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Epidemiological Trends and Projections of Incidence, Prevalence, and Disease Related Mortality Associated With Peripheral Arterial Disease: Observations Using Nationwide Danish Data

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WHAT THIS PAPER ADDS

Peripheral arterial disease (PAD) is an increasing public concern. Given recent changes in the prevalence of atherosclerotic risk factors, up to date estimates of incidence, prevalence, and mortality are required to understand the burden. Within an unselected nationwide population, the incidence and all cause death declined from 2000 to 2018. Concurrently, prevalence increased and was projected to continuously rise over the coming decade, emphasising the growing burden in ageing populations. Despite cautious optimism about declining incidence and mortality, the increasing prevalence underscores that PAD remains a public healthcare burden with a continued need for optimal healthcare services and extensive costs in years to come.

Objective: Peripheral arterial disease (PAD) trends remain unclear because contemporary data are sparse and conflicting. This nationwide cohort study quantified changes in PAD incidence, prevalence, and all cause mortality, and projected prevalence development through to 2040.

Methods: Population based registries covering the entire Danish population aged $\geq$ 40 years from 2000 to 2018 were linked to assess trends in PAD incidence, prevalence, and all cause mortality, overall and by sex and age groups. Based on observed trends in incidence and mortality, and estimated future annual age distribution and population mortality, the PAD prevalence through to 2040 was projected.

Results: The Danish population aged 40 — 99 years in 2000 — 2018 included 4 811 281 individuals, among whom 145 870 incident PAD diagnoses were identified. The age and sex standardised PAD incidence decreased from 2.26 per 1 000 person years in 2000 to 1.65 in 2018 (incidence RR 0.74, 95% CI 0.72 — 0.77). The incidence was approximately 20% higher in men than women but declined similarly over time. Concurrently, PAD prevalence in the Danish adult population increased from 1.3% to 1.6% (prevalence ratio 1.28, 95% CI 1.26 — 1.30). Among patients aged $\geq$ 80 years, the prevalence reached 5.7% in women and 7.9% in men. The age and sex standardised annual mortality among patients with PAD decreased from 9.8% in 2000 to 7.2% in 2018 (mortality ratio 0.75, 95% CI 0.72 — 0.78). Projections of PAD prevalence demonstrated that the rising PAD prevalence will continue until around 2030, followed by a decline towards 2040. Among individuals aged $\geq$ 80 years, the prevalence was projected to plateau at 8.9% for men and 6.2% for women before declining.

Conclusion: Within an unselected nationwide population, the incidence and all cause mortality of PAD have declined over the last two decades. Concurrently, prevalence increased and is projected to increase further over the coming decade, emphasising the growing burden of this common atherosclerotic disease in ageing populations.

Keywords: Epidemiology, Incidence, Mortality, Peripheral arterial disease, Prevalence, Projections
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INTRODUCTION

Peripheral arterial disease (PAD) is the third leading cause of atherosclerotic morbidity after coronary heart disease and stroke. It is a complex and progressive atherosclerotic disease of the peripheral vasculature, resulting in cardiovascular and limb associated complications including exertional limb symptoms, ischaemic ulcers, gangrene, and amputations.[1,2] Advanced disease with critical limb ischaemia carries a one year mortality rate close to 50%.[3,4]

Previous studies have indicated that the global burden of PAD continues to grow in parallel with the expanding burden of atherosclerotic risk factors and ageing populations.[5–7] The Global Burden of Disease study recently demonstrated that the global number of prevalent PAD cases has risen consistently since 1990.[8] Concomitantly, disability adjusted life years, years of life lost, and years lived with disability have also increased.[8] Between 2010 and 2015, the numbers of persons living with PAD increased by 17%, affecting 237 million individuals in 2015 with an estimated prevalence of ~3% at 40 — 44 years of age and ~18% at 75 — 79 years in high income countries.[5,6] However, most studies were conducted in the late 1990s and early 2000s,[9–11] and it has been suggested that the incidence of PAD is beginning to decrease.[12,13] Even if the incidence is decreasing, the prevalence may still increase if screening practice changes and populations live longer.[13] Given recent changes in the prevalence of atherosclerotic risk factors (e.g., epidemics of diabetes[14] and obesity,[15] and declining prevalence of smoking[16,17]), contemporary estimates of PAD prevalence are needed to appreciate the potential burden of PAD.

