

Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis

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Summary

Background Lower extremity peripheral artery disease is the third leading cause of atherosclerotic cardiovascular morbidity, following coronary artery disease and stroke. This study provides the first comparison of the prevalence of peripheral artery disease between high-income countries (HIC) and low-income or middle-income countries (LMIC), establishes the primary risk factors for peripheral artery disease in these settings, and estimates the number of people living with peripheral artery disease regionally and globally.

Methods We did a systematic review of the literature on the prevalence of peripheral artery disease in which we searched for community-based studies since 1997 that defined peripheral artery disease as an ankle brachial index (ABI) lower than or equal to 0.90. We used epidemiological modelling to define age-specific and sex-specific prevalence rates in HIC and in LMIC and combined them with UN population numbers for 2000 and 2010 to estimate the global prevalence of peripheral artery disease. Within a subset of studies, we did meta-analyses of odds ratios (ORs) associated with 15 putative risk factors for peripheral artery disease to estimate their effect size in HIC and LMIC. We then used the risk factors to predict peripheral artery disease numbers in eight WHO regions (three HIC and five LMIC).

Findings 34 studies satisfied the inclusion criteria, 22 from HIC and 12 from LMIC, including 112 027 participants, of which 9347 had peripheral artery disease. Sex-specific prevalence rates increased with age and were broadly similar in HIC and LMIC and in men and women. The prevalence in HIC at age 45–49 years was 5.28% (95% CI 3.38–8.17%) in women and 5.41% (3.41–8.49%) in men, and at age 85–89 years, it was 18.38% (11.16–28.76%) in women and 18.83% (12.03–28.25%) in men. Prevalence in men was lower in LMIC than in HIC (2.89% [2.04–4.07%] at 45–49 years and 14.94% [9.58–22.56%] at 85–89 years). In LMIC, rates were higher in women than in men, especially at younger ages (6.31% [4.86–8.15%] of women aged 45–49 years). Smoking was an important risk factor in both HIC and LMIC, with meta-OR for current smoking of 2.72 (95% CI 2.39–3.09) in HIC and 1.42 (1.25–1.62) in LMIC, followed by diabetes (1.88 [1.66–2.14] vs 1.47 [1.29–1.68]), hypertension (1.55 [1.42–1.71] vs 1.36 [1.24–1.50]), and hypercholesterolaemia (1.19 [1.07–1.33] vs 1.14 [1.03–1.25]). Globally, 202 million people were living with peripheral artery disease in 2010, 69.7% of them in LMIC, including 54.8 million in southeast Asia and 45.9 million in the western Pacific Region. During the preceding decade the number of individuals with peripheral artery disease increased by 28.7% in LMIC and 13.1% in HIC.

Interpretation In the 21st century, peripheral artery disease has become a global problem. Governments, non-governmental organisations, and the private sector in LMIC need to address the social and economic consequences, and assess the best strategies for optimum treatment and prevention of this disease.

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Introduction

Chronic non-communicable diseases (NCDs) are now the leading cause of morbidity and mortality not only in high-income countries (HIC), but also in low-income or middle-income countries (LMIC).^{1,2} Over the next decade, the global burden of NCDs will grow rapidly, driven mainly by an ageing world population and increased exposure to chronic disease risk factors in LMIC.^{3,4} The global pandemic of NCDs was the main topic of a UN high-level meeting in 2011.⁵ One of the first tasks required for a coordinated and cost-effective response is to quantify the current burden of the most important NCDs and

their global and regional spread. This effort will probably be met with a paucity of information from most LMIC, which will be particularly true for diseases that are still relatively neglected even in HIC. One of the best examples is lower limb peripheral artery disease, the third leading cause of atherosclerotic vascular morbidity after coronary heart disease and stroke. About 10–20% of people with peripheral artery disease have intermittent claudication,^{6,7} another 50% have atypical leg symptoms,⁷ and those without exertional leg pain have poor mobility compared with individuals without peripheral artery disease.⁸ Patients with and without leg ischaemic

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symptoms have roughly a three-fold increase in risk of mortality and major cardiovascular events (heart attack and stroke) compared with those without peripheral artery disease.^{9–11}

To develop effective policies and programmes for the global prevention and management of peripheral artery disease, population surveillance data and studies of risk factors are crucial, but lacking in many HIC and particularly in LMIC. Currently, there are no reliable estimates of the global prevalence of peripheral artery disease. Moreover, in assessing the global transition in cardiovascular disease in recent years,¹² attention has been focused on the decline in coronary heart disease and stroke in HIC, the corresponding increase in many LMIC, and the risk factors that might be driving this change.^{13,14} Little attention has been paid to peripheral artery disease.

We did a rigorous systematic analysis of all the evidence available in the public domain to identify epidemiological studies of peripheral artery disease of acceptable quality. Using the information from those studies, we aimed to: (1) provide the first comparison of age-specific and sex-specific prevalence of peripheral artery disease between HIC and LMIC; (2) establish the main risk factors for peripheral artery disease in HIC and LMIC; and (3) provide robust estimates of the number of people living with peripheral artery disease regionally and globally.

