Peripheral artery disease: epidemiology and global perspectives

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Abstract | Global populations are undergoing a major epidemiological transition in which the burden of atherosclerotic cardiovascular diseases is shifting rapidly from high-income to low-income and middle-income countries (LMICs). Peripheral artery disease (PAD) is no exception, so that greater focus is now required on the prevention and management of this disease in less-advantaged countries. In this Review, we examine the epidemiology of PAD and, where feasible, take a global perspective. However, the dearth of publications in LMICs means an unavoidable over-reliance on studies in high-income countries. Research to date suggests that PAD might affect a greater proportion of women than men in LMICs. Although factors such as poverty, industrialization, and infection might conceivably influence the development of PAD in such settings, the ageing of the population and increase in traditional cardiovascular risk factors, such as smoking, diabetes mellitus, and hypertension, are likely to be the main driving forces.

The epidemiology of peripheral artery disease (PAD) has been studied extensively in Western countries in the past 30 years, and comprehensive descriptions have been provided on the frequency, determinants, and prognosis of the disease[1–4]. Given the epidemiological transition in cardiovascular diseases in which a substantial increase in frequency has occurred in low-income and middle-income countries (LMICs)[5], we attempt to include a more global perspective of the epidemiology in this Review. However, given that information is often lacking on the epidemiology of PAD in resource-poor settings, much reliance is still made on research in Western countries and sometimes on studies of other atherosclerotic diseases, particularly coronary heart disease and ischaemic stroke. In this Review on PAD, we describe measurement in populations, worldwide frequency, risk factors, and burden of disease.

The term 'peripheral artery disease' is used frequently in the medical literature, but with considerable variation in definition according to the affected arteries and categories of included diseases, for example, atherosclerosis, fibromuscular dysplasia, and vasculitis. In this Review, use of the term is restricted to atherosclerotic disease involving arteries serving the lower limb. This is equivalent to the term 'peripheral vascular disease' used commonly in clinical practice, but also sometimes used to include venous and lymphatic disease.

The clinical spectrum of disease is wide and includes individuals who are asymptomatic as well as those with leg symptoms, notably intermittent claudication in which pain in the calf occurs on exercise and is relieved by rest. At the severest end of the clinical spectrum is critical limb ischaemia (CLI), which comprises rest pain, ulceration, and gangrene, and can lead to amputation.

Measurement in populations

Ankle–brachial index

The ankle–brachial index (ABI) is the ratio of systolic blood pressure at the ankle to that in the arm[6] (FIG. 1). The rationale for this measurement is that when PAD is sufficiently severe to alter arterial flow in the lower limb at rest, the blood pressure at the ankle falls. To distinguish a decreased arterial pressure owing to obstructive arterial disease from general hypotension related to other conditions, the arterial pressure at the ankle is compared with that at the arm by calculating the ratio. Atherosclerosis affects the upper limb less commonly than the lower limb but, to avoid bias owing to subclavian stenosis, the higher pressure of the two arms is taken when calculating the ABI. Physiologically, the ABI is >1 because of the pulse amplification phenomenon. An ABI of 1.10–1.25 is considered normal and <0.90 as definitely abnormal. A high ABI (>1.40) is usually indicative of individuals with stiff vessels in whom around two-thirds have PAD[7]. Overall, the ABI provides good sensitivity (80%) and excellent specificity (95%) to detect PAD[8]. Assessment of resting ABI can miss individuals with PAD whose disease is only uncovered after exercise, but including a post-exercise ABI in large epidemiological studies is often not feasible. Given the ease of measurement using

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Key points

- The ankle–brachial index is the most appropriate measure to use in describing the global distribution of peripheral artery disease (PAD)
- Worldwide estimates indicate that the greatest numbers of patients with PAD are in Southeast Asia and Western Pacific regions; many individuals are asymptomatic
- A large proportion of symptomatic patients have atypical leg pain rather than intermittent claudication; patients without pain often have substantial functional impairment
- Traditional cardiovascular risk factors (smoking, hypertension, diabetes mellitus, and dyslipidaemia) and the ageing of the population are important determinants of PAD in all countries
- In low-income and middle-income countries especially, environmental factors such as poverty, industrialization, and infection could affect the risk of developing PAD
- PAD impairs quality of life and is associated with a greatly increased risk of major cardiovascular events and death; PAD is an important cause of amputation worldwide

inexpensive equipment, the ABI is considered to be the first-line screening test to define both symptomatic and asymptomatic PAD objectively in epidemiological studies, as well as in the clinical setting.

In 2012, the determination of the ABI was standardized[8]. Variations in the methods of measuring limb blood pressures and calculating ABI before its standardization can partly explain discrepancies in the epidemiology of PAD reported in similar populations. Also, small differences have been observed in population values of the ABI according to sex and ethnicity, with a slightly lower ABI in women (−0.02 compared with men) and in African-American individuals (−0.02 compared with white individuals)[9]. In a screening survey of 29,000 adults with no history of cardiovascular disease in central Scotland, the mean ABI was 1.01 (SD 0.11) in women and 1.06 (SD 0.13) in men[10]. Whether this difference was owing to 'normal' physiological variation between the sexes or was disease-related is unclear. The ABI is associated with height; men on average are taller than women, but adjustment for height and cardiovascular risk factors only partly reduces the sex-specific difference[9]. Consequently, a single threshold (0.90) might not discriminate precisely the actual prevalence of PAD between these subgroups. Whether different thresholds by sex should be used remains controversial and is not implemented in epidemiological studies.

Questionnaires

Several questionnaires have been used to detect in a standardized manner the presence of intermittent claudication. The first questionnaire on intermittent claudication proposed by Rose *et al.*[11] is not used now, because two modified ones — the San Diego Claudication Questionnaire (SDCQ)[12] and the Edinburgh Claudication Questionnaire (ECQ)[13] — show improved sensitivity, and all have excellent specificity. These questionnaires have been translated into other languages[14–17], but further validated translations are required to enable use worldwide.

Although use of these questionnaires, in addition to measurement of the ABI, provides more precise data on the prevalence of symptomatic and asymptomatic PAD, these questionnaires have limitations by not covering the whole range of symptomatic disease. Indeed, many patients can have an atypical presentation of claudication, or do not present with pain because they do not walk sufficiently owing to other comorbidities[18]. Assessment of the range of PAD symptoms can be important, because the type of symptom is related to the degree of walking impairment[18]. Also, more severe clinical presentations (pain at rest and ulcers or gangrene) cannot be detected with these questionnaires. Beyond claudication questionnaires, other indicators such as revascularization and amputation rates have been used as proxy measures of severe PAD in populations[19].

Routine health statistics

Mortality statistics are often used to describe the global distribution of disease, including PAD[20], because most countries collect data on deaths. Also, ascertainment of deaths is usually easier than other methods of identifying cases of disease. However, the usefulness of mortality data in describing the epidemiology of PAD is very limited, because nearly all patients with PAD die from coronary heart disease, stroke, or cancer[3,21], and the cause of death is described as such. Very few patients die from PAD per se; in these cases, death is mostly caused by complications of CLI or of surgery.

Likewise, health-service statistics, such as diagnostic discharge data, are usually unhelpful owing to lack of availability in many countries. Also, when published, disease rates can be influenced more by variations in health-care-seeking behaviour and clinical decision-making than the true frequency of disease. Even in Western countries with an advanced health-care system, such as in the USA, patient and clinician awareness of PAD can be poor, resulting in underdiagnosis[22]. Furthermore, considerable imprecision can occur in diagnostic coding owing to the wide range of clinical manifestations, the lack of detailed knowledge of PAD by coders, and the use of nonspecific International Classification of Diseases (ICD)-10 codes such as 170.2 (atherosclerosis of arteries of extremities) and 173.9 (peripheral vascular disease unspecified)[23].

