or biomarker measurements are obtained more routinely.

CONCLUSION

Missing data represent a major barrier to the use of prognostic models for HF risk in routine clinical practice, as complete-case application is rarely feasible. While imputation methods allow model use, predicted risks may vary substantially depending on how missing data are handled, further hampering the implementation of prognostic models in clinical practice.

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Table S0: *Model-specific eligibility criteria applied to UPOD*

Model (year)	***Target derivation population***	***Eligibility criteria applied in UPOD***	***Derived variables***
Jacobs (2017)	Elderly (70+)	Included Age ≥ 70	BMI computed from weight/height. Sex recoded: female=1, male=0. Antihypertensive medication use (AntiHT) defined as any ATC starting with C02/C03/C07/C08/C09.
Said (2024)	Type 2 diabetes (T2D)	Included T2D = 1	BMI computed from weight/height. Calcium channel blocker use (CCB) defined as any ATC starting with C08.
Khan (2019)	Adults free of established CVD	Included CVD = 0 AND CHD = 0 AND MI = 0	BMI computed from weight/height. (Other variables extracted as available: SBP, glucose, lipids, QRS duration, smoking, treatment status flags.)
Chahal (2014)	General population		BMI computed from weight/height. (Model applied broadly within UPOD cohort subset.)
Ergatoudes (2018)	General population men	Included gender = male	BMI computed from weight/height. (Inflammatory marker CRP extracted where available.)
Kannel (1999)	General population (Framingham)		BMI computed from weight/height. LVH derived from LV mass index (LVMI_new): LVH=1 if female LVMI > 122 or male LVMI > 149, else 0.
Nambi (2013)	General population (Black/White, USA)		Race not available in UPOD → assumed "white" for all. BMI computed from weight/height. Antihypertensive medication use (AntiHT) defined as any ATC starting with C02/C03/C07/C08/C09.
Pfister (2013)	T2D with macrovascular disease	Included T2D =	Diuretic use defined as any ATC starting with C03. Pioglitazone use defined as A10BG03. DM duration >10 years not available → set to 0 for all. Microalbuminuria positivity derived as Microalbuminuria > 30 (1=yes, 0=no).

Table S1: *Studies excluded after full-text assessment*

Author (year)	*Domain*	*Outcome*	*Determinants*	*Validation*	*Reason for exclusion*
Choi et al (2012)	Adults free of CVD or HF (USA)	Incidence HF	Age, sex, ethnicity, systolic blood pressure, use of anti-hypertensive treatment, presence of diabetes mellitus, current smoking, LDL-cholesterol, HDL-cholesterol, statin use, glomerular filtration rate, and LV mass index.	NR	Outcome
Wong et al (2013)	Adult with impaired glucose tolerance (UK)	Incidence HF hospitalisation	Age, waist circumference, history of coronary heart disease, clinically significant abnormal ECG, history of AF or flutter, log UACR, history COPD/emphysema/chronic bronchitis, SBP, Haemoglobin, Height, clinically insignificant abnormal ECG	NR	Outcome
Schnabel et al (2014)	Individuals with AF (USA – Framingham cohort)	Incidence HF	Age, body mass index, weight, blood pressure variables, diabetes, significant murmur, ECG LV hypertrophy, prevalent myocardial infarction, and prevalent cardiovascular disease	NR	Outcome
Klip et al (2015)	Adult 28-75 years (NL)	Incidence HF	Age, sex, BMI, heart rate, smoking, the presence of diabetes, hypertension or hypercholesterolemia, a history of MI or stroke, LVH on electrocardiogram, renal function, and levels of hs-CRP and UAE, HB	NR	Outcome
Butler et al (2008)	Adults 70-79 years (USA)	Incidence HF	Age, history of smoking and CHD, left ventricular hypertrophy, systolic blood pressure and heart rate, and serum glucose, albumin, and creatinine levels	Internal (bootstrapping)	Outcome
Velagaleti et al (2010)	Offspring of the Framingham cohort (USA)	Incidence HF	Age, sex, body mass index, systolic blood pressure, hypertension treatment, diabetes mellitus, ratio of total cholesterol to high-density lipoprotein cholesterol, smoking, prevalent MI, and valvular heart disease.	Internal (split sample)	Outcome
Agarwal et al (2012)	Adults 45-64 years (USA)	Incidence HF	Age, ethnicity, sex, heart rate, SBP, BP-lowering medication use, DM, prevalence of CHD, Current smoker, Former smoker, BMI, Log NT-proBNP	Internal/External	Outcome
Smith et al (2010)	Adults (Sweden)	Incidence HF	Age, sex, BMI, SBP, DBP, antihypertensive treatment, LDL, history MI, History DM, Current smoking, lnMR-proANP, lnNT-proBNP, MR-proADM, lnCRP, CystC, lnCopeptin	NR	Outcome

Table S1: *Continued*

Author (year)	*Domain*	*Outcome*	*Determinants*	*Validation*	*Reason for exclusion*
deFilippi et al (2010)	Adults >65 years (USA)	Incidence HF	cTnT, systolic blood pressure, glucose, albumin, CHD, smoking, creatinine, heart rate, and electrocardiographic determined left ventricular hypertrophy.	NR	Outcome
Wannamethee et al (2013)	Adult men (UK)	Incidence HF	NT-proBNP, smoking, physical activity, social class, alcohol intake, LV hypertrophy, systolic blood pressure, antihypertensive drugs, history of MI, angina, eGFR, FEV1, albumin, CRP, heart rate, AF, ECG evidence of ischaemia and silent MI.	External	Outcome
Kalogeropoulos et al (2010)	Population-based cohort (USA)	Incidence HF	age; history of coronary heart disease; smoking status; systolic blood pressure; heart rate; serum glucose, creatinine, and albumin levels; and left ventricular hypertrophy by ECG	Internal	Outcome
Goyal et al (2010)	EHR > 18 years (USA)	Incidence HF	Age, sex, hypertension, DM, CHD, AF, valvular heart disease	NR	Outcome
Kalogeropoulos et al (2010)	Population-based cohort (USA)	Incidence HF	age; history of coronary heart disease; smoking status; systolic blood pressure; heart rate; serum glucose, creatinine, and albumin levels; and left ventricular hypertrophy by ECG, Interleukin-6, TNF-am CRP,	NR	Outcome
deFilippi et al (2011)	Adults > 65 years	Incidence HF	age, sex, and race, cardiovascular disease history, systolic blood pressure, diabetes, cholesterol, creatinine, and body mass index, use of antihypertensive medications, and major ECG abnormalities, NT-proBNP	NR	Outcome
Kalogeropoulos et al (2012)	Population-based cohort. Patients 65-100 years (USA)	Incidence HF	age; history of coronary heart disease; smoking status; systolic blood pressure; heart rate; serum glucose, creatinine, and albumin levels; and left ventricular hypertrophy by ECG, LVEF, E/A, LA, LVISd, LVIDd, LVMI, NT-proBNP	NR	Outcome
Wang et al (2012)	Offspring of the Framingham cohort (USA)	Incidence major cardiovascular event (includes HF)	age, sex, body mass index, systolic blood pressure, hypertension therapy, diabetes mellitus, cigarette smoking, total cholesterol, HDL, AF, major cardiovascular disease, ECG left ventricular hypertrophy, heart murmur, soluble ST2, GDF-15; hsTnI, BNP; and hsCRP.	NR	Outcome