This study investigated trends in PAD incidence, prevalence, and mortality in the Danish population. It assessed the influence of age, birth cohort, and period of diagnosis on prevalence trends, and then made projections of PAD prevalence development through to 2040.

METHODS

Setting and data sources

This nationwide study was conducted in Denmark where all ~5 800 000 inhabitants are provided with state funded healthcare free of charge.[18] All residents are assigned a unique 10 digit civil registration system (CRS) number, which is used for all healthcare contacts, including hospitalisations and prescription medicine, and facilitates complete individual level linkage between nationwide Danish registries.[19] This study linked data from the CRS, which has provided complete day to day accounts of the Danish population since 1968 (including information about sex, date of birth, vital status, and emigration status[19]) and the National Patient Register (DNPR), which has collected data on all admissions and discharges from non-psychiatric hospitals since 1977 and outpatient visits since 1995.[20] Each hospital discharge or outpatient visit is recorded in the DNPR with one primary diagnosis and up to 20 secondary diagnoses coded according to the International Classification of Diseases 8th revision (ICD-8) during 1977 — 1993, and ICD-10 thereafter. Information about the annual composition and mortality of the Danish population, and the expected population size and one year mortality in one year age groups was obtained from the population prognosis 2022 — 2060 from Statistics Denmark.[21,22]

Ethics and data availability

The study was based on data from Statistics Denmark and approved by the Danish Data Protection Agency through institutional registration (record number 2017-509-00006), which does not require ethical approval according to Danish law. Owing to data protection rules, individual level data are not allowed to be shared. Researchers who fulfil the requirements set by the data providers could obtain similar data.

Study population

The Danish population aged ≥ 40 years between 2000 — 2018 served as the source cohort. Population level information on the Danish population on 1 January each year, annual number of deaths, immigrants, and emigrants in one year age groups was obtained from publicly available statistics at Statistics Denmark (www.statistikbanken.dk).

Individuals with peripheral artery disease

Peripheral artery disease was identified by primary or secondary inpatient or outpatient clinic diagnoses in the DNPR using ICD-10 codes: I702, I739A, and I739C. In the Danish version of ICD-10, 739A corresponds to intermittent claudication, and I739C refers to pain at rest of ischaemic nature of the lower extremities. Prevalent cases of PAD were also identified using ICD-8 codes: 44020, 44030, 44390, 4444, and 445. Peripheral artery disease diagnoses given to individuals aged < 40 years were excluded because ischaemia in younger individuals is rare and generally unrelated to chronic progressive PAD. An incident case was defined as a patient with an admission or outpatient clinic contact with PAD during 2000 — 2018, whose preceding complete hospital history, potentially back to 1977, lacked a PAD diagnosis. In the DNPR, the positive predictive value of PAD diagnoses is ~70%, but higher for primary (~76%) and inpatient (~81%) diagnoses.[23] The diagnosis was considered to be definitive and patients were classified as prevalent until death, censoring at emigration, or end of study (31 December 2018). Patients diagnosed before 1 January 2000 were included as prevalent cases. To align with the population data provided by Statistics Denmark, patients were censored at 100 years of age.

Statistical analyses

Trend analyses. Annual incidence rates were calculated as the number of incident PAD diagnoses divided by the population at risk (entire population minus prevalent cases on 1 January each year). Incidence rates were expressed as incident cases per 1 000 person years. Annual prevalence

proportions were calculated by dividing the number of prevalent PAD cases by the census population estimate on 1 January each year, expressed as prevalent cases per 100 persons (%) in the population. The annual mortality was calculated by dividing the annual number of all cause deaths in individuals with PAD by the number of persons living with PAD in Denmark on 1 January each year.