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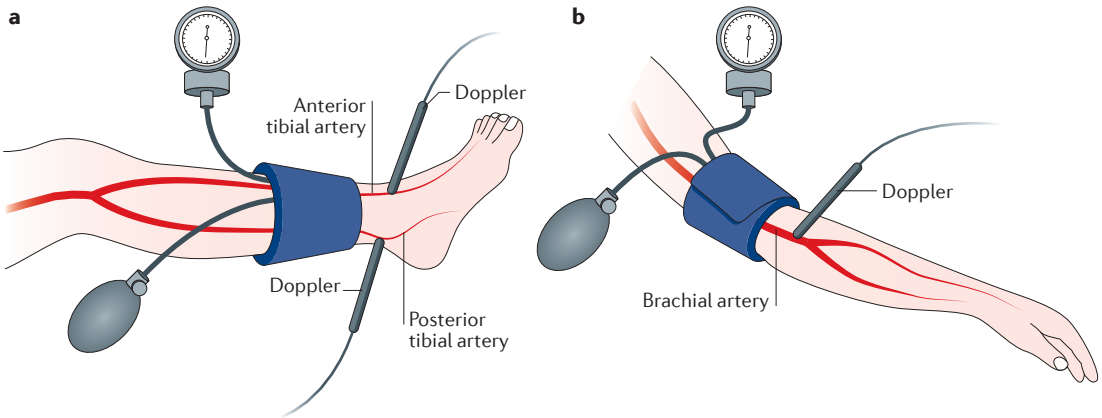

Figure 1 | **Measurement and calculation of ankle–brachial index (ABI) in diagnosing peripheral artery disease.** ABI is the ratio of **a** | the higher systolic blood pressure between the posterior tibial artery and the dorsalis pedis artery to **b** | the higher systolic blood pressure between both arms. Note that the dorsalis pedis artery is just distal to the anterior tibial artery shown in the figure. Reprinted from Tendera, M. *et al.* ESC guidelines on the diagnosis of peripheral artery diseases. *Eur. Heart J.* **32** (22), 2851–2906 (2011), with permission from Oxford University Press and the European Society of Cardiology.

Worldwide frequency

Low ankle–brachial index

In 2013, the global distribution of PAD was studied in a systematic review of population prevalence with the use of an ABI ≤0.9 as an indicator of disease[24]. Prevalence was compared between populations living in high-income countries and those living in LMICs (FIG. 2). In high-income countries, the prevalence of PAD seemed to be similar in men and women, and to increase consistently with age from around 5% at age 45–49 years to 18% at age 85–89 years. In LMICs, prevalence rates also increased consistently with age but, compared with high-income countries, age-specific rates seemed to be lower in men and slightly higher in women (up to age 65 years). In LMICs, prevalence rates seemed to be higher in women than in men, with more pronounced relative differences at younger ages (6.3% versus 2.9% at age 45–49 years compared with 12.3% versus 10.1% at age 75–79 years).

Using the age-specific and sex-specific results on prevalence in high-income and LMICs, the numbers of cases of PAD in years 2000 and 2010 in these countries were estimated according to the age and sex distributions of the populations[24]. Over the 10-year period, the number of cases worldwide was estimated to increase by around one-quarter to approximately 200 million, but with a higher relative increase in LMICs (29%) than in high-income countries (13%) (FIG. 3). Such estimates show the profound effect that a changing age structure of the population is likely to have on the worldwide distribution of PAD. Further analysis at WHO Regional level, including adjustment for the prevalence of risk factors[25], suggested that the greatest number of PAD cases in 2010 were in the LMICs in Southeast Asia and Western Pacific regions.

Evidence on the prevalence of PAD in LMICs has been derived from surveys including the ABI in individual countries. No multinational comparison studies are available, so the true variation in prevalence between countries is not clearly known. Even within countries, differences might vary according to characteristics of the selected populations and variation in measurement techniques. In China, for example, the prevalence in five surveys of populations with average ages 60–70 years varied between 2.5% and 6.9% in men and 1.7% and 10.4% in women[26–30]. By contrast, in a study in sub-Saharan Africa involving two countries (the Republic of the Congo and the Central African Republic), in which the same survey methods were used, a probable real difference in prevalence was found between the two countries (12.2% versus 17.4%; $P=0.007$)[31]. Many more surveys using standardized methods to measure PAD in LMICs are required to build up an accurate picture of the distribution of disease.

A fairly consistent finding in surveys in LMICs is the higher prevalence of a low ABI in women than in men. The reasons for this difference are not well established, although, as previously mentioned, small differences in ABI population distributions, with ABI often lower in women than in men, might be part of the explanation. Sex-specific differences in height could be more pronounced in some LMICs, leading to a lower ABI in women than in men. The principal risk factor for PAD — smoking — is generally more common in men than in women in LMICs[25], and is therefore unlikely to contribute to the female preponderance. However, women might be exposed to second-hand cigarette smoke. Another potential reason for the sex differential is a possible survival advantage from coronary heart disease and stroke in women, leading to development of PAD in an atherosclerotic-prone individual, although this explanation is unlikely, given that higher female-to-male ratios are particularly pronounced at younger ages[24]. This age difference could, however, be associated with the finding that, as PAD becomes more severe (as it does with age), men are more commonly affected[32].

Intermittent claudication

Surveys using the ABI provide estimates of the overall prevalence of disease, but they do not per se indicate the extent of symptomatic PAD. Evidence from