Table S1: *Continued*

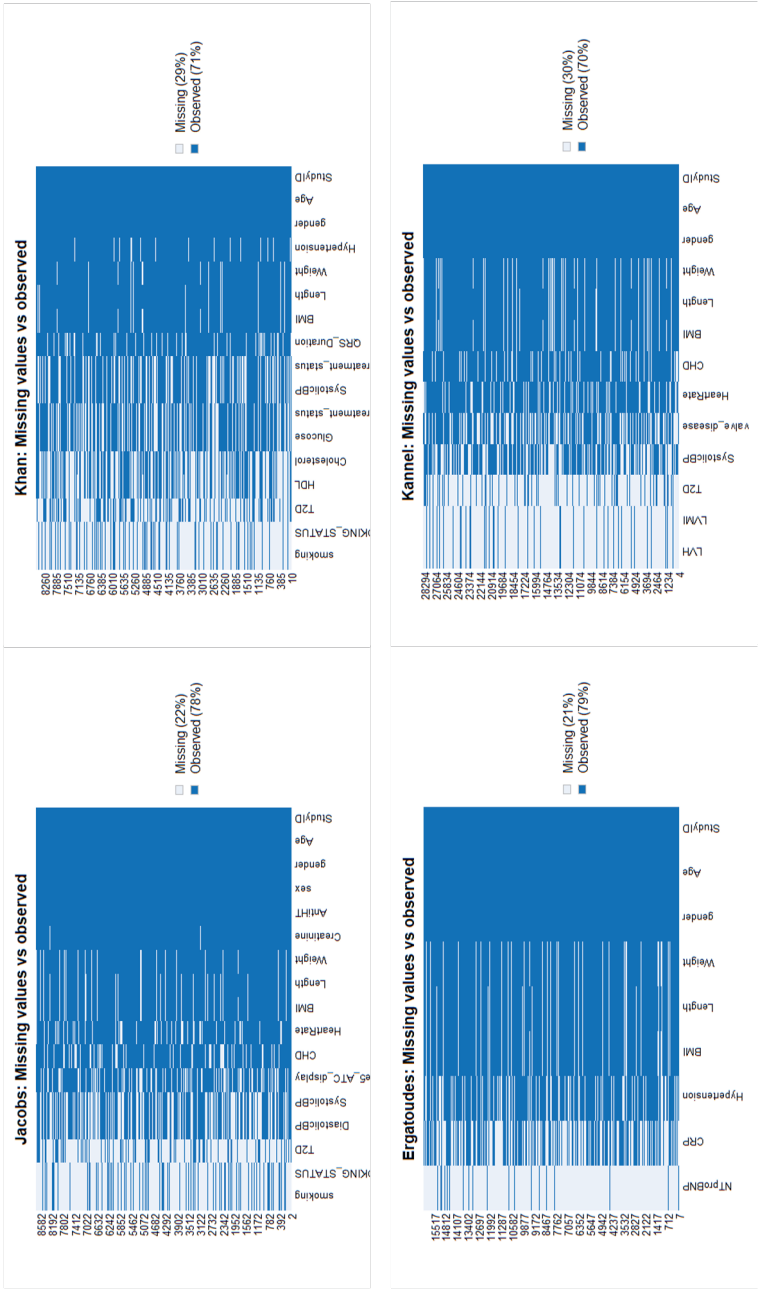
Author (year)	Domain	Outcome	Determinants	Validation	Reason for exclusion
Wang et al (2023)	Participants in NHANES with prediabetes or diabetes (USA)	Risk of HF	Poverty-to-income ratio (PIR), age, myocardial infarction condition, coronary heart disease condition, chest pain condition, and taking glucose-lowering medication condition.	Internal	Predictors included
Farajidavar et al (2022)	de-identified data of patients attending King's College Hospital NHS Foundation Trust in London (UK)	Risk HFpEF	Age, AO V2 MAX, Aortic Valve Insufficient, AF, BMI, DM, Disease, Diuretics, EF (CUBED, MOD-BP, MOD-SP2, MOD-SP4), Fasting, Full blood count normal, Furosemide, Height, Hypertensive disease, Hypokinesia, LA VOLUME (2D BIPLANE), O/E-blood pressure reading, Patient address, Pitting oedema, RR, SBP, Severe (severity modifier), Swelling of lower limb, TV, Weight.	Internal (randomly sample)	Predictors included
Huang et al (2022)	Chronic heart failure patients (China)	HF prognosis	Autophagy-related genes (ARGs), Single nucleotide polymorphisms, gender, age, hypertension, DM, hyperlipidaemia, smoking, SBP, DBP, LVEF, Beta-blocker use, GRS, TRF, GRF, and NT-proBNP	NR	Outcome
Gaziano et al (2021)	Primary care patients (USA)	Incidence HFpEF	Age, sex, race, ethnicity, SBP, DBP, BMI, HDL-c, LDL-c, Total cholesterol, Ln-triglycerides, eGFR, Sodium, Potassium, Current smoker, Statin medication, Antihypertensive medication, ACE inhibitors, ARB, Beta-blockers, Calcium channel blockers, Diuretics, previous MI, previous CAD, Diabetes, COPD, AF, Anaemia.	Internal	Outcome
Arshi et al (2021)	Population-based study. Rotterdam study (NL)	Prediction of heart failure	ACC/AHA model: age, total and HDL cholesterol, SBP, antihypertensive treatment, current smoking, and history of DM. ARIC model: age, heart rate, SBP, antihypertensive treatment, history of DM, history of CHD, smoking status (current, former, never), BMI and NT-proBNP. The health ABC model: age, history of CHD, LVH, SBP, heart rate, smoking status (current, former, never), glucose, and creatinine. Additionally included NT-proBNP in the ACC/AHA model as a predictor (ACC/AHA + NT-proBNP model). All models were separately developed for men and women.	Internal validation	Outcome

Table S1: *Continued*

Author (year)	Domain	Outcome	Determinants	Validation	Reason for exclusion
Bavishi et al (2020)	Patients 30-79 from outpatient dept for preventive care (USA)	Risk HF	PCP-HF Model: age, gender, race, current smoking, BMI, SBP, hypertension treatment, fasting glucose DM treatment, total cholesterol, HDL-C, and QRS duration.	*External validation	Model
Bennis et al (2022)	GP data (NL)	Prediction of HF	Age, gender, Contact with GP, Side effect medication DMT2, Chronic anaemia, analgesics, senile dementia, tested monofilaments left foot, HDL-c, blood sediment, chronic (diabetes) ulcus, Chronic acute MI, BB agents, tested urea, Chronic seborrheic eczema, antithrombotic agents, iron deficiency, glycohemoglobin, Control visit DMT2	Internal (Cross-validation)	Outcome
Brouwers et al (2014)	Community-based cohort (NL)	New-Onset HF	age, sex, body mass index, smoking status, systolic blood pressure, atrial fibrillation, plasma glucose, and total cholesterol levels, NT-proBNP, MR-proANP, MR-proADM, CT-proET-1, hs-TnT, Copeptin, Procalcitonin, hs-CRP, Cystatin-C, UAE, Renin, Aldosterone, ARR	NR	Outcome
Choi et al (2016)	EHR primary care patients (USA)	Diagnosis HF	Disease diagnosis, medication orders, procedure orders	Internal (Cross-validation)	Outcome
Ho et al (2016)	Four Community-based cohorts (USA/NL)	Incidence HF	Age, Male, SBP, BMI, Antihypertensive treatment, Previous MI, DM, Current smoker. LV hypertrophy, Left bundle branch block	Internal/external validation	Outcome
Osataphan (2025)	Patients with atherosclerotic risk	Heart failure risk	ARIC model – Same as Nambi		Same derivation and Model than other included study
Yuan (2018)	Patients with HF				Population
Li et al (2022)	Data from general practice (England)	Cardiovascular events including HF, stroke and CHD	Age, ethnicity, Indices of multiple deprivation, SBP, SD of SBP, BMI, Total cholesterol/HLD ratio, smoking status, Family history of CHD, Diabetes, Treated hypertension, Rheumatoid arthritis, AF, CKD, Migraine, Corticosteroid use. Systemic lupus, Atypical antipsychotics drugs, severe mental illness, HIV/AIDS, Erectile dysfunction, Sex, CHD, LVH, Valve disease, Heart rate, Total cholesterol, HLD.	Internal/External validation	Outcome