Incidence rates, prevalence proportions, and mortality rates were calculated within calendar year, sex, and one year age groups, and reported overall and by sex and age group (40 – 59, 60 – 79, and ≥ 80 years). The joint effects of age, calendar period, and birth cohort on prevalence trends was visualised by a Lexis diagram applying a colour scheme where blue colours indicate lower prevalence and red indicate high prevalence. To present comparable annual incidence, prevalence, and mortality rates across calendar years, estimates for the age and sex distribution in Denmark in 2000 were standardised.

Projected prevalence of peripheral artery disease. Based on observed trends in incidence and mortality and the projected future annual age distribution, this study estimated the future prevalence of PAD in Denmark until 2040 using the Markov model. For full details, please see Supplementary material on extended statistical analyses. As the model depends on the unknown future trends in PAD incidence and mortality and the population mortality, three different hypothetical scenarios for the future incidence and mortality of PAD were formulated using the projected population mortality data.[22] In the main model, it was assumed that the trend in reduced incidence observed from 2000 to 2018 would continue; this way, the yearly incidence reduction also represents the future annual reduction in incidence. Based on the observed mortality rate in patients with PAD and the population mortality, 2000 – 2018, the excess mortality was estimated within age and year associated with PAD. In the main analysis, it was assumed that any future changes in mortality rate among patients with PAD would only reflect changes in population mortality, corresponding to a constant excess mortality over the projection period as in 2018.

To assess the robustness of the assumptions underlying the projections, a conservative scenario assuming a steady state model where observed incidence in 2018 would remain constant in the future (i.e., the observed decline in incidence would level off) was estimated. Another scenario allowing a yearly change in the excess mortality associated with PAD over the projection period was also estimated. The reported projected absolute number of patients with PAD was based on the projections of prevalence and expected population size.

Sensitivity analysis

Since ICD-10 code I74 (arterial embolism and thrombosis) may reflect incident PAD patients with acute limb ischaemia, the trend analyses were repeated using a second case definition including ICD-10 I74 to access how this influenced the estimates.

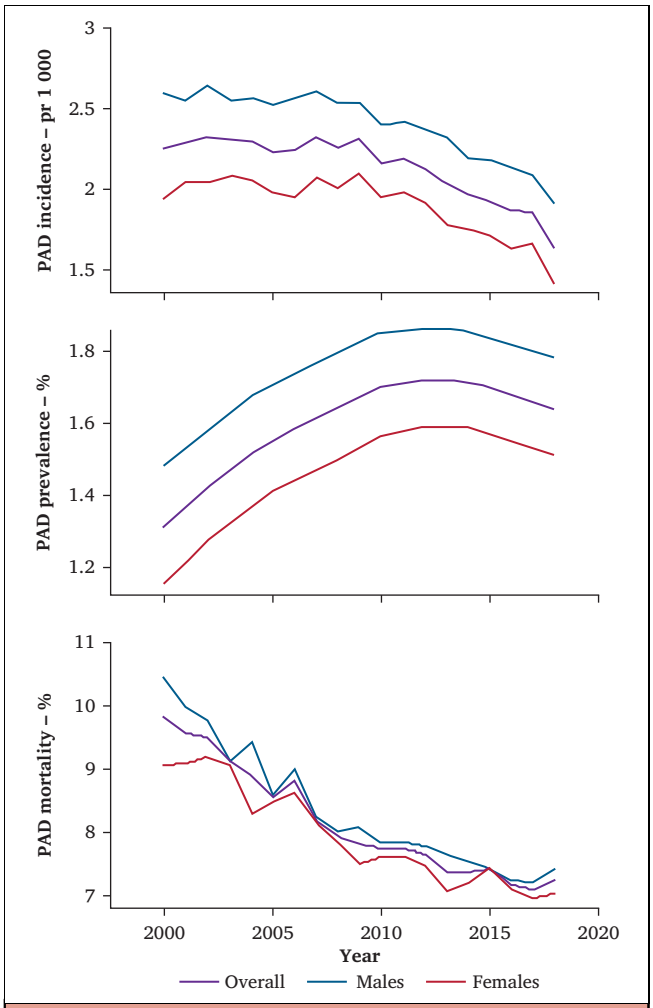

Figure 1. Peripheral arterial disease (PAD) in Denmark from 2000 to 2018. (A) Annual overall and sex stratified incidence; (B) Prevalence; (C) All cause mortality.