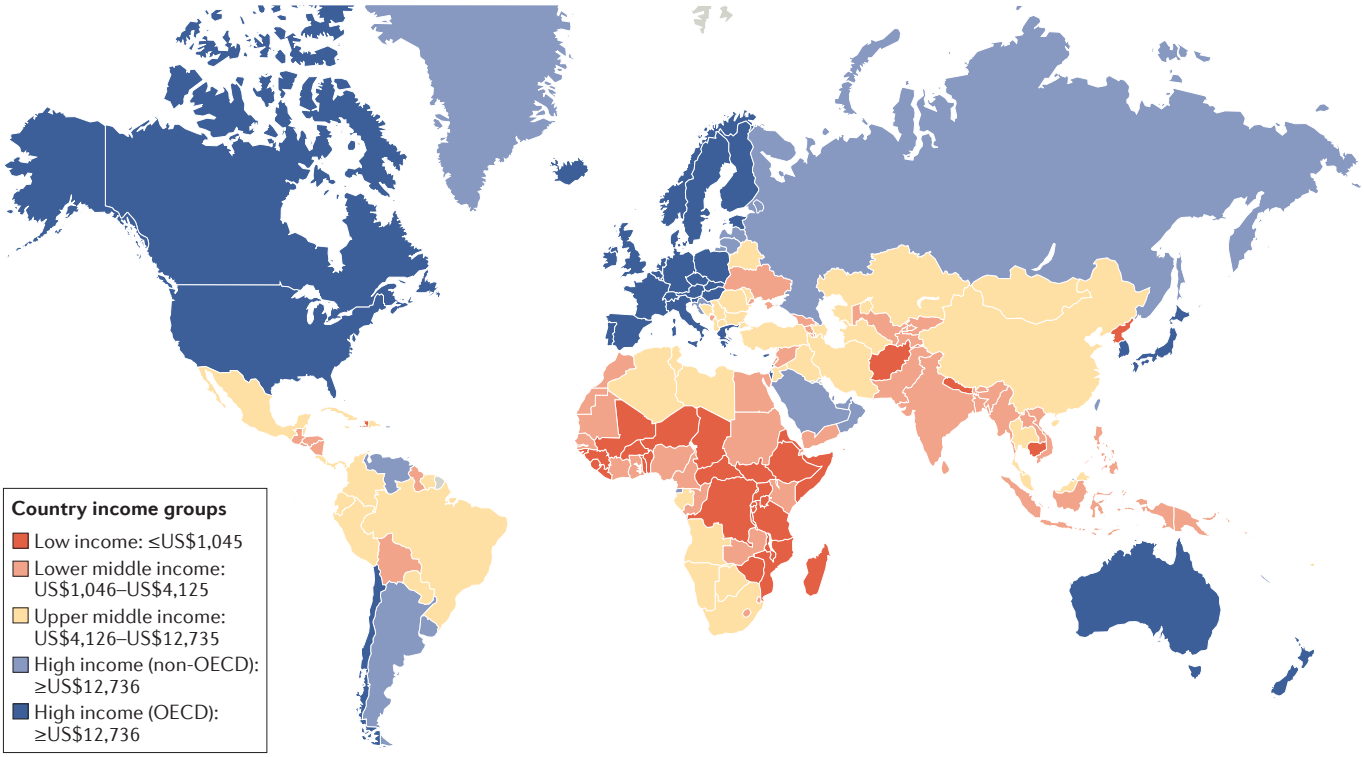

Figure 2 | **Classification of high-income, middle-income, and low-income countries.** The map classifies all World Bank country member economies and all other economies with populations >30,000. Economies are divided among income groups according to 2015 gross national income per capita. OECD, Organisation for Economic Co-operation and Development. Source: The World Bank Group. Reprinted with permission from ChartsBin statistics collector team 2016, *Country Income Groups (World Bank Classification)*, http://chartsbin.com/view/2438.

Western countries suggests some variation occurs in the population of individuals with a low ABI who have intermittent claudication[33,34]. The Copenhagen City Heart Study[35] found that the proportion of individuals with a low ABI who had claudication increased with age from 0% in those aged 35–44 years to 31% in those aged 65–74 years, and then decreased at older ages, presumably because more patients were unable to exercise sufficiently to generate symptoms or concurrent neuropathy limited pain sensitivity. At similar levels of ABI, women report intermittent claudication less often than men. Similarly, non-white ethnic groups report intermittent claudication less often than white individuals[18,36].

The prevalence of intermittent claudication has been investigated widely using questionnaires in the USA and Europe, but less so in resource-poor countries, where validated questionnaires are often unavailable. A review of several large epidemiological studies in Western countries found that the prevalence was <1% in those aged <50 years, increasing to 6% in those aged >65 years[37]. Prevalence is often higher in men than in women[3], but sometimes no clear sex-specific differences have been found[38]. The incidence of claudication has a similar pattern to that of prevalence[1,3].

The presence of ischaemic leg pain other than typical intermittent claudication in the calf can occur frequently in patients with PAD. 'Atypical' pain can be classified in three categories: non-calf pain in the thigh or buttock that starts with walking and is relieved by rest (although this pain normally occurs with aortoiliac disease); pain in the leg or buttock on walking, but also sometimes when standing still or sitting; and pain in the leg on walking, but the patient can carry on walking[12,18]. The incidence and prevalence in the general population of PAD with these atypical categories of pain is very limited, even in Western countries. In the general population in one study in the Netherlands, 1.6% had intermittent claudication whereas 5.0% had atypical symptoms (1.2% non-calf pain; 3.7% calf pain but not classic claudication)[39]. However, ABI levels were not reported, so the cause of the pain might not have been PAD.

Critical limb ischaemia

CLI is uncommon in the population as a whole, and the incidence has not been widely investigated because very large numbers of people need to be studied to produce precise estimates. In one study identifying all vascular events occurring in 2002–2005 in Oxfordshire, England, the annual incidence of CLI was 220 per million[40]. A population study in Sweden found a prevalence in individuals aged 60–90 years of 1.2% when the diagnosis of CLI was made only on the basis of an ankle pressure <70 mmHg, and of 0.5% when these individuals also had rest pain[38]. The prevalence increased with age and was twice as high in women as in men. An investigation of Medicare and Medicaid claims for CLI between 2003

and 2008 found a prevalence and annual incidence of 2.35% and 0.35%, respectively, in the US population aged >40 years[19].

The only worldwide evidence on the frequency of CLI is available with the use of rates of amputation. The Global Lower Extremity Amputation Study Group used a standardized method to collect data on amputation rates in centres in Europe, North America, and East Asia[41]. The annual incidence of first major amputation for any cause varied considerably, between 2.8 per 100,000 in Madrid, Spain, to 43.9 per 100.000 in the Navajo population, USA (the latter rate probably owing to a very high prevalence of diabetes mellitus). Lower incidence rates were found in Italy, Japan, Spain, and Taiwan than in England and the USA. The study group concluded that differences were most likely owing to variation in the incidence of CLI, a cause of amputation in at least half of the patients in every centre. Nevertheless, as a proxy indicator of CLI, amputation rates must be interpreted with considerable caution.

Risk factors

The traditional cardiovascular risk factors (smoking, diabetes, dyslipidaemia, hypertension) and several metabolic and inflammatory variables have been studied widely in relation to PAD in Western countries[1]. These factors are considered briefly in this section in addition to other factors that might influence global disparities in PAD, including ethnicity and genotype, poverty and industrialization, and infection.

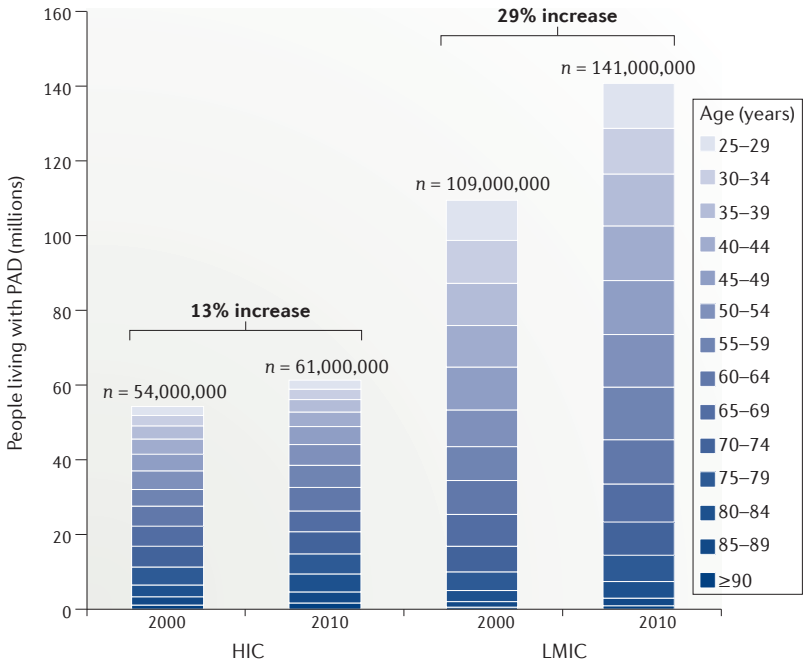

Figure 3 | **Number of people with PAD in 2000 and 2010, grouped by age in HICs and LMICs[24].** The numbers of patients are estimated by applying age-specific and sex-specific prevalence rates of a low ankle–brachial index (≤0.9) to age groups within the populations. A greater increase in prevalence occurred between 2000 and 2010 in LMICs than in HICs. More than half of the patients in LMICs were aged <55 years and were likely to be asymptomatic. HIC, high-income country; LMIC, low-income or middle-income country; PAD, peripheral artery disease.

Traditional risk factors

Cigarette smoking. Cigarette smoking has been known to be an important risk factor for PAD for >1 century and numerous studies have shown a strong and consistent association between smoking and all categories of PAD[1]. Smoking is the most important risk factor for the development of PAD and at least doubles the risk compared with that of a nonsmoker[1]. The greater the amount smoked, either at the time when assessed or cumulatively over a lifetime, the greater the risk of acquiring PAD and the worse the severity of disease. Smoking would seem to increase the risk of PAD more than that of coronary heart disease[42]. Smoking cessation is associated with a reduced risk of PAD, but is likely to take >20 years of cessation to reduce the level of risk to that of individuals who have never smoked[43]. Smoking also increases the risk of asymptomatic PAD[42], which raises the possibility that younger adult smokers might already be increasing their risk of PAD many years before the onset of clinical disease. The global effect of smoking is unlikely to abate substantially. Recent projections indicate that the number of smokers will increase from 794 million in 2010 to 872 million in 2030, although the prevalence per head of population will fall slightly, especially in high-income countries[44].