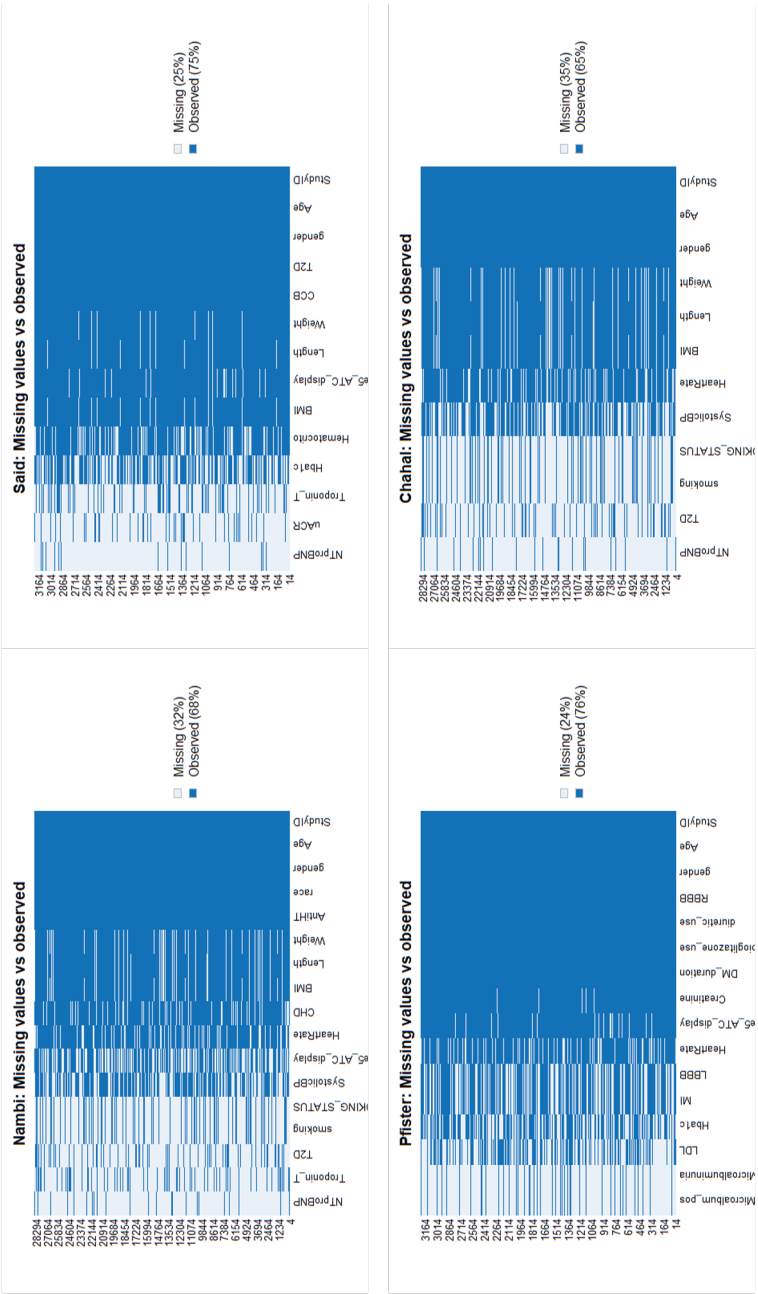
Table S2: *Missing values in the entire UPOD cohort*

Variable	***Missing (N)***	***Missing (5)***
Sex	0	0.00
Age	0	0.00
Creatinine	166	0.58
eGFR	166	0.58
Weight	2582	9.08
Length	2951	10.38
Heart Rate	4872	17.14
QRS duration	4876	17.15
Hypertension	6821	23.99
Haematocrit	7861	27.65
Glucose	10082	35.46
Systolic BP	11866	41.74
Diastolic BP	11892	41.83
Mean BP	11904	41.87
Cholesterol	14087	49.55
HDL	14361	50.52
CRP	14467	50.89
LDL	17432	61.32
HbA1c	21559	75.83
Smoking status	21786	76.63
Troponin T	22369	78.68
LVMI	24773	87.14
Microalbuminuria	26623	93.65
Proteinuria	26655	93.76
uACR	26887	94.58
NTproBNP	26897	94.61
Cystatin C	28360	99.76

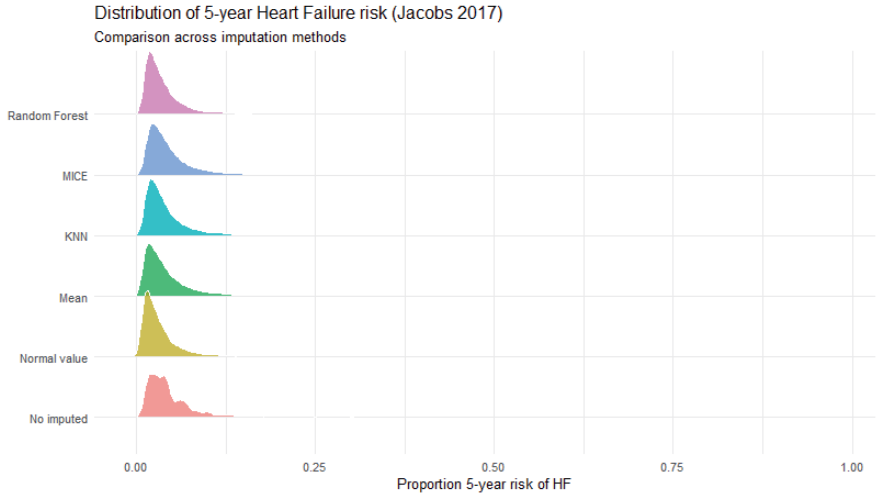


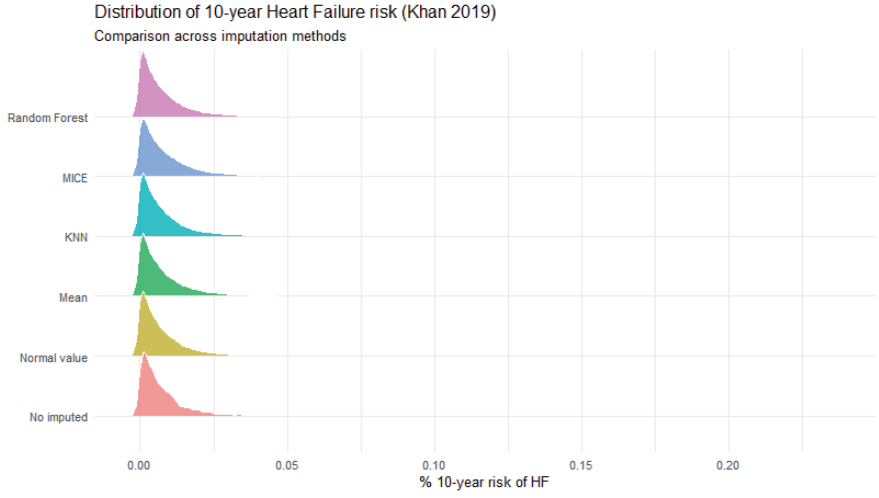
Figures S1: *Missing value pattern per model*