RESULTS

The study population included 4 811 281 individuals, with a total follow up of 51.4 million person years.

Incidence of peripheral artery disease

The overall age and sex standardised incidence of PAD decreased from 2.26 per 1 000 person years in 2000 to 1.65 in 2018, representing an incidence rate ratio (IRR) of 0.74 (95% CI 0.72 – 0.77) (Fig. 1A, Table 1). The incidence was approximately 20% higher in men than in women but similarly decreased over time. The decrease was less pronounced in women aged ≥ 80 years than in men (IRR of 0.89 in women *vs.* 0.72 in men).

Prevalence of peripheral artery disease

The overall age and sex standardised prevalence increased from 1.3% in 2000 to 1.6% in 2018, with a prevalence ratio (PR) of 1.28 (95% CI 1.26 – 1.30) (1.32 in women *vs.* 1.25 in men). This corresponded to a 68% increase (61% in women *vs.* 75% in men) in the number of adults aged ≥ 40 years living with PAD from 2000 to 2018 (Fig. 1B, Table 2).

Table 1. Age and sex specific incidence of peripheral arterial disease, 2000–2018, in Denmark

Group	2000		2010		2018		Incidence rate ratio 2018 *vs.* 2000, IRR (95% CI)
	PAD / population at risk – *n**	Incidence rate*	PAD / population at risk – *n*†	Incidence rate*	PAD / population at risk – *n*†	Incidence rate*	
Overall – y							
40–59	1 079/1 468 000	0.74	1 013/1 520 000	0.68	768/1 556 000	0.49	0.66 (0.60–0.72)
60–79	3 185/810 000	3.98	3 538/1 008 000	3.70	3 312/1 157 000	2.82	0.72 (0.69–0.76)
≥80	1 312/189 000	6.94	1 466/201 000	7.21	1 310/226 000	5.67	0.81 (0.75–0.88)
All ages	5 576/2 467 000	2.26	6 017/2 731 000	2.17	5 390/2 937 000	1.65	0.74 (0.72–0.77)
Females – y							
40–59	405/727 000	0.56	363/755,000	0.48	249/775 000	0.31	0.57 (0.48–0.66)
60–79	1 409/440 000	3.2	1475/527,000	3.02	1 297/602 000	2.19	0.69 (0.64–0.74)
≥80	719/128 000	5.62	877/131,000	6.64	701/139 000	5.02	0.89 (0.80–0.98)
All ages	2 533/1 294 000	1.96	2 715/1 413 000	1.95	2 247/1 516 000	1.42	0.73 (0.69–0.78)
Males – y							
40–59	674/741 000	0.91	650/766 000	0.86	519/781 000	0.65	0.71 (0.64–0.80)
60–79	17 76/371 000	4.79	2 063/482 000	4.50	2 015/556 000	3.58	0.75 (0.70–0.79)
≥80	593/60 882	9.71	589/70 000	8.39	609/86 000	7.02	0.72 (0.65–0.81)
All ages	3 043/117 2000	2.60	3 302/1 318 000	2.41	3 143/1 423 000	1.91	0.75 (0.71–0.79)

PAD = peripheral arterial disease; CI = confidence interval.
* Incidence rate per 1 000 person years. Rates are standardised to the 2000 Danish population.
† Population at risk is estimated as the entire population minus prevalent PAD cases on 1 January each year, minus half the number of deaths and emigrants, and plus half the number of immigrants that given year. Estimates are rounded to nearest 1 000.

General population ageing could not account for this increase since the Danish adult population increased by 20% during this period (Table 2). Most of the increase occurred among adults aged ≥ 80 years (PR 1.89, 95% CI 1.84 – 1.94), whereas the prevalence among adults aged 40 – 59 years declined over time (PR 0.82, 95% CI 0.79 – 0.85). In 2018, the prevalence of PAD was 5.7% in women aged ≥ 80 years and 7.9% in men aged ≥ 80 years.