Diabetes mellitus. Diabetes has been shown in many epidemiological studies to be associated with the risk of both asymptomatic and symptomatic PAD, including disease with atypical symptoms[1,4,18]. The risk of intermittent claudication is about twice as high in patients with diabetes as in individuals without diabetes. The risks of PAD increase with the severity of diabetes: for every 1% increase in haemoglobin A1c level, the risk of PAD increases by 26%[45]. Furthermore, the duration of diabetes and use of insulin are associated with increased risk[46]. The relative risks of CLI associated with diabetes are much higher than those of intermittent claudication, with the risk of major amputation around fivefold higher in patients with diabetes than in individuals without diabetes[47]. This finding is probably owing to diabetes-associated sensory neuropathy, microangiopathy, and infection, as well as a specific pattern of PAD affecting more-distal arteries with fewer possibilities for revascularization. The worldwide epidemic of diabetes associated with increasing levels of obesity is likely to lead to a higher proportion of PAD cases being diabetes-related, especially with a concomitant decrease in cigarette consumption, at least in Western countries. Projected trends from 2013 to 2035 indicate that the number of patients with diabetes will increase universally from 382 million to 592 million[48].

Dyslipidaemia. Dyslipidaemia has been investigated in epidemiological studies on the aetiology of PAD, but because the various lipid fractions are highly interrelated, identifying the most important factor(s) has proven difficult. Serum triglyceride levels were shown in many early clinical studies to be strongly related to PAD, but in most large epidemiological studies have not been independently related after adjusting for other lipids[3]. By contrast, total cholesterol levels remained associated with PAD in multivariate analysis in most studies, as did

low HDL-cholesterol levels[49–51]. Indeed, a combined ratio of total to HDL cholesterol seems to be the best predictor of PAD. In the Physicians' Health Study[52] of incident PAD, the ratio of total to HDL cholesterol had the strongest association with PAD of any lipid measure, so that patients in the top quartile of the ratio had nearly four times the risk of claudication compared with those in the bottom quartile. The San Diego Population Study[53] also found that the total to HDL cholesterol ratio was an independent predictor of PAD. Studies have also shown that plasma lipoprotein(a) and apolipoprotein B levels were independently related to the risk of developing PAD[54,55].

Hypertension. Hypertension has been associated in most epidemiological studies with an increased risk of PAD, but the relationship has not been as strong as those for smoking or diabetes. When blood pressure levels have been examined, systolic pressure has been invariably related to risk of PAD, in contrast to diastolic pressure which is often not significantly associated[49,50]. Determining the strength of high blood pressure as a risk factor is difficult because of the possibility that a higher pressure in the legs might have a counter effect by delaying the onset of claudication. Although the relative risks of PAD in many studies might be modest compared with other risk factors, the high prevalence of hypertension in the population, especially in elderly individuals, might result in a substantial contribution to the total burden of disease[51]. Also, hypertension is an emerging risk factor in LMICs, such as in west Africa[56], and might have an important effect on the development of PAD.

Among the traditional cardiovascular risk factors, cigarette smoking and diabetes are the strongest and most consistently related to an increased risk of PAD. Furthermore, in studies in the USA, the effect of risk factors has been found to be cumulative, with substantially greater risks of PAD the higher the number of risk factors present[43,57]. The risk factors found in high-income countries are also related to PAD in LMICs, although the strengths of the associations are slightly lower in cross-sectional studies (FIG. 4). This observation might be owing to the rapid transition in adoption of Western lifestyles in these countries, so that the population has a shorter exposure to the risk factors. Nevertheless, the importance of these risk factors emphasizes that cardiovascular prevention programmes will have an effect not only on coronary heart disease and stroke, but also on PAD.

Metabolism and inflammation

Obesity. Evidence on the relationship between obesity and risk of PAD is quite conflicting: most studies show no association, and others indicate a slightly increased risk, a U-shaped relationship, or a protective effect[1]. These disparate results occur on univariate analysis and on multivariate analysis adjusting for confounding factors such as smoking and dyslipidaemia. The reason for these inconsistencies is unclear, although it has been postulated that PAD in older people is often associated with other chronic illnesses that might contribute to weight loss. The Cardiovascular Health Study[58] found that, although BMI in the elderly population

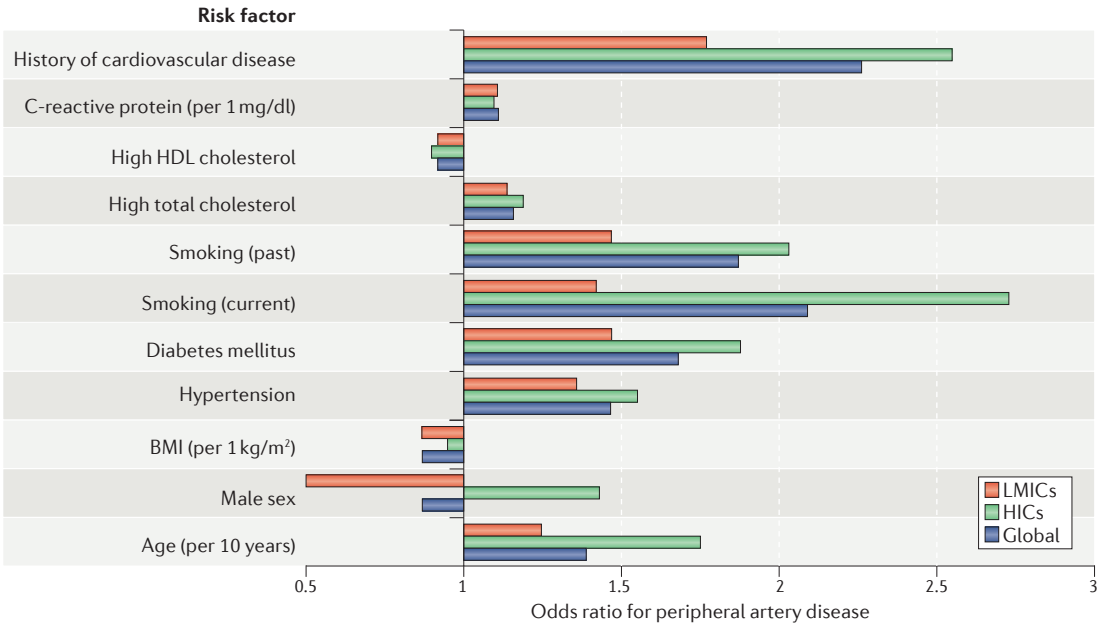

Figure 4 | **Risk factors for peripheral artery disease in HICs and LMICs.** The odds ratios for peripheral artery disease, which are based on multivariate analyses of risk factors, have a similar pattern in HICs and LMICs, except for an increased risk for men compared with women in HICs and vice versa in LMICs. For the traditional risk factors of smoking, diabetes mellitus, and hypertension, the odds ratios were higher in HICs than in LMICs, which might be caused by a shorter duration of exposure in LMICs. HIC, high-income country, LMIC, low-income and middle-income country. Reprinted with permission from Criqui, M. H. & Aboyans, V. Epidemiology of peripheral artery disease. *Circ. Res.* **116** (9), 1509–1536 (2015).