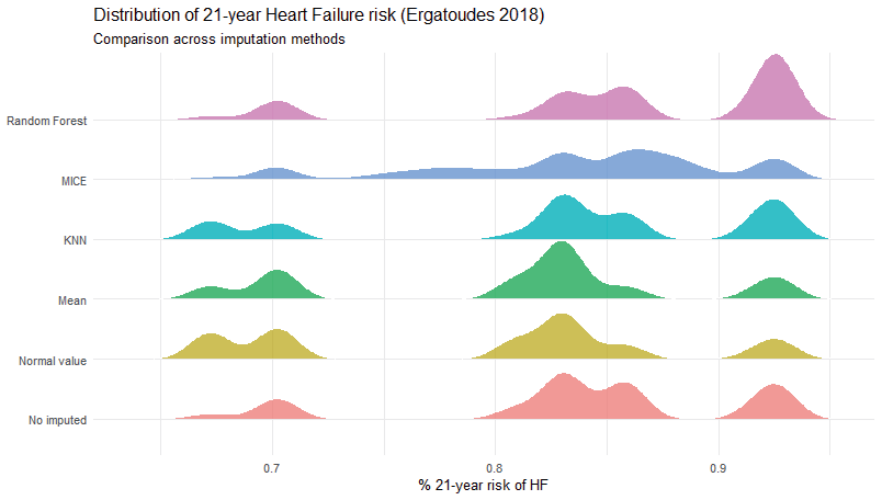
Figures S1: *Continued*

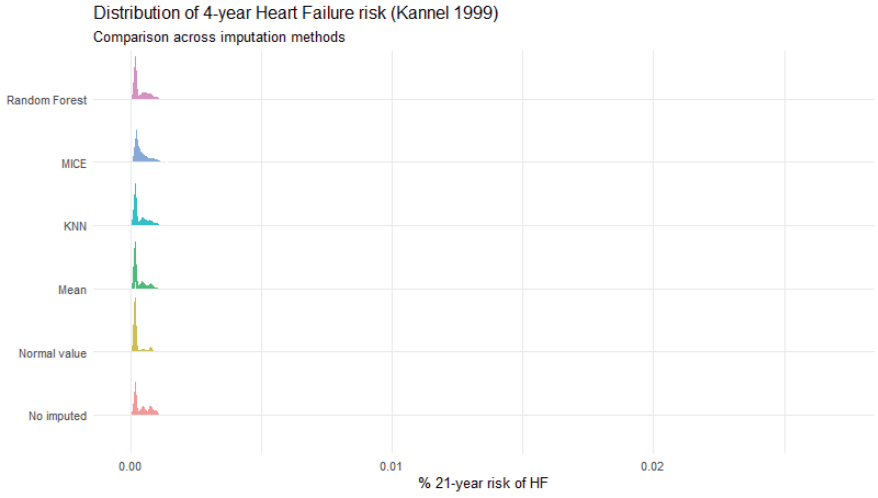


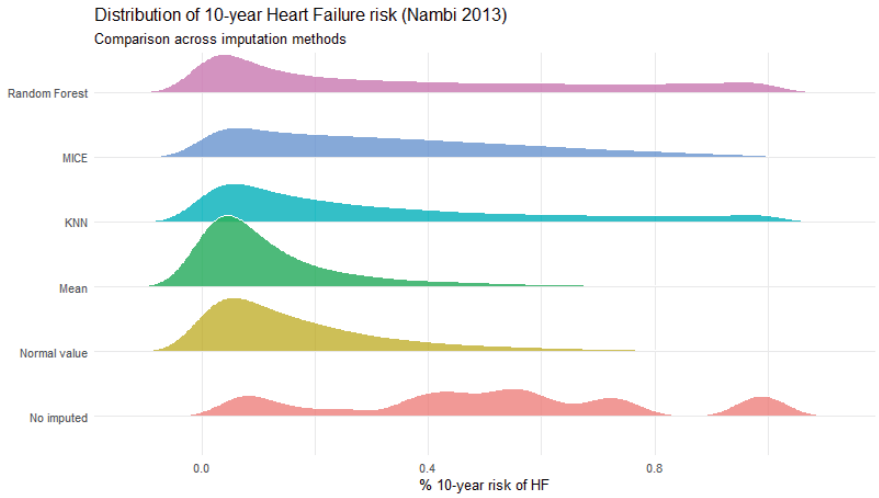
Figures S2: *Risk distribution across models stratified by imputation methods.*






Distribution of 21-year Heart Failure risk (Ergatoudes 2018)
Comparison across imputation methods
Random Forest
MICE
KNN
Mean
Normal value
No imputed
0.7
0.8
0.9
% 21-year risk of HF


Distribution of 4-year Heart Failure risk (Kannel 1999)
Comparison across imputation methods
Random Forest
MICE
KNN
Mean
Normal value
No imputed
0.00
0.01
0.02
% 21-year risk of HF


Distribution of 10-year Heart Failure risk (Nambi 2013)
Comparison across imputation methods
Random Forest
MICE
KNN
Mean
Normal value
No imputed
0.0
0.4
0.8
% 10-year risk of HF

PART

IV

Chapter

9

General Discussion & Conclusions

Summary of chapters

The increasing prevalence of cardiovascular and kidney disease advocates for better understanding how these conditions develop concurrently to inform potential ways for prevention, diagnosis and treatment. In this thesis, across eight chapters, using epidemiological state-of-the-art methodology and real-world data, we aimed to advance our understanding of sex differences, prognostic factors, and longitudinal changes in peripheral artery disease (PAD), chronic kidney disease (CKD), and left ventricular diastolic dysfunction (LVDD).

In **Chapter 2**, using a systematic review and meta-analysis approach we found that women with PAD present more often with atypical leg symptoms and rest pain, whereas men are more likely to report the classical intermittent claudication. The results were consistent across different subgroup analyses by age, history of diabetes mellitus (DM) and hypertension. These sex differences may lead to delayed diagnosis or misclassification, which ultimately might contribute to the under-treatment in women.[1-4]

In **Chapter 3**, we investigated the prognostic factors and prognostic models for mortality in patients with PAD. In this systematic review, we found that while numerous prognostic factors such as age, DM, hypertension, smoking status, and sex, were consistently associated with higher mortality outcomes, relatively few prognostic models exist. The imbalance between the abundance of known prognostic factors and the limited number of validated models evidenced the gap in translating epidemiological knowledge into practical clinical tools that inform clinical practice.

Chapters 4 and 5 explored further on sex differences. In **Chapter 4**, an observational study using routine clinical data, we assessed whether women and men consult differently with the general practitioner (GP) prior to diagnosis of PAD. Overall, the frequency of GP visits in the six months leading to diagnosis was similar between women and men with the number of consultations increasing the month before diagnosis for both sexes, often due to musculoskeletal complaints. **Chapter 5** focussed on the long-term outcomes of PAD. In this chapter, we conducted a nationwide record linkage study to evaluate sex differences in mortality following the first hospitalisation for lower extremity PAD. Our findings showed that long-term outcomes remain poor, with substantially increased mortality risks at 1-year and 5-year follow-up after hospitalisation, reflecting the progressive and systemic nature of atherosclerotic disease.

In Chapters 6 and 7 we focused on patients in tertiary care, where individuals typically present with more advanced disease and complex comorbidities. These chapters examined the association between kidney dysfunction and cardiac dysfunction, specifically CKD and LVDD. In **Chapter 6**, we conducted a cross-sectional study using

routine care data and found that abnormalities in echocardiographic markers indicative of LVDD became increasingly prevalent as kidney function declined. These findings were further reinforced in **Chapter 7**, a longitudinal study confirming that reductions in estimated glomerular filtration rate (eGFR) over time were paralleled by a progressive deterioration in echocardiographic parameter indicative of LVDD. This association remained stable during follow-up, with similar trajectories observed across different levels of kidney function. Together, these results showed the interconnected nature of kidney and cardiac dysfunction and suggest that, in patients with CKD, monitoring diastolic function may serve to early identify cardiac remodelling and facilitate risk stratification.

Finally, in **Chapter 8** we evaluated the missingness of the predictors underlying the prognostic models used to predict HF risk using data from EHR. We found that, across models, the availability of all required predictors was rare. Suggesting that the direct application of HF risk models in routine EHR data is challenging and possible in only a few cases. Hence, we further assessed the impact of different imputation strategies on the predicted risk estimates. While these models can generate risk estimates when missing data are addressed through imputation, the predicted risk estimates varied considerably with respect to results from non-imputed data and across imputation strategies.

Why sex differences matter

Sex differences in cardiovascular health are increasingly recognised as a critical determinant of disease risk, clinical presentation, treatment response, and outcomes. Men and women differ not only in biological factors such as sex hormones, body composition, and vascular biology, but also in behavioural, social, and structural determinants that influence exposure to risk factors, symptom perception, and access to healthcare.[5,6] These differences have important implications for cardiovascular prevention, diagnosis, and management, as a sex-neutral approach may overlook clinically relevant variation and contribute to inequities in care. Consequently, understanding and integrating sex differences into cardiovascular research has become a key priority in contemporary epidemiology and clinical practice. A significant part of this thesis is therefore dedicated to exploring sex differences.

In PAD the literature has traditionally focused on the influence of sex differences on mortality or long-term cardiovascular outcomes, with far less attention to sex differences in symptom presentation. In Chapter 2, we addressed this gap through a systematic review and meta-analyses that adds to the literature by showing that clinical presentation differs between sexes. These differences in clinical presentation may

contribute to the persisting underdiagnosis experienced by women and the differences in treatment and outcomes between women and men described by some authors.