The prevalence in subgroups of age, calendar years, and birth cohorts are shown in Figure 2. Within all calendar periods and birth cohorts, the prevalence rose with age, apart from the first five years of the study where prevalence remained low across all age groups. Age groups < 60 years experienced relatively constant low prevalence over time, whereas the prevalence in the oldest age groups rose over time. The prevalence was particularly high in birth cohorts between 1920 and 1930 and decreasing with younger birth cohorts.

All cause mortality

Overall, the annual age and sex standardised all cause mortality among patients with PAD decreased from 9.8% in 2000 to 7.2% in 2018, representing a mortality rate ratio (MRR) of 0.75 (95% CI 0.72 – 0.78) (Fig. 1C, Table 3). This decrease was greater in men than women (MRR 0.71 *vs.* 0.80), and in individuals aged 60 – 79 years compared with the younger and older age groups (MRR 0.69 *vs.* 0.84 and 0.79, respectively) (Table 3). The mortality rate among patients with PAD was 1.5 to 14 fold higher than the general population of the same age and sex (Supplementary Fig. S1). This excess mortality was highest in the youngest age groups and slightly increased over time across age groups (by 1.1%, 95% CI 1.0 – 1.2% per year) in both men and women (Supplementary Fig. S2).

Projected peripheral artery disease prevalence

The observed and projected prevalence of PAD in Denmark from 2000 to 2040 in men and women is shown in Figure 3 (main model). Supplementary Figures S3 and S4 present prevalence, number of PAD patients, and population size to 2040 according to the different model scenarios. According to the main projection, the observed rise in the national prevalence of PAD will continue until around 2025, with a subsequent plateau until 2030 followed by a decline towards 2040 (Fig. 3). Among individuals aged ≥ 80 years, the prevalence is projected to reach 6.5% before beginning to decline; for men it is projected to reach 8.9% *vs.* 6.2% for women (Supplementary Table S1). Under the assumption that the incidence will remain stable from 2018 onwards, the prevalence will continue to rise towards 2040, whereas when accounting for the observed increasing excess mortality of PAD patients compared with the general population of 1.1%/year, the decline in PAD prevalence towards 2040 will be steeper (Supplementary Fig. S3, Supplementary Table S1). The predicted absolute numbers of patients living with PAD by sex and age group are provided in Supplementary Table S2.

Sensitivity analysis

Using a PAD case definition including ICD-10 code I74 resulted in slightly higher estimates of incidence and prevalence, whereas mortality was unchanged (Supplementary Table S3).

DISCUSSION

Based on 19 years of population based data comprising more than 4.8 million Danish adults, this nationwide study showed that after standardisation for age and sex, the

Table 2. Age and sex specific prevalence of peripheral arterial disease, 2000–2018, in Denmark

Group	2000		2010		2018		Prevalence ratio 2018 *vs.* 2000, PR (95% CI)
	PAD / population – *n**	Prevalence – %	PAD / population – *n**	Prevalence – %	PAD / population – *n**	Prevalence – %	
Overall – y							
40–59	5 558/1 476 000	0.4	5 473/1 529 000	0.4	4 941/1 562 000	0.3	0.82 (0.79–0.85)
60–79	20 481/842 000	2.4	29 564/1 048 000	3.0	33 979/1 201 000	3.0	1.15 (1.13–1.17)
≥80	7 115/208 000	3.4	13 419/227 000	5.9	16 850/256 000	6.4	1.89 (1.84–1.94)
All ages	33 154/2 526 000	1.3	48 456/2 803 000	1.7	55 770/3 019 000	1.6	1.28 (1.26–1.30)
Females – y							
40–59	2 212/730 000	0.3	2 257/758 000	0.3	1 934/777 000	0.2	0.80 (0.76–0.85)
60–79	9 046/454 000	2.0	12 288/544 000	2.5	13 754/619 000	2.3	1.14 (1.11–1.17)
≥80	4 072/140 000	2.9	7 596/146 000	5.2	8 924/156 000	5.7	1.96 (1.89–2.03)
All ages	15 330/1 324 000	1.2	22 141/1 448 000	1.6	24 612/1 552 000	1.5	1.32 (1.30–1.35)
Males – y							
40–59	3 346/746 000	0.5	3 216/771 000	0.4	3 008/785 000	0.4	0.83 (0.79–0.87)
60–79	11 435/388 000	3.0	17 276/504 000	3.6	20 225/582 000	3.4	1.16 (1.14–1.19)
≥80	3 043/69 000	4.4	5 823/81 000	7.2	7 926/100 000	7.9	1.79 (1.72–1.87)
All ages	17 824/1 203 000	1.5	26 315/1 356 000	1.9	31 159/1 466 000	1.8	1.25 (1.22–1.27)