Table 1 | **Prevalence of PAD in the USA by age, ethnicity, and sex**

Ethnicity	Prevalence of PAD (%) by age (years)				
	40–49	50–59	60–69	70–79	≥80
Male					
Non-Hispanic white	1.4	1.9	5.4	9.2	22.6
African	1.2	5.0	13.2	24.4	59.0
Hispanic	0.2	3.4	4.3	9.6	22.5
Asian	1.2	0.9	3.5	9.8	21.5
American Indian	2.6	4.5	6.1	11.7	28.7
Female					
Non-Hispanic white	1.9	4.3	5.1	7.9	18.2
African	3.0	3.4	8.9	20.0	35.0
Hispanic	0.3	0.4	3.1	6.9	18.2
Asian	0.0	1.4	0.7	7.9	18.2
American Indian	3.2	3.9	8.6	14.7	33.8

PAD, peripheral artery disease. Modified from Allison, M. A. *et al.* Ethnic-specific prevalence of peripheral arterial disease in the United States. *Am. J. Prev. Med.* **32** (4), 328–333 © (2007), with permission from Elsevier.

was inversely associated with both prevalent and incident PAD, BMI was positively associated with PAD when smokers and those in poor health were excluded. In keeping with findings in coronary heart disease, central obesity (waist–hip ratio), rather than total obesity, has been found to be more consistently associated with the risk of PAD[34]. Lack of exercise can contribute to increased levels of obesity.

Hyperhomocysteinaemia. Hyperhomocysteinaemia has been associated with PAD in several clinical and population studies, although the strength of association has often been modest[59]. An odds ratio of 1.7 was found in a large, European, case–control study, but was of borderline significance[60]. An odds ratio of 1.9 comparing the top versus bottom quintiles of homocysteine level in the US National Health and Nutrition Examination Study[61] was attenuated and became nonsignificant after controlling for smoking and other factors that affect homocysteine levels. These findings suggest that homocysteine could be an intermediary factor or that confounding factors cause a spurious association between homocysteine and PAD. Further doubts on the role of plasma homocysteine in the aetiology of PAD have been raised by the lack of an association between homocysteine level and progression of PAD[62].

Inflammation. Plasma fibrinogen and C-reactive protein are two inflammatory markers that have been related to symptomatic and asymptomatic PAD, in both cross-sectional and longitudinal studies[52,63]. In the Physicians' Health Study[52], the risk of intermittent claudication was more than twice as high for fibrinogen or C-reactive protein when comparing the top quartile of plasma concentrations versus the bottom quartile, independently of other risk factors. Fibrinogen is also a thrombotic factor and determinant of blood viscosity, and is one of several haematological factors that have been associated with PAD[63]. Other markers of inflammation, such as interleukin-6, have been linked to the prevalence of PAD[64], but the extent to which inflammation is a cause and/or consequence of disease has not been well established.

Ethnicity and genotype

Ethnicity. Early research on the epidemiology of PAD was carried out on predominantly white populations, but subsequent studies have compared the frequency of PAD in different ethnic groups. These studies have been mostly within the USA. In a pooling study of seven US population, cross-sectional studies, the prevalence of PAD in adults aged >40 years was found to be highest in African-American individuals (8.8%), then native American (6.1%) and non-Hispanic white individuals (5.5%), and lowest in Hispanic (2.8%) and Asian individuals (2.6%)[65]. These differences occurred in men and women and at most ages (TABLE 1). Another systematic review of studies comparing people of south Asian and white European descent found a lower prevalence of PAD among south Asian individuals in the general population[66]. In the Multi Ethnic Study of Atherosclerosis[67], a higher rate of PAD in African-American individuals and lower rate in Hispanic and Asian individuals was still found after adjusting for social status and traditional and novel cardiovascular risk factors. Similar findings were noted in the GENOA study[68]. Ethnic differences are, therefore, unlikely to be caused simply by lifestyle differences between the groups. Ethnic differences in ABI levels might, however, be the result of physiological variation rather than the presence of PAD[69]. In contrast to coronary heart disease, there have been no multinational or migration studies that can help to determine the reasons for ethnic variation.

Genotype. The heritability of PAD has been examined in family studies and summarized[64]. Results from the US National Heart, Lung, and Blood Institute Twin Study[70] suggested that 48% of variability in ABI levels was owing to genotype, independently of cardiovascular risk factors. In the Framingham Offspring Study[71], 21% of the interindividual variability in the ABI could be attributed to genetic determinants, 14% to cardiovascular risk factors, and 65% could not be explained by either. In the GENOA study[72], heritability was 35% reducing to about 20% after adjustment for cardiovascular risk factors. These studies suggest a modest heritability for PAD.

As for the genotypes that might contribute to this heritability, several small, case–control studies have examined specific associations between gene polymorphisms and PAD[73]. Although associations have been shown with many genotypes, for example for fibrinogen[74,75], a unique genotype related to PAD, replicated in more than one study, has not been identified. In a collaborative meta-analysis of 21 genome-wide association studies and PAD[76], only three genes on chromosome 9p21 were associated with PAD. Susceptibility loci, such as *ATXN2-SH2B3*, have also been discovered with the use of genome-wide association studies[77]. In another collaboration, the Candidate-Gene Association Resource

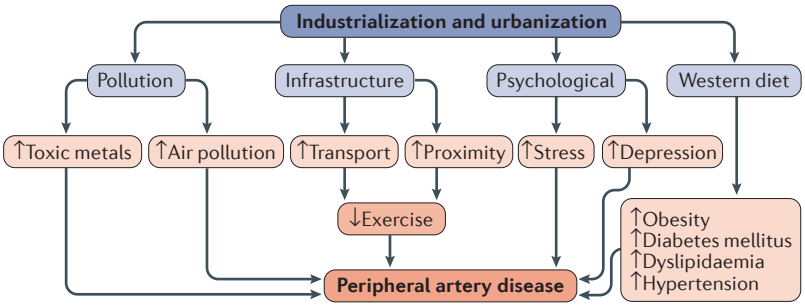

Figure 5 | **Possible effects of industrialization and urbanization in low-income and middle-income countries on risk of peripheral artery disease.** Rapid economic development with industrialization and urbanization can lead to an increase in less-studied risk factors for peripheral artery disease. Supposedly beneficial developments such as improved transport links can be counterproductive by increasing the risk of disease. Note that lack of exercise might promote development of peripheral artery disease, but might also lead to a reduced detection of exercise-related symptoms.

Consortium found no strong genetic associations with PAD[78]. Notwithstanding these somewhat disappointing results, such studies have the potential to identify new genetic markers pointing to novel mechanisms in the pathogenesis of PAD.

Poverty and industrialization

Poverty. PAD, in keeping with other cardiovascular diseases, would seem to be more common in those individuals of lower socioeconomic status. In the Edinburgh Artery Study[79], a lower ABI was associated with less educational achievement, a higher deprivation score, and lower socioeconomic status, especially in men. These associations were partly explained by smoking, but not by other cardiovascular risk factors. Likewise, the prevalence of PAD was higher in poorer socioeconomic groups in the USA[80]. In most LMICs in which PAD is emerging, poverty is extremely widespread. However, a paradoxical situation might exist to that in high-income countries, in which PAD is found among higher socioeconomic groups able to adopt unhealthy Western lifestyles, albeit that in some countries such as India, smoking seems to be particularly prevalent among the rural poor[81].

Industrialization. In LMICs, the rapid consequences of industrialization might affect the risk of acquiring PAD. Potential mechanisms are shown in FIG. 5. Long-term air pollution exposure has been shown to have an effect on the development of atherosclerotic diseases, including PAD[82]. In Germany, pollution (in particular that from road traffic) was associated with a reduced ABI in those individuals exposed[83]. In a study in China, urban living was associated with a twofold to threefold increased risk of PAD compared with those individuals living in rural areas, independently of traditional cardiovascular risk factors[30]. Given the high levels of air pollution in Chinese cities, this risk factor might conceivably contribute to the urban–rural differential in rates of PAD. By-products of industry, including toxic metals such as lead and cadmium, have also been related to an increased risk of PAD[84,85].