Delayed diagnosis or underdiagnosis is also influenced by other factors. Older age at diagnosis often coincides with increased frailty, which may influence therapeutic decision-making. Evidence shows that women are more likely to be classified as frail than men. Consequently, clinicians might adopt more conservative treatment strategies in older women, either due to perceived vulnerability or concerns about adverse effects.[1,7-9] For example, a study involving U.S. veterans found that only 59% of women received antiplatelet therapy compared to 78% of men,[7] despite having the same clinical criteria for cardiovascular risk medication. [10,11]

Sex differences extend beyond disease presentation to prognosis and outcomes. In Chapter 3, sex was identified as a significant prognostic factor for mortality outcomes in patients with PAD, with some studies showing higher mortality among men. Yet, sex was rarely included in multivariable analyses. While it may be argued that no model is perfect and that no model can incorporate every relevant prognostic factor, and that other covariates (e.g., hormones, comorbidities) may capture some sex-related effects, or that developing separate models for men and women may be impractical, there remains room for improvement. Rather than focusing exclusively on the development of new models, researchers should prioritise the validation and refinement of existing models, evaluating whether the inclusion of additional variables, such as sex, improves predictive performance and increases clinical applicability.

In other chronic conditions such as CKD and heart failure, sex differences are also evident. Globally, the overall prevalence of CKD is higher in women, however, men are more likely to progress to end-stage kidney disease (ESKD).[12] This observation might be interpreted as evidence that men experience faster disease progression. An alternative explanation is that women, who on average have a longer life expectancy and often develop CKD at older ages, may be more likely to die from competing causes before reaching ESKD, thereby reducing the observed incidence of ESKD among women.

In general, we cannot understand sex differences only through biological mechanisms. They are shaped by other social and structural determinants that influence, for example, exposure to risk factors and access to healthcare. Women, particularly in older age, often experience greater economic vulnerability and lower income, which can limit access to healthcare and delay diagnosis. These disadvantages compound over time. For example, women with PAD are more likely to present later and with greater functional impairment (Chapter 4), while in CKD they are less frequently referred for nephrology evaluation or kidney replacement therapies despite similar disease severity. [12, 13]

Behavioural patterns further contribute to these disparities. Men typically exhibit higher rates of behavioural risk factors such as smoking and alcohol use, which accelerates vascular and kidney injury, whereas women tend to engage more in preventive

behaviours yet delay seeking care or report symptoms less assertively. In PAD, this manifests as underreporting of leg symptoms, in CKD and LVDD, it contributes to delayed recognition of early disease and suboptimal control of comorbidities such as hypertension and DM.

In this thesis, I do not claim that all health disparities can be explained solely by sex differences, as numerous other factors contribute to these inequities. Rather, my aim is to highlight the importance of incorporating sex as a critical variable in research and clinical practice. Adopting a less sex-neutral approach represents a meaningful step toward reducing disparities. Although there are contexts in which sex may not be a relevant factor, for the diseases discussed in this thesis we demonstrate, through evidence generated by myself and other authors, that sex differences significantly influence disease presentation, prognosis, and diagnosis.

Our contributions to the field include the integration of findings from systematic reviews, meta-analyses, and clinical data, which collectively evidenced the need for a more sex-specific approach in study design, diagnostic processes, and clinical management. Future research should aim to understand the biological and sociocultural mechanisms driving sex disparities, using longitudinal analyses and models that are sex-stratified or sex-specific. Moreover, better integration of sex as a variable in prognostic models may be essential for achieving equitable, evidence-based care for both women and men.

The importance of prognostication

In an era increasingly shaped by precision medicine, prognostic research plays an important role in advancing towards personalised medicine. Studies assessing individual prognostic factors (i.e., variables that independently predict outcomes), as well as prognostic models that combine these factors into algorithms to estimate an absolute individual risk, are essential tools in clinical practice.[14]

Prognostic models are important not just for risk estimation, but also for clinical decision making.[15] The identification of patients at higher or lower risk of adverse outcomes allow clinicians to select treatment strategies and determine who might benefit of more intensive or conservative care. This is particularly important in the management of chronic and progressive conditions such as PAD, CKD, and LVDD. Unlike acute conditions, where treatment pathways are typically defined by immediate clinical priorities, chronic diseases evolve over years and are influenced by multiple factors. Prognostic models help clinicians anticipate disease progression, choose the appropriate timing for interventions, and allocate healthcare resources more effectively.

A simple but illustrative example is the use of eGFR and albuminuria levels for risk stratification in CKD.[16] This classification, recommended in the Kidney Disease:

Improving Global Outcomes (KDIGO) guidelines, categorises patients into risk strata based on the combination of kidney function and kidney damage. Although it is primarily intended for disease staging rather than individualised risk prediction, it illustrates how prognostic information can be translated into clinical guidance. Specifically, higher-risk categories are associated with an increased likelihood of disease progression and cardiovascular complications and therefore prompt more intensive monitoring. In this way, the KDIGO framework demonstrates how integrating prognostic information into clinical guidelines can support structured and timely clinical decision-making.

While the value of prognostic information is clear, translating models from research to everyday clinical practice remains challenging. The implementation of prognostic models in routine care faces considerable barriers. It is not surprising that multiple models have been developed for important clinical outcomes, different research groups often use different datasets, populations, and methodological approaches to predict similar endpoints (e.g., mortality, amputation, or cardiovascular events). On one hand, this diversity of models can be beneficial, as it encourages innovation and allows researchers to refine existing tools. On the other hand, the abundance of models can paradoxically affect clinical implementation. The lack of consensus on which model to use may reduce clinicians' confidence in applying these tools in practice, particularly when different models produce inconsistent risk estimates for the same patient.

In **Chapter 3** and **Chapter 8**, we provided evidence that considerable heterogeneity exists among studies assessing prognostic factors and models for mortality outcomes in PAD and HF risk, respectively. These differences extend beyond the variables included in multivariable models to how predictors are defined, the cut-offs applied to continuous variables, and the statistical weight assigned to each factor. Such variability limits its clinical use and complicates comparison across models.

One approach to address this heterogeneity is through model validation. Traditionally, external validation has been considered essential to confirm whether a model performs reliably across populations and settings different from those in which it was developed.[17] However, recent perspectives challenge the idea that external validation is always necessary. As discussed by La Roi-Teeuw et al. (2024),[18] external validation should not be considered a universal requirement for all models, especially in the context of machine learning or artificial intelligence (AI) models that are continuously updated using local data. In these cases, calibration may be more appropriate than repeated external validation, allowing models to adapt dynamically to their clinical environment while maintaining accuracy.

Even models that undergo external validation may have limited applicability to specific subgroups. **Chapters 6** and **7** of this thesis illustrated this point in the context of LVDD and HFpEF. The echocardiographic diagnostic algorithms proposed by Nagueh et al.[19] and Pieske et al.[20] include parameters such as the left atrial maximum volume index

(LAVI), which cannot be reliably assessed in patients with atrial fibrillation (AF) due to the absence of coordinated atrial contraction and beat-to-beat variability.[19] This resulted in the exclusion of patients with AF from our cohorts. This exclusion, however, does not constitute selection bias but reflects clinical reasoning, the algorithm's assumptions are invalid in AF physiology. This evidenced an important point, many prognostic models are designed for very specific populations and may be not generalisable to real-world, heterogeneous clinical settings.

Beyond validation, methodological rigor is another challenge. As shown in **Chapter 3**, numerous prognostic models suffer from inadequate handling of missing data, inconsistent variable definitions, limited transparency regarding predictor selection, and poor reporting of calibration and discrimination. Despite their apparent clinical appeal, such shortcomings undermine reliability and partly explain why no prognostic model is currently recommended in PAD guidelines.[21]

To improve both the scientific and clinical value of prognostic research, several priorities emerge. First, researchers should emphasise transparency and reproducibility, adhering to reporting guidelines such as TRIPOD and TRIPOD-AI.[22,23] Second, more attention should be given to updating, recalibrating, and validating existing model across diverse populations and settings. Third, future efforts should focus on including prognostic models into EHRs. This would minimise the burden on clinicians to calculate the risk estimates manually. In that way, researchers would be creating prognostic tools not only based on statistical significance but also considering that these tools would have a clinical relevance in the future and ease future implementation.

From cross-sectional to longitudinal studies

The integration of longitudinal data into clinical prediction models holds great promise. Most prognostic models are built using information collected at a single point or index date. While this provides a static estimate of risk, it ignores that patient characteristics and exposures change over time. Incorporating time-varying predictors, such as blood pressure, eGFR, or medication use, can improve the predictive accuracy and capture temporal patterns that precede adverse outcomes. This is particularly valuable in chronic conditions such as PAD, CKD, and LVDD, where disease progression is nonlinear, that is, patients do not deteriorate in a steady, predictable way but may experience long periods of stability interrupted by sudden declines or acute events.