PAD = peripheral arterial disease; CI = confidence interval. Rates are standardised to the year 2000 Danish population.
* Rounded to nearest 1 000.

incidence of PAD and the all cause mortality rate among affected individuals decreased by 26% and 25%, respectively. Concomitantly, the prevalence increased by 128%. This increase occurred in both men and women and was particularly pronounced for individuals born before 1940, whereas the prevalence decreased over time in those aged 40 — 59 years. Future predictions estimated that PAD prevalence will continue to rise until around 2030, followed by a decline towards 2040.

Previous studies

It is believed that this is the first study to comprehensively examine trends in PAD using unselected whole country data and provide robust evidence of a declining incidence in a Western European population. Most previous studies are affected by lack of accurate tracking of incidence, prevalence, and mortality over time, and population data on incidence trends remain sparse. A fall in revascularisation rates among patients with symptomatic PAD was previously demonstrated between 2010 and 2016; in particular, rates of revascularisation among patients with intermittent claudication declined by 43%, whereas rates remained relatively constant among patients with chronic limb threatening and acute ischaemia.[24] As the previous study was confined to patients with symptomatic PAD who underwent revascularisation, it was unable to distinguish whether this decline was associated with an overall decrease in the incidence of patients diagnosed with PAD or whether it was driven by increasing recognition of the efficacy of conservative medical and exercise treatment of atherosclerotic lesions in patients suffering from intermittent claudication.[25,26] The current finding of a decreasing incidence is corroborated by two contemporary UK studies that demonstrated declines of 55% between 2000 and 2014[27] and 15% between 2006 and 2015,[12] respectively, and a recent German study demonstrating an annual 4.4% decrease in incidence between 2008 and 2016 based on health insurance data.[13]

Consistent with previous studies,[5–7,28] the current study found an increasing prevalence among elderly patients with PAD between 2000 and 2018, which was projected to continue for at least 5 — 10 years before stabilising and beginning to decline towards 2040. A nationwide analysis of all PAD related hospitalisations in Germany demonstrated a 21% increase in PAD prevalence between 2005 and 2009;[28] however, it used case related Diagnosis Related Group data without any patient—individual linkage, which hindered the valid estimation of the patient related prevalence. A recent study based on ambulatory claims data covering 87% of the

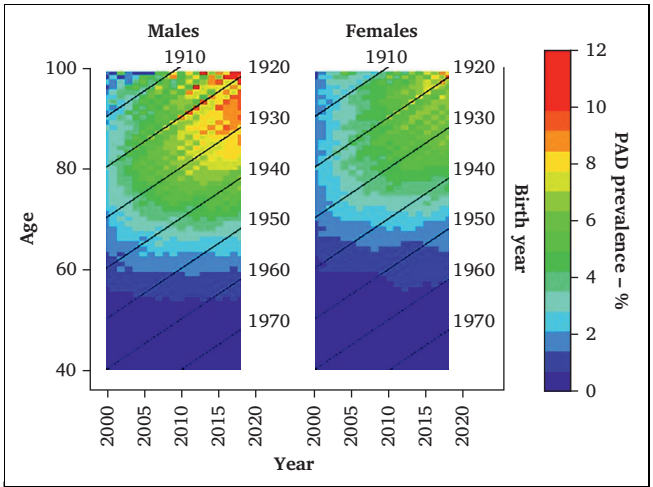

Figure 2. Lexis diagrams of sex stratified peripheral arterial disease (PAD) prevalence patterns by age, period, and birth cohort in Denmark from 2000 to 2018.