Advances in mechanization and expansion in means of transport can lead to a more sedentary lifestyle and decreased levels of exercise. As well as improving walking in patients with established PAD, exercise might have a protective effect in preventing the development of the disease[86]. Furthermore, industrialization and the associated urbanization might well have psychological consequences on those individuals undergoing rapid change in their environment and life circumstances. These effects, such as stress and depression, might contribute to an increased risk of developing PAD[87,88].

Infection

A possible role for infection in the pathogenesis of atherosclerotic disease has been pursued for >40 years. Numerous pathogens have been implicated, including *Chlamydia pneumoniae*, *Helicobacter pylori*, periodontal bacteria, *Hepatitis A virus*, *Herpes simplex virus*, and *Cytomegalovirus*[89,90]. Immunoepidemiological studies have demonstrated associations between prevalence of antibodies to these pathogens and increased risk of cardiovascular diseases, including PAD[91,92]. However, randomized, controlled trials have not shown a convincing effect of antichlamydial antibiotics in reducing cardiovascular events in patients with coronary heart disease[93,94], nor in improving exercise performance or quality of life in those with intermittent claudication[95]. In the context of the global transition of PAD, the extent to which infections commonly found in resource-poor settings might influence the risk of acquiring atherosclerotic disease has been largely under-researched. Three such infections are tuberculosis, HIV, and malaria[96]. Also, the potential effect of widespread periodontal infection is of interest.

Tuberculosis. In patients with tuberculosis, pathogenic mechanisms typically involved in infection, such as increased expression of proinflammatory cytokines and immune activation[97,98], could promote atherogenesis, including PAD[52]. A few epidemiological studies have shown a link between tuberculosis and cardiovascular disease[99], but in a large cohort study in Taiwan comparing 10,168 newly diagnosed patients with tuberculosis and 40,672 healthy controls, the patients had a 40% increased risk of developing an acute coronary syndrome, after adjusting for cardiovascular risk factors[100]. Likewise, a 50% increase was found in ischaemic stroke[101], but no data have been presented on the risk of developing PAD. Indeed, overall, evidence on whether tuberculosis is associated with an increased risk of PAD is lacking, although similar findings to those observed for other atherosclerotic diseases might be expected.

HIV infection. Several cohort studies on HIV infection, almost universally conducted in high-income countries, have shown an approximately twofold increase in the risk of coronary heart disease in patients with HIV infection, with the risk often twice as high in women as in men[102]. Although patients with HIV infection tend to have a high prevalence of cardiovascular risk factors, the increased risk of coronary heart disease remains independently

associated, suggesting more specific HIV factors, such as CD4 count, viral load, and certain antiretroviral therapies, might be implicated. HIV status has also been associated independently with other manifestations of atherosclerosis[103,104], including PAD[105,106]. In a comparison of 540 patients with HIV infection and 524 controls in the Netherlands, PAD was found in 2.6% of patients and 0.6% of controls ($P = 0.008$)[105]. Furthermore, the association between HIV and all cardiovascular and metabolic diseases in that study was independent of age and smoking. Similarly, in a smaller case–control study in China, patients with HIV infection were found to have a lower ABI than healthy controls ($P < 0.001$), and an association between HIV and lower ABI was independent of traditional cardiovascular risk factors[106].

Malaria. Malaria has not been implicated as a risk factor for atherosclerotic disease, including PAD. Severe falciparum malaria is associated with coagulation, fibrinolysis, and inflammation[107], and can cause microvascular dysfunction in which infected red blood cells obstruct capillaries leading to tissue hypoxia and injury[108,109]. These acute effects would be unlikely, however, to influence the development of atherosclerosis in larger vessels. Although severe malaria occurs most commonly in children, a role for malaria in atherogenesis is not necessarily precluded. After repeated exposure to the malaria parasite with age, naturally acquired immunity develops and suppresses the density of parasites resulting in chronic asymptomatic infection[110]. Epidemiological studies of asymptomatic *Plasmodium* species infection have shown an association with elevated levels of proinflammatory cytokines, C-reactive protein, and other inflammatory markers[111,112]. This chronic asymptomatic parasitaemia and associated inflammation, particularly in later life when atherosclerosis might be most progressive, could potentially be associated with an increased risk of PAD in malaria-endemic areas. Furthermore, malaria might conceivably have an influence on early programming of risk of PAD, because malaria is a common cause of low birth weight[113], which has been related to an increased risk of cardiovascular disease[114], including PAD[115], in adulthood.

Periodontal infection. Periodontal infection occurs in a substantial proportion of the global population especially in elderly individuals. As much as 50% of the adult population aged >30 years have signs of periodontitis, of whom 10% have severe disease[116]. Although in high-income countries periodontitis has a downward trend, the global trend including LMICs is unknown owing to a lack of robust data. However, an accumulation of studies has shown an association between periodontitis and cardiovascular diseases and events[117,118]. Possible causal mechanisms might be related to local and systemic inflammatory and immune responses, but periodontitis and cardiovascular disease also share common risk factors including age, smoking, diabetes, and poor socioeconomic status[118]. Most studies are on coronary and cerebrovascular disease, but small, case–control studies have found strong associations between periodontitis and PAD, adjusted for other risk factors[119,120]. Whether these associations are causal is unknown; the results of large longitudinal studies might provide stronger evidence on this issue.

Although epidemiological information on the degree to which infection is a risk factor for PAD is sparse, especially in resource-poor settings, evidence from other cardiovascular diseases and from animal, laboratory, and pathological studies indicate that infection could contribute to atherogenesis[89]. Tuberculosis, HIV infection, malaria, and periodontal infection might conceivably increase individual risk of PAD, but no convincing global evidence is currently available that infection might be having a major effect in enhancing or ameliorating the worldwide transition in PAD, which is probably being driven predominantly by lifestyle factors and the ageing of the population.

Burden of disease

Data on the extent of the effect of PAD on an individual and on the community are derived primarily from studies in the Western world. This section describes the quality of life (QOL), limb prognosis, cardiovascular events, and mortality in different categories of patients with PAD, as well as the overall global and regional burden.

Quality of life

The QOL in groups of patients with PAD, including comparison with QOL in other diseases, provides a useful clinical and public-health perspective on the disease. Currently, about six general QOL questionnaires and seven disease-specific QOL questionnaires have been used to assess PAD[121].

In the general population, QOL in patients with claudication has been shown to be worse than in healthy individuals, and to be associated mostly with decline in aspects related to physical rather than mental functioning[122]. The effect in patients with claudication was very similar to those with angina. In the PARTNERS programme based on a nationwide survey in primary care in the USA, which included both symptomatic and asymptomatic PAD, the QOL burden was found to be as great as in those individuals with other cardiovascular diseases[123]. Physical function was most affected and, not surprisingly, was related to the underlying symptoms associated with each disease state. For patients with PAD, both intermittent claudication and atypical leg symptoms were implicated. The effects on social and psychological functioning have been shown to be quite modest compared with physical functioning, but might include a reduction in ability to do things and in feelings of dependency[124].

Patients with CLI have worse QOL than patients with intermittent claudication, particularly in terms of the suffering and distress caused by pain[125]. These patients have a health status similar to that of patients who are seriously ill with cancer. Also, physical functioning, bodily pain, and general health perceptions are similar or worse than in patients with congestive heart failure or a recent myocardial infarction. For patients with severe CLI who are not suitable for surgery or angioplasty,

their QOL scores have been found to be below the averages for the general population on every health dimension, although physical functioning and bodily pain were most affected[126].