Despite these advantages, longitudinal modelling is not universally applied. Developing dynamic prediction models is statistically demanding because data are often incomplete, follow-up intervals are irregular, and time-varying confounders are difficult to handle (**Chapter 7**). Moreover, not every clinical setting collects sufficient repeated

measures to support such approaches. For this reason, most existing prognostic models still rely on baseline information, which is simpler to obtain and interpret.
Another methodological challenge is the presence of competing risks. For instance, in patients with PAD, death from cardiovascular causes may occur before an amputation can take place. In such cases, the occurrence of one event precludes the observation of another. Ignoring competing events can lead to biased estimates. This bias arises because individuals must survive long enough to experience the event of interest, thereby distorting the true relationship between predictors and outcomes.
To fully exploit the potential of longitudinal data, advanced statistical methods are required. Techniques such as multistate models can estimate transitions between disease stages and incorporate repeated measurements over time. For example, a patient with CKD may transition from CKD without heart failure to CKD with symptomatic heart failure, and eventually to dialysis or death. Multistate models quantify the probabilities of these transitions, offering clinicians a clearer view of disease evolution and prognosis.[24] In parallel, machine learning and artificial intelligence (AI) approaches, such as recurrent neural networks and dynamic survival models, might help to identify patterns that are not be evident through traditional methods.
In this thesis, we used routinely collected clinical data to evaluate how changes in echocardiographic parameters and kidney function influence disease trajectories over time (**Chapter 7**). Future research should build on this work by developing dynamic, interpretable prediction tools that integrate longitudinal data, account for competing risks, and can be continuously updated within EHRs systems. Such tools could support personalised, real-time risk assessment and more adaptive clinical decision making.

The use of electronic health records in research

The integration of EHRs into routine care has transformed the landscape of clinical epidemiology, creating new opportunities for longitudinal studies.
As mentioned in our introduction, while EHRs offer several advantages including access to real-world, diverse populations and repeated longitudinal measurements, it presents significant challenges. For example, missing data is often an issue when working with data collected in clinical settings.
This thesis used EHRs to study consultation patterns and mortality trends in patients with PAD (**Chapters 4** and **5**), to evaluate association and trajectories of kidney function and echocardiographic parameters indicative of LVDD in individuals with CKD (**Chapter 6** and **7**), and to assess how different approaches to handling missing data affect the applicability and stability of heart HF risk predictions models in EHR settings (**Chapter 8**). These analyses demonstrate that despite the limitations, data collected in EHRs is a highly valuable source of information to explore disease progression, healthcare

utilisation, and outcomes in ways that would be difficult to achieve through traditional cohort studies or clinical trials due to costs, ethical and logistical limitations.
The next step is to move from descriptive and retrospective analyses toward predictive and adaptive systems that continuously learn from EHR data, learning health systems (LHS). For instance, integrating longitudinal EHRs information into dynamic prognostic models could enable real-time risk estimation that evolves as new data become available. LHS could transform EHRs from passive repositories into active tools for quality improvement. Achieving this, however, requires more than computational power, it depends on robust data governance, interoperability across systems, and strong partnerships between clinicians, data scientists, and policymakers for interpretation of clinically relevant questions and findings.
This thesis demonstrated that the use of EHRs can bridge the gap between epidemiology and clinical practice. If we embrace the complexity of real-world data, we can move toward a truly responsive healthcare system, one that learns from every patient to improve care for the next.

Clinical implications and future directions

This thesis contributes to our understanding of chronic vascular and kidney disease from complementary perspectives. Across different studies, we examined PAD, CKD, and LVDD as distinct conditions that share common risk factors, prognostic challenges, and opportunities for earlier detection. The overlapping epidemiology and mechanisms place them within the broader context of the cardiovascular-kidney-metabolic syndrome, a term that emphasises how vascular, kidney, and metabolic dysfunction often coexist and reinforce one another.
From a clinical perspective, the findings provided evidence of the value of early identification of high-risk patients. In this thesis, even mild declines in kidney function were linked to structural and functional cardiac changes consistent with early LVDD. Recognising these early markers could allow clinicians to intervene sooner, perhaps slowing disease progression and improving long-term outcomes. However, this potential for earlier detection must be balanced against the risk of overdiagnosis and overtreatment. Widespread echocardiographic screening of all CKD patients, for instance, may be neither feasible nor desirable. Apart from the resource implications, this approach could lead to unnecessary anxiety for patients, medicalisation, or interventions without proven benefit. The challenge lies in identifying those subgroups most likely to benefit. Prognostic models integrated into EHRs could help identify when additional testing adds value.
Sex differences represent another important clinical consideration. In this thesis we showed that women with PAD are frequently diagnosed later than men and often

present with atypical symptoms. These differences are not only biological but also social, reflecting disparities in symptom recognition and health-seeking behaviour. Addressing sex disparities requires more than awareness. It calls for revising diagnostic criteria, ensuring equitable inclusion in clinical research, and training healthcare providers to recognise how disease manifests differently between sexes. Incorporating sex-specific predictors into risk models and ensuring that new algorithms are tested and calibrated separately in men and women are essential steps toward personalised, equitable care.

The use of EHR data offers a bridge between research findings and everyday clinical practice. This thesis showed that routinely collected data can reveal clinically meaningful patterns in disease trajectories and healthcare utilisation. EHRs can help identify patients at risk and monitor changes over time, bridging the gap between epidemiology and practice. Yet, it demands that we accept the imperfections of real-world data and learn to interpret them in context. Missing data, irregular follow-up, and variability in measurement frequency are not merely flaws but reflections of how clinical practice operates.

Perhaps one of the most pressing challenges is to make care sustainable. The coexistence of PAD, CKD, and LVDD illustrates how patients increasingly present with multimorbidity. Coordinating clinical care for the multimorbid patient is complex. Every additional diagnostic test or consultation, while potentially beneficial for an individual, adds cost and workload to systems already under pressure. The way forward may lie in developing targeted, risk-based approaches to guide when specialist input or advanced testing is warranted, and when routine monitoring suffices. Shared digital infrastructure, combined with collaborative protocols, could support efficient multidisciplinary care without overwhelming resources.

In conclusion, this thesis shows that embracing the complexity of real-world data can help connect epidemiology with everyday clinical care. The integration of longitudinal data, attention to diversity, and collaboration across disciplines are not just methodological refinements but essential steps toward a better health system.

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Appendices

Comprehensive English Summary

Heart and kidney diseases are among the most common long-term health problems worldwide. Many people do not realise that these conditions are closely connected. When the heart, blood vessels, or kidneys stop working properly, problems in one organ can cause problems in the others. This interaction is known as the cardiorenal connection. Three conditions play an important role in this, peripheral arterial disease (poor blood flow to the limbs, most commonly the legs), chronic kidney disease, and a type of early heart dysfunction called diastolic dysfunction. They often occur together and share many of the same risk factors, such as high blood pressure, diabetes, smoking, and ageing.

The goal of this thesis was to better understand these conditions and how they affect different groups of patients. To do this, I used real-world data from electronic health records, which reflect everyday clinical practice, and modern research methods. The work focuses on three main themes: differences between women and men, factors that predict poor outcomes, and how health changes over time.

A major finding of this research is that women and men often experience peripheral arterial disease differently. Women tend to report less typical symptoms, which can make the disease harder to recognise early. Men more often describe the classic symptom of pain in the legs while walking that goes away with rest. Because women's symptoms are more varied, they are at risk of being diagnosed later. This matters, because earlier diagnosis can lead to better treatment and improved long-term outcomes.

The thesis also shows that even though many factors are known to increase the risk of complications in peripheral artery disease, only a small number of prediction tools exist to help doctors identify high-risk patients. Some of these tools leave out important information, such as the patient's sex. As a result, they may not work equally well for everyone.

Another part of the thesis focused on the connection between kidney function and the heart. As kidney function gets worse, the heart can have more difficulty relaxing and filling with blood, which is an early sign of heart failure. This work showed that these changes in the heart happen gradually and are already present in people who do not yet have symptoms. This finding supports the idea that heart and kidney disease should be monitored together rather than separately.