Table 3. Age and sex specific one year all cause mortality among patients with peripheral arterial disease, 2000–2018, in Denmark

Group	2000		2010		2018		Mortality ratio 2018 *vs.* 2000, (95% CI)
	Deaths / population with PAD – *n**	Mortality – %	Deaths / population with PAD – *n**	Mortality – %	Deaths / population with PAD – *n**	Mortality – %	
Overall – y							
40–59	167/5 558	3.0	144/5 473	2.7	128/4 941	2.5	0.84 (0.67–1.06)
60–79	1 714/20 481	8.4	1 841/29 564	6.3	2 046/33 979	5.8	0.69 (0.65–0.74)
≥80	1 370/7 115	19.3	2 221/13 419	15.9	2 768/16 850	15.1	0.79 (0.75–0.84)
All ages	3 251/33 154	9.8	4 206/48 456	7.7	4 942/55 770	7.2	0.75 (0.72–0.78)
Females – y							
40–59	58/2 212	2.6	47/2 257	2.1	37/1 934	1.9	0.71 (0.47–1.07)
60–79	638/9 046	7.1	704/12 288	5.8	699/13 754	5.0	0.71 (0.64–0.78)
≥80	694/4 072	17.0	1 177/7 596	14.7	1 401/8 924	14.4	0.85 (0.78–0.92)
All ages	1 390/15 330	9.1	1 928/22 141	7.6	2 137/24 612	7.0	0.80 (0.75–0.85)
Males – y							
40–59	109/3 346	3.3	97/3 216	3.0	91/3 008	2.9	0.91 (0.69–1.20)
60–79	1 076/11 435	9.4	11 37/17 276	6.7	1 347/20 225	6.4	0.68 (0.63–0.73)
≥80	676/3 043	22.2	1 044/5 823	17.4	1 367/7 926	16.0	0.73 (0.68–0.80)
All ages	1 861/17 824	10.4	2 278/26 315	7.8	2 805/31 159	7.4	0.71 (0.68–0.75)

PAD = peripheral arterial disease; CI = confidence interval. Rates are standardised to the 2000 Danish population.
* Population at risk per 1/1.

total German population revealed an increase in prevalence from 1.85% in 2009 to 3.14% in 2018,[7] while another German study observed a 23% increase in prevalence between 2008 and 2016 using longitudinally linked claims data.[13] At odds with these trends, the prevalence of symptomatic PAD in the UK decreased from 3.4% in 2000 to 2.4% in 2014.[27] The critical issue is that most studies rely on data on hospitalised cohorts, thereby restricting them to patients who were correctly diagnosed, coded, and treated in the hospital care system;[29] however, up to 50% of patients with PAD have no symptoms[1,2] and may not be detected by hospital registries. This explains the higher prevalence in screening studies enrolling asymptomatic people where the recent DANCAVAS trial reported a PAD prevalence of 11.5% in men aged 65 – 74 years during 2014 – 2017,[30] while the prevalence was 24% in a recent study from the Hamburg City Health Study.[31] Thus, the concomitant burden of PAD remains largely unknown. A recent systematic review estimated a global prevalence of 7.4% and 5.1% in high income and low income countries, respectively.[6] Compared with the Global Peripheral Artery Disease Study of 2013,[5] this represents an approximate 45% increase in the global PAD prevalence. The current prevalence estimates are lower than reported in these reviews. It is hypothesised that this is because they included studies that identified PAD by an ABI value ≤ 0.90, while the current study identified PAD based on discharge diagnoses submitted by physicians. Accordingly, the current study may be more likely to include individuals with more advanced symptomatic PAD and therefore underestimate the overall burden of PAD, which is commonly known to be underdiagnosed.[29]