Prognosis of limb disease

Intermittent claudication. Although atherosclerosis tends to be progressive throughout life in many individuals, studies over the years have shown that, for patients with intermittent claudication, a downward clinical spiral ending with CLI and amputation is not the norm[3]. Indeed, over a 2-year period, maximal walking distance in 50% of patients will remain about the same, and in 25% will improve[127]. This symptomatic stabilization or improvement might be associated with an increase in collaterals, metabolic adaptation of ischaemic muscles, development of neuropathy limiting sensation, change in gait to use of more nonischaemic muscles, and reduction in smoking leading to improvements in haematology, blood flow, and oxygenation. However, although patients might report that their symptoms are improving or remaining stable, a decline in walking ability is often observed on objective measurement[128,129]. Also, a worsening of walking ability can occur to such an extent that an ischaemic threshold is not reached and, therefore, pain does not occur. In a systematic review of follow-up studies[130], only about 20% of patients with claudication were found to deteriorate significantly over a 5-year period. Of those who deteriorate during the first 5 years, around two-thirds have worsening of claudication and up to one-third develop CLI, with <5% of all patients with claudication requiring amputation[37]. Greater deterioration can be influenced by the patient's ABI level and most of the risk factors for acquiring PAD[131].

Atypical leg pain. For patients with PAD identified by a low ABI and atypical leg pain, less information is available on the progression of disease in the legs. As part of the Walking And Leg Circulation Study, patients in various symptom categories were followed up for 2 years[128] and then for 7 years[132] to assess speed of functional decline. Those patients with PAD who, at baseline, had leg pain on exertion and at rest had greater subsequent loss of mobility at 2 years compared with individuals without PAD, and at 7 years compared with patients with claudication. Conversely, those patients with leg pain who were able to carry on walking despite the pain were less likely to have subsequent loss of mobility than patients with claudication.

Asymptomatic individuals. Asymptomatic individuals with PAD, usually identified by a low ABI, have not been followed up in many studies to determine progression of disease in their legs, although deterioration is likely to be similar to that in patients with intermittent claudication. Indeed, the absence of symptoms in some individuals with a low ABI might simply reflect their lack of activity. This situation might partly explain why some patients develop CLI without prior symptoms of claudication. Additionally, some patients, although not having pain, might have reduced functional capacity in their legs[18,133] and greater subsequent decline than individuals without PAD[128,132]. The transition from asymptomatic to early symptomatic disease was examined in the Edinburgh Artery Study[134], in which the 5-year incidence of intermittent claudication was 9.3% in those patients with asymptomatic PAD at baseline (abnormal ABI and/or reactive hyperaemia test) compared with 3.2% in those with no evidence of PAD at baseline. Similar results were found in the Limburg study[135], in which 9% of asymptomatic patients with PAD developed intermittent claudication over the ensuing 7.2 years. Mean decline in ABI in the general population, excluding individuals with intermittent claudication, has been shown to be about −0.03 over a 5-year period[136]. A greater reduction in ABI is likely to occur in patients with asymptomatic PAD (ABI ≤0.90) than in normal individuals because such patients have more cardiovascular risk factors and these factors, especially smoking, are associated with an increased decline in ABI[137,138]. The risk factors for progression of PAD differ according to whether large or small vessels are mostly affected, with diabetes being the major risk factor for the latter[131].

Critical limb ischaemia. The natural history of very severe symptomatic PAD cannot be described accurately, because most patients receive revascularization, primary amputation, or medical treatment, or have very limited survival. The mode of treatment varies greatly between centres, but typically in Western countries around half of patients with CLI have some form of revascularization, although this rate can be as high as 90% in some specialist centres. Follow-up data are available for patients not amenable to surgery, but such groups are not typical of all patients with CLI. For example, in the TAMARIS trial[139] of gene therapy in patients unsuitable for revascularization, after 1 year of follow-up in the placebo group, 21% of patients had had an amputation and 15% had died. The approximate 1-year outcome for all patients presenting with CLI is that 30% will have had an amputation, and only 45% will be alive with both legs intact[140].

Cardiovascular events and mortality

Patients with PAD often have concomitant coronary and cerebral artery disease. In the REACH registry involving 44 countries worldwide, 39% of patients with PAD also had coronary artery disease, 10% also had cerebral artery disease, and 13% had both conditions in addition to PAD; <40% of patients with PAD did not have concomitant coronary or cerebral artery disease[141]. Not surprisingly, these conditions are common causes of death. In earlier studies of patients with PAD, 40–60% of deaths were caused by coronary artery disease, 10–20% by cerebral artery disease, and ~10% were owing to other cardiovascular causes such as ruptured aortic aneurysm; <30% of deaths were attributed to noncardiovascular causes[3]. In some subsequent studies in the USA, however, as many deaths were caused by cancer as cardiovascular disease[21], possibly owing to the effect of statins and other secondary prevention measures. Results from the REACH registry indicate that the greater the number of vascular sites affected by disease,

the higher the mortality[142]. Moreover, mortality seems to be higher in symptomatic compared with asymptomatic PAD[130,143–147] (FIG. 6). Also, the 1-year incidence of all major cardiovascular events in the REACH registry was one-third higher in patients with PAD than in those with coronary or cerebral artery disease[142].

Asymptomatic individuals. The Ankle Brachial Index Collaboration investigated cardiovascular events and mortality in 16 population-based cohorts of mostly asymptomatic individuals with a low ABI[148]. In both men and women, the risk of death was greater the lower the ABI was below 1.11. The 10-year cardiovascular mortality (18.7%) in men with a low ABI (≤0.90) was 4.2 times higher than in those with a normal ABI, and for women the cardiovascular mortality (12.6%) was 3.5 times higher. An increased risk persisted after adjusting for cardiovascular risk factors, including Framingham Risk Scores. Similar results were found for all-cause mortality and for major coronary events. These results emphasize the very high increased risks of cardiovascular events and death in individuals with asymptomatic PAD.

Intermittent claudication. Patients with intermittent claudication, almost all of whom have PAD as measured by a low ABI, have a higher mortality and cardiovascular event rate than individuals without claudication, with relative risks typically around 2.0–4.0. In the Whitehall Study[149] of >18,000 men, the 10-year all-cause mortality in patients with claudication was 28.1%, and the relative risk of cardiovascular death after adjusting for risk factors was 2.7. As would be expected, the absolute risks of death in patients with claudication increase with age and are higher in men than in women, but the relative risks compared with individuals without claudication have a reverse pattern, being highest in young women and lowest in old men[150]. Intermittent claudication also increases the risk of stroke as well as coronary heart disease.

Critical limb ischaemia. Patients with CLI have death and cardiovascular event rates that are particularly high: 20–25% die within 1 year of presentation, and 40–50% within 5 years[151]. In the COPART registry of 940 patients with PAD in southwest France, mortality after 1 year of follow-up was 23.1% for those with rest pain, and 28.7% for those with tissue loss[152]. Limited evidence is available on the incidence of nonfatal myocardial infarction and stroke in patients with CLI. In the FRENA prospective registry of 90 such patients, 2% had had a nonfatal myocardial infarction, and 8% a nonfatal stroke at 1 year of follow-up[153], whereas in an analysis of public health insurance data in Germany, the respective figures at 4 years of follow-up were 10% and 8%[154].

Global and regional burden

Estimating the number of symptomatic patients with PAD worldwide is difficult owing to the lack of validated surveys of symptomatic disease in LMICs. Projecting from the distributions of a low ABI might be prone to error owing to probable variations in symptom experience between populations. However, using data from one fairly typical study[35], which unusually included younger individuals (aged <50 years), and applying the age-specific rates of claudication in those with a low ABI to the number of cases worldwide with a low ABI[24], the number of patients with claudication is around 27 million. An additional 33 million might be expected to have atypical pain[36]. Furthermore, many pain-free individuals with a low ABI have substantial functional impairment[18,133] and increased rates of functional decline[128,132]. Although limited direct survey information exists about the burden of PAD in LMICs, an analysis combining data from the Global Burden of Diseases programme[155] and from a systematic review of prevalence surveys[24] described the burden of PAD at global and regional levels[156]. The principal measure of population burden was the Disability Adjusted Life Year (DALY), which is a composite of the years of life lost owing to premature death caused by PAD and the years lived with disability owing to the disease[155]. The main source of disability for PAD was intermittent claudication, and the disability weight assigned to the condition was based on responses to a survey of lay people in Bangladesh, Indonesia, Peru, Tanzania, and the USA and on results of an international survey of health professionals.