Finally, the thesis explored the strengths and limitations of using electronic health records for research. These records contain valuable information about large and diverse groups of patients, making it possible to study real-life disease patterns. However, important data are often missing, which can make it difficult, for example, to apply certain prediction tools in practice.

Nederlandse Samenvatting

Hart- en vaatziekten en chronische nierschade vormen een steeds grotere belasting voor de volksgezondheid. Deze aandoeningen komen vaak gelijktijdig voor en beïnvloeden elkaar via complexe fysiologische processen, een samenhang die doorgaans wordt aangeduid als het cardiorenale syndroom (CRS). Perifeer arterieel vaatlijden (PAV), chronische nierschade (CNS) en linkerventrikel diastolische disfunctie (LVDD) zijn belangrijke manifestaties binnen dit syndroom. Zij delen gemeenschappelijke risicofactoren en treden vaak op bij dezelfde patiënten.
Het doel van dit proefschrift is om het inzicht in deze onderling verbonden aandoeningen te vergroten door hun epidemiologie, diagnose en prognose te bestuderen. Met behulp van real-world data afkomstig uit elektronische patiëntendossiers en moderne epidemiologische methoden richten de acht hoofdstukken zich op sekseverschillen, prognostische factoren en ziektebeloop in PAV, CNS en LVDD.

Sekseverschillen bij PAV

Sekse speelt een belangrijke rol in cardiovasculaire gezondheid. Mannen en vrouwen verschillen niet alleen biologisch, maar ook in gedragsmatige, sociale en structurele factoren die van invloed zijn op blootstelling aan risicofactoren, symptoominterpretatie en toegang tot zorg. Het herkennen en begrijpen van sekseverschillen is daarom essentieel voor een juiste diagnose en een eerlijke behandeling.
Het proefschrift start met de vraag hoe vrouwen en mannen zich presenteren met PAV. In **Hoofdstuk 2** worden resultaten samengebracht uit een systematische review en meta-analyse van studies bij patiënten met PAV in de onderste extremiteiten. Hieruit blijkt dat vrouwen vaker atypische beenklachten of rustpijn rapporteren, terwijl mannen vaker de klassieke claudicatio intermittens beschrijven, met pijn of vermoeidheid tijdens inspanning die vermindert in rust. Deze patronen kwamen consequent terug in verschillende leeftijdsgroepen en bij patiënten met comorbiditeiten zoals hypertensie en diabetes. Dit suggereert dat diagnostische trajecten die vooral op “typische” symptomen zijn gebaseerd, het risico op onderdiagnostiek bij vrouwen vergroten.
Hoofdstuk 3 onderzoekt welke factoren de mortaliteit bij PAV voorspellen en beoordeelt de kwaliteit en beschikbaarheid van bestaande prognostische modellen. Hoewel factoren zoals leeftijd, diabetes, roken, hypertensie en sekse herhaaldelijk samenhangen met sterfte, bestaan er slechts enkele prognostische modellen. Bovendien nemen sommige modellen belangrijke variabelen, zoals sekse, niet mee, ondanks hun aantoonbare prognostische waarde. Dit wijst op een kloof tussen

beschikbare epidemiologische kennis en de ontwikkeling of validatie van praktische hulpmiddelen voor de kliniek.
In Hoofdstuk 4 en 5 worden sekseverschillen verder onderzocht. **Hoofdstuk 4** bekijkt of het zorggebruik voorafgaand aan de diagnose verschilt tussen mannen en vrouwen. Analyse van data uit de huisartsenpraktijk liet zien dat het aantal consulten in de zes maanden vóór de diagnose vergelijkbaar was tussen mannen en vrouwen. In de laatste maand voor de diagnose steeg het aantal consulten voor beide groepen, vaak in verband met musculoskeletale klachten. Dit wijst erop dat verschillen in zorgzoekend gedrag de diagnostische achterstand bij vrouwen waarschijnlijk niet volledig verklaren.
Hoofdstuk 5 richt zich op de langetermijnuitkomsten na een eerste ziekenhuisopname wegens PAV. Long-term mortaliteit bleek hoog te blijven, ook vijf jaar na ontslag. Dit onderstreept het progressieve en systemische karakter van PAV en benadrukt het belang van vroege herkenning, adequate risicostratificatie en langdurige follow-up.

De relatie tussen CNS en LVDD

Binnen het cardiorenale systeem kunnen vasculaire en hemodynamische veranderingen leiden tot nierschade. Omgekeerd vergroot verslechterende nierfunctie het risico op LVDD en uiteindelijk hartfalen. Hoofdstukken 6 en 7 richten zich op deze wisselwerking in tertiaire zorg, waar patiënten vaak complexe en gevorderde ziektebeelden hebben.
In **Hoofdstuk 6** laat een dwarsdoorsnede-analyse zien dat afwijkingen in echocardiografische parameters van de diastolische functie vaker voorkomen naarmate de nierfunctie slechter wordt. In **Hoofdstuk 7** wordt deze relatie longitudinaal onderzocht. Een lagere nierfunctie bleek geassocieerd met iets hogere waarden van diastolische parameters die wijzen op LVDD. Deze verschillen bleven relatief stabiel gedurende de follow-up en er was geen bewijs voor verschillen in verandering over de tijd tussen verschillende stadia van nierschade.

Wat real-world data ons kan leren, en de beperkingen ervan

Gegevens uit elektronische patiëntendossiers bieden waardevolle mogelijkheden om ziekteprogressie, zorggebruik en klinische uitkomsten te bestuderen in realistische zorgsituaties. Omdat dit proefschrift veel gebruikmaakt van dergelijke data, richt **Hoofdstuk 8** zich op een belangrijke methodologische uitdaging, ontbrekende gegevens. Veel prognostische modellen, vooral die voor het voorspellen van hartfalen, vereisen klinische variabelen die niet altijd in de dagelijkse praktijk worden vastgelegd. In dit hoofdstuk onderzochten we hoe verschillende methoden om ontbrekende data in te vullen de risicoschattingen beïnvloeden. De beschikbaarheid van alle benodigde voorspellende variabelen bleek zeldzaam en de geschatte risico's varieerden afhankelijk van de gekozen imputatiemethode. Dit maakt duidelijk dat toepassing van dergelijke

modellen in real-world EPD-data in de praktijk maar beperkt mogelijk is. Zelfs wanneer ontbrekende waarden worden geïmputeerd, kunnen de resulterende risicoschattingen sterk verschillen, zowel ten opzichte van niet-geïmputeerde data als tussen de verschillende imputationstrategieën. Hierdoor hangt de bruikbaarheid van prognostische modellen niet alleen af van de gebruikte statistiek, maar ook van de beschikbaarheid en kwaliteit van de benodigde gegevens.

Integratie van de bevindingen

Gezamenlijk laten de resultaten zien dat PAV, CNS en LVDD niet als afzonderlijke aandoeningen moeten worden beschouwd, maar als nauw met elkaar verbonden ziekteprocessen met gedeelde risicofactoren en overlappende mechanismen. Een geïntegreerde benadering van preventie, diagnostiek en behandeling is daarom noodzakelijk.

Daarnaast benadrukt dit proefschrift het belang van sekse als bepalende factor in hoe ziekten zich ontwikkelen en manifesteren. Het herkennen van deze verschillen is essentieel voor een meer rechtvaardige en gepersonaliseerde patiëntenzorg.

Tot slot toont dit werk zowel de waarde als de uitdagingen van het gebruik van real-world data. Elektronische patiëntendossiers maken onderzoek mogelijk in diverse en brede patiëntgroepen, maar vragen om zorgvuldige methoden om betrouwbare en toepasbare conclusies te trekken.

Resumen en Español

Las enfermedades cardiovasculares y la enfermedad renal crónica representan una carga cada vez mayor para la salud pública. Estas afecciones suelen coexistir e influirse mutuamente a través de procesos fisiológicos complejos, una interacción que generalmente se conoce como síndrome cardiorrenal (SCR). La enfermedad arterial periférica (EAP), la enfermedad renal crónica (ERC) y la disfunción diastólica del ventrículo izquierdo (DDVI) constituyen manifestaciones importantes de este síndrome. Comparten factores de riesgo comunes y con frecuencia se presentan en los mismos pacientes.