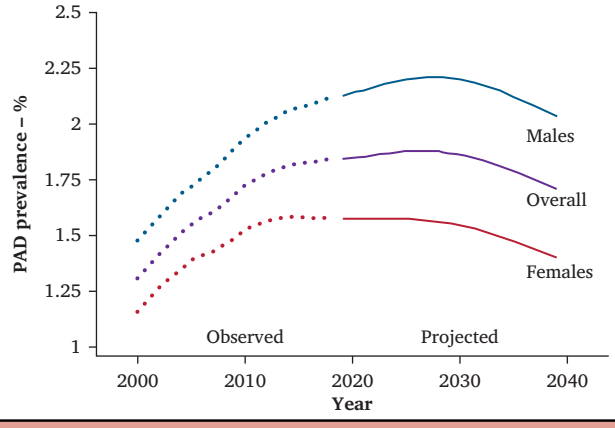

Figure 3. Observed and projected prevalence of peripheral arterial disease (PAD) in Denmark from 2000 to 2040.

Potential explanations and implications

As indicated in the current study, the changing trends reflect a complex function of age, sex, calendar period, and birth cohort, with several factors operating dynamically on the population. Since 2000, increasing emphasis has been put on measures to reduce risk factors at individual and community levels, including public bans on smoking,[16] lower target levels of low density lipoprotein cholesterol[32] and blood pressure,[33] and increasing use of cardioprotective medications (e.g., statins, antihypertensives, and antiplatelets).[12,24,27] This has resulted in better control of risk factors,[32] which combined with implementation of evidence based guidelines and treatments may explain the decreasing incidence and mortality rate.[34,35]

Peripheral artery disease prevalence is influenced by the rate at which new patients are diagnosed and their survival. While incidence and mortality continuously decreased from 2000 to 2018, the prevalence increased and was projected

to further increase until reaching a plateau between 2025 and 2030, depending on model assumptions. This increase may be driven by population ageing and increasing survival. The projected decrease towards 2040 reflects that the decreasing incidence is expected to exceed the improved survival. This development may be seen as proof of effectiveness of preventive measures. However, despite overall improvements, the current findings showed important differences between sexes in trends over time. Although incidence, prevalence, and mortality were higher among men, the decline in incidence and mortality was lower in women aged $\geq$ 80 years, while prevalence increased, compared with men of same age. The underlying reasons for these differences are probably multifactorial[36] and warrant further investigation to clarify potential gender inequalities. Additionally, widespread increases in diabetes[14] and obesity[15] could undermine gains achieved in risk factor control and cause resurgence of PAD incidence. Therefore, it is vital for decision makers in public health to continue prioritising efforts to prevent PAD.[37] Knowledge about recent and future trends in PAD provided in the current study can support guidelines about the burden of PAD in the population and inform healthcare providers and policy makers so that they can optimise healthcare for individuals with PAD and efficiently plan future health services.

Strengths and limitations

Strengths of this study include the long observation period, the population based design with complete follow up until death or emigration within a uniform healthcare system, reducing the potential for selection biases arising from selective inclusion of insurance plans, specific hospitals, ethnicities, regions, or socioeconomic levels.

This study also had limitations. In line with most previous studies, the main limitation was the use of physician diagnosed PAD, which is more likely to register symptomatic as opposed to asymptomatic PAD. This, in addition to the fact that PAD is typically underdiagnosed by physicians,[38] probably led to an underestimate of the burden of PAD in the population. However, execution of well designed screening studies in asymptomatic target populations remain a major challenge to date. All cause mortality data from the CRS are highly valid and complete[19] but the results are contingent on the validity of PAD diagnoses in the DNRP. Finally, these data only reflect one population sample, and these findings may not be fully generalisable to other populations and healthcare settings.

Conclusions

This nationwide cohort study provides a comprehensive assessment of the temporal changes in PAD incidence, prevalence, and mortality between 2000 and 2018 across age, sex, and birth cohorts in the Danish population. Despite cautious optimism about declining trends in incidence and all cause mortality among patients with PAD, the prevalence increased, and PAD will remain a problem with a continuing need for healthcare services and extensive costs to manage PAD and its complications in years to come.

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Data availability statement: According to Danish data protection legislation, linked individual level register data analysed in the study cannot be shared or made publicly available. Register data are stored at the Statistics Denmark and Danish residents can file applications for data access to The Danish Health Data Agency.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2023.08.005.

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