The largest DALY rates per 100,000 population in both 1990 and 2010 were found in the high-income regions of Australasia, Western Europe, and North America[156] (FIG. 7). The rates in 2010 were, respectively, 40.5 (95% CI 26.5–64.6), 47.9 (95% CI 34.1–67.1), and 40.4 (95% CI 26.7–66.3). Although rates were consistently greater in higher-income than in lower-income regions, the rate of growth in DALYs between 1990 and

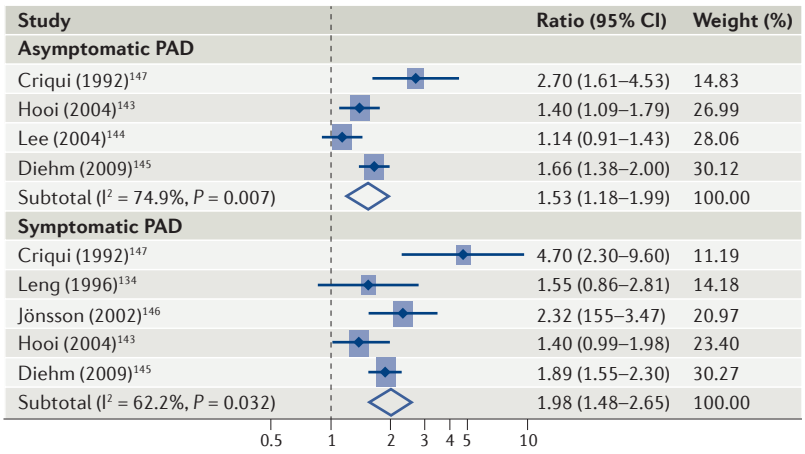

Figure 6 | **Systematic review of all-cause mortality ratios in patients with asymptomatic or symptomatic PAD compared with individuals without PAD.** The results are fairly consistent between the individual studies, and show an increased mortality for individuals with either symptomatic or asymptomatic PAD. The higher mortality ratios for the 1992 publication reflect stricter diagnostic criteria for PAD in that study. Asymptomatic PAD defined as ankle–brachial index <0.9 without clinical manifestations. Symptomatic PAD defined as diagnosed intermittent claudication or critical limb ischaemia. Reference group with no PAD, defined as no symptoms and ankle–brachial index 0.9–1.4. PAD, peripheral artery disease. Reprinted with permission from Sigvant, B. *et al.* The risk of disease progression in peripheral arterial disease is higher than expected: a meta-analysis of mortality and disease progression in peripheral arterial disease. *Eur. J. Vasc. Endovasc. Surg.* **51** (3), 395–403 © (2016), with permission from Elsevier.

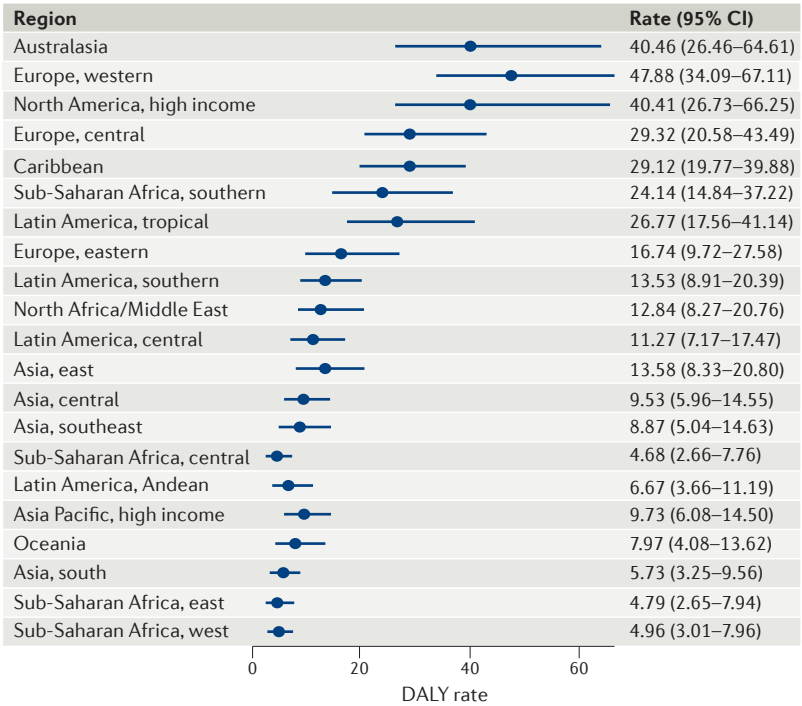

Figure 7 | **DALYs from peripheral artery disease per 100,000 population in world regions in 2010.** DALYs are a composite of years of life lost owing to premature death and years lived with disability. Around the world, the DALY rate for peripheral artery disease tends to be higher in more developed regions. DALY, disability-adjusted life year. Modified from Sampson, U. K. *et al.* Global and regional burden of death and disability from peripheral artery disease: 21 regions, 1990 to 2010. *Glob. Heart* **9** (1), 145–158.e21 © (2014), with permission from Elsevier.

2010 was greater in the lower-income regions, occurring in both men and women. These findings are consistent with those observed on the prevalence of PAD using the ABI, in which a marked increase was found between 2000 and 2010, more so in LMICs[24]. However, in contrast to the DALY burden, the number of patients with PAD based on the ABI measurement was greater in LMICs than in high-income regions. This discrepancy is probably owing to the large number of asymptomatic cases in younger adults in LMICs who would not contribute to the disability component of the DALY estimates.

Compared with other cardiovascular diseases, the global burden of PAD, as measured by DALYs, is small. In 2010, the global burden attributed to PAD was around 1 million DALYs, in contrast to >100 million for ischaemic heart disease, although the relative growth between 1990 and 2010 was threefold higher for PAD[155].

Conclusions

The frequency of PAD seems to be increasing rapidly in LMICs, with some evidence that women might be more affected than men. A large number of cases are occurring in the Southeast Asia and Western Pacific regions. Surveys indicate that some populations in sub-Saharan Africa have the disease. Although this Review suggests that factors such as poverty, industrialization, ethnicity, and infection might conceivably influence the development of PAD, the traditional cardiovascular risk factors of smoking, diabetes, dyslipidaemia, and hypertension are likely to be the principal risk factors driving the epidemiological transition. The increasing survival of the general populations also has an important effect by allowing the development of chronic diseases especially at older ages, as is the case with PAD.

Clearly, the increase in PAD in LMICs is set to continue but, as this Review has shown, there is a dearth of epidemiological research based in these countries. The ABI is a good indicator of PAD, and should be used more widely for the purposes of research and for estimating the population prevalence of PAD. The current WHO Global Non Communicable Diseases Action Plan 2013–2020, which includes ambitious targets to reduce cardiovascular risk factors[157], is hoped to have some effect on limiting the continuing growth of PAD by slowing the relentless upward trend in risk factors observed in LMICs[158]. Fortunately, measures to prevent coronary heart disease and stroke will also have an effect on PAD, so that separate initiatives are not necessarily required, although cardiovascular prevention programmes should highlight PAD as well as coronary and cerebrovascular disease. The increasing burden of PAD in resource-limited countries means that many government authorities will need to set priorities for the management of this condition.

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