El objetivo de esta tesis es mejorar el conocimiento sobre estas enfermedades interrelacionadas mediante el estudio de su epidemiología, diagnóstico y pronóstico. Utilizando datos del mundo real procedentes de historias clínicas electrónicas y métodos epidemiológicos modernos, los ocho capítulos se centran en las diferencias por sexo, los factores pronósticos y la evolución clínica de la EAP, la ERC y la DDVI.

Diferencias por sexo en la enfermedad arterial periférica

El sexo desempeña un papel importante en la salud cardiovascular. Hombres y mujeres difieren no solo desde el punto de vista biológico, sino también en factores conductuales, sociales y estructurales que influyen en la exposición a los factores de riesgo, la interpretación de los síntomas y el acceso a la atención sanitaria. Reconocer y comprender estas diferencias es, por tanto, esencial para lograr un diagnóstico adecuado y un tratamiento equitativo.

Esta tesis comienza abordando cómo se presentan la EAP en mujeres y hombres. En el **Capítulo 2** se sintetizan los resultados de una revisión sistemática y un metaanálisis de estudios realizados en pacientes con EAP de las extremidades inferiores. Los resultados muestran que las mujeres presentan con mayor frecuencia síntomas atípicos en las piernas o dolor en reposo, mientras que los hombres presentan más a menudo la claudicación intermitente clásica, caracterizada por dolor o fatiga durante el ejercicio que desaparece con el reposo. Estos patrones fueron consistentes en diferentes grupos de edad y en pacientes con comorbilidades como hipertensión y diabetes. Estos hallazgos sugieren que los procesos diagnósticos basados principalmente en síntomas "típicos" pueden aumentar el riesgo de infra diagnóstico en las mujeres.

El **Capítulo 3** investiga qué factores predicen la mortalidad en la EAP y evalúa la calidad y disponibilidad de los modelos pronósticos existentes. Aunque factores como la edad, la diabetes, el tabaquismo, la hipertensión y el sexo se asocian repetidamente con la mortalidad, existen pocos modelos pronósticos disponibles. Además, algunos de estos modelos no incluyen variables importantes, como el sexo, a pesar de su demostrado

valor pronóstico. Esto pone de manifiesto una brecha entre el conocimiento epidemiológico disponible y el desarrollo o validación de herramientas pronósticas útiles para la práctica clínica.

En los **Capítulos 4 y 5** se profundiza en las diferencias entre hombres y mujeres. El **Capítulo 4** analiza si el uso de los servicios de atención sanitaria antes del diagnóstico difiere según el sexo. El análisis de datos procedentes de atención primaria mostró que el número de consultas durante los seis meses previos al diagnóstico fue similar entre hombres y mujeres. Durante el último mes antes del diagnóstico, el número de consultas aumentó en ambos grupos, con frecuencia debido a síntomas musculoesqueléticos. Esto sugiere que las diferencias en la búsqueda de atención médica probablemente no explican por completo el retraso diagnóstico observado en las mujeres.

El **Capítulo 5** se centra en los resultados a largo plazo tras la primera hospitalización por EAP. La mortalidad a largo plazo permaneció elevada incluso cinco años después del alta hospitalaria. Este hallazgo resalta la naturaleza progresiva y sistémica de la EAP y pone de relieve la importancia del reconocimiento precoz, una adecuada estratificación del riesgo y un seguimiento prolongado.

La relación entre la enfermedad renal crónica y la disfunción diastólica del ventrículo izquierdo

Dentro del sistema cardiorrenal, los cambios vasculares y hemodinámicos pueden provocar daño renal. A su vez, el deterioro de la función renal incrementa el riesgo de desarrollar DDVI y, finalmente, insuficiencia cardiaca. Los **Capítulos 6 y 7** estudian esta interacción en el ámbito de la atención terciaria, donde los pacientes suelen presentar enfermedades complejas y avanzadas.

En el **Capítulo 6**, un análisis transversal muestra que las alteraciones en los parámetros ecocardiográficos de la función diastólica son más frecuentes a medida que empeora la función renal. En el **Capítulo 7**, esta relación se evalúa de forma longitudinal. Una menor función renal se asoció con valores ligeramente más elevados de parámetros diastólicos indicativos de DDVI. Estas diferencias permanecieron relativamente estables durante el seguimiento y no se encontraron evidencias de que la evolución en el tiempo difiriera entre los distintos estadios de enfermedad renal.

Lo que los datos del mundo real pueden enseñarnos y sus limitaciones

Los datos procedentes de las historias clínicas electrónicas ofrecen valiosas oportunidades para estudiar la progresión de las enfermedades, la utilización de los servicios sanitarios y los resultados clínicos en condiciones de práctica clínica habitual.

Dado que esta tesis se basa ampliamente en este tipo de datos, el **Capítulo 8** aborda un importante desafío metodológico, los datos faltantes.
Muchos modelos pronósticos, especialmente aquellos destinados a predecir insuficiencia cardiaca, requieren variables clínicas que no siempre se registran en la práctica diaria. En este capítulo evaluamos cómo distintos métodos de imputación de datos faltantes afectan las estimaciones del riesgo. La disponibilidad de todas las variables predictoras necesarias fue escasa y los riesgos estimados variaron en función del método de imputación utilizado. Esto demuestra que la aplicación de estos modelos en datos del mundo real procedentes de historias clínicas electrónicas es limitada en la práctica. Incluso cuando los valores faltantes se imputan, las estimaciones de riesgo resultantes pueden diferir considerablemente, tanto respecto a los datos no imputados como entre las distintas estrategias de imputación. Por ello, la utilidad de los modelos pronósticos depende no solo de los métodos estadísticos empleados, sino también de la disponibilidad y calidad de los datos necesarios.

Integración de los hallazgos

En conjunto, los resultados de esta tesis muestran que la EAP, la ERC y la DDVI no deben considerarse enfermedades independientes, sino procesos patológicos estrechamente relacionados que comparten factores de riesgo y mecanismos fisiopatológicos. Por ello, es necesaria una estrategia integrada para la prevención, el diagnóstico y el tratamiento de estas enfermedades.
Asimismo, esta tesis destaca la importancia del sexo como un factor determinante en la forma en que las enfermedades se desarrollan y se manifiestan. Reconocer estas diferencias es fundamental para avanzar hacia una atención sanitaria más equitativa y personalizada.
Por último, este trabajo demuestra tanto el valor como los desafíos del uso de datos del mundo real. Las historias clínicas electrónicas permiten realizar investigaciones en poblaciones amplias y diversas, pero también requieren métodos rigurosos para obtener conclusiones fiables y aplicables.

About the Author

Cindy Porras was born on April 19, 1989, in Caucasia, Colombia, and grew up in Medellín, Colombia. In 2013, she obtained her degree as a Medical Doctor from Corporación Universitaria Remington. After graduating, she worked for several years as a medical doctor in emergency departments in public hospitals in Medellín, where she gained extensive clinical experience and developed a strong commitment to patient care, often in resource-limited settings.

Over time, she became increasingly interested in understanding disease beyond individual patients, particularly in how data and research could inform better clinical decisions and improve outcomes at a broader level. This motivated her to pursue a master's degree in clinical epidemiology at Utrecht University in the Netherlands. During her master's programme, she developed a strong interest in cardiovascular epidemiology, working with clinical data, and generating scientific evidence.

In 2022, Cindy started her PhD at the Department of Nephrology at the University Medical Centre Utrecht. Her research focuses on cardiovascular and kidney disease, combining observational studies using routine healthcare data with systematic reviews and meta-analyses.

Following the completion of her PhD, Cindy joined Erasmus University Medical Centre as an Epidemiologist and Principal Investigator of Real-World Studies within the DARWIN EU® Coordination Centre, where she contributes to the generation of real-world evidence to support regulatory decision-making and improve patient care.

List of Publications

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Cindy P. Porras, Roemer J. Janse, Gemma Valera-Arevalo, Mark C.H. de Groot, Saskia Haitjema, Marianne C. Verhaar, Michiel L. Bots, Robin W.M. Vernooij. The hidden barrier for heart failure risk prediction models: missing data and variation in predictions resulting from imputation methods

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"Keep Ithaka always in your mind. Arriving there is what you're destined for. But don't hurry the journey at all. Better if it lasts for years, so you're old by the time you reach the island, wealthy with all you've gained on the way, not expecting Ithaka to make you rich…"

– C. P. Cavafy

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