Methods

Study design

The methods consisted of the following stages: (1) literature search for studies on prevalence of peripheral artery disease; (2) extraction of data from these studies; (3) modelling of age-specific and sex-specific prevalence in HIC and LMIC based on the extracted data; (4) application of age-specific and sex-specific prevalence data to UN Population Division's populations¹⁵ in HIC and LMIC to provide estimates of numbers of individuals living with peripheral artery disease in 2000 and 2010; (5) identification of multivariate associations of risk factors and peripheral artery disease in HIC and LMIC based on data in prevalence studies from the literature search; and (6) use of the relevant risk factor associations and WHO data on regional prevalence of the risk factors¹⁶ to estimate the number of people living with peripheral artery disease in WHO regions. These six stages are described in detail in the appendix A, together with datasets and calculations (appendix B). Here, we summarise the stages.

Search strategy and selection criteria

We did a systematic review of the published literature on peripheral artery disease in the legs. Initially, we searched for papers that described the incidence or prevalence of peripheral artery disease up to June, 2011, using the following databases: Medline (1950–), Embase (1980–), AMED (1985–), CINAHL (1982–), and LILACS (2008–). Due to the small number of studies identified from some

world regions, we did an additional broader search on studies of peripheral artery disease specific to these regions. We searched conference proceedings, consulted experts, and requested additional data from investigators. We used community-based studies in which most data were collected after the beginning of 1997 and which had a standardised case definition of peripheral artery disease. The most accurate method to ascertain peripheral artery disease in the community is the ankle brachial index (ABI)—a non-invasive test of the ratio of systolic pressure at the ankle to that in the arm.¹⁷ Therefore, studies eligible for assessing peripheral artery disease prevalence were those that included an ABI measurement and defined peripheral artery disease as ABI lower than 0·90 or equal to or lower than 0·90. We did not set criteria for the measurement and calculation of the ABI, while recognising that inconsistencies might have had some effect on prevalence rates.^{17,18} 34 studies met all the above criteria.^{19–52}

Data extraction

We abstracted data for the prevalence of peripheral artery disease by age and sex from every paper and entered them into a Microsoft Excel database. For the 34 retained studies,^{19–52} the extracted data included study characteristics (setting, duration, design, etc), diagnostic criteria, and mean age and the sex of the study participants. We created a separate dataset with 101 datapoints on age-specific prevalence of peripheral artery disease for both sexes combined, 92 for male individuals only, and 86 for female individuals only. We used this dataset for modelling the relation between age (in years) and prevalence of peripheral artery disease in male and in female individuals, separately in HIC and LMIC (as defined by the World Bank).⁵³

Most retained studies also investigated the associations of potential risk factors with peripheral artery disease in exposed participants compared with non-exposed participants. At least three independent studies investigated 15 suspected risk factors, which was our threshold for inclusion in the subsequent analyses. Estimates of odds ratios (ORs) in individual studies were based on both univariate and multivariate study designs. We used only those ORs based on a multivariate study design in which similar definitions of risk factors were used and the ORs were reported with an estimate of uncertainty. We included 22 such studies, providing 165 datapoints on OR estimates for risk factors and CIs. A separate database with information on the 15 risk factors used in the meta-analyses is available in the appendix (B).

Epidemiological modelling of age-specific prevalence

We used meta-regression to model the prevalence of disease in the population. This approach has been used widely in assessing the global prevalence of NCDs and the strengths and limitations been compared with other methods.⁵⁴

See Online for appendices

We developed four statistical models (for male and female individuals in HIC and LMIC) based on 178 datapoints from 34 studies that established the relation between the age and prevalence of peripheral artery disease in male and female individuals separately. We used the binomial distribution to model prevalence by mean age, taking into account the sample size and the occurrence of repeated samples from the same site or study. Given that:

$$\text{prevalence} = p = \frac{\text{number of cases}}{\text{number of examinees in sample}}$$

then, using the logit link:

$$\text{logit}(p) = \log_e \left(\frac{p}{1-p} \right) = a + b_1 x_1 + b_2 x_2 + \dots = \log_e (\text{odds})$$

as age is the covariate of interest,

$$\log_e \left(\frac{p}{1-p} \right) = a + b * (\text{age})$$

Thus,

$$\text{odds of prevalence case} = \frac{p}{1-p} = e^{a+b*(\text{age})}$$

and

$$\text{probability of case (= prevalence = } p) = \frac{e^{a+b*(\text{age})}}{1 + e^{a+b*(\text{age})}}$$

We included the study number as a repeated measure in the model building, and fitted with different covariance structures: independent, exchangeable, and autoregressive. As a rule, the models with an independent covariance structure best fitted the data, and we used them in the final analysis. Age was fitted as fixed effect because it was the variable of interest. The inclusion of study as a random factor was found to have no influence on the predictors of goodness of fit.

Estimation of global population with peripheral artery disease in 2000 and 2010 and meta-analyses of risk factors

We multiplied the estimates of age-specific and sex-specific prevalence for the median year of every 5-year age group (starting from 25–29 years to 100–104 years) with corresponding world and regional populations in 2000 and 2010, obtained from the UN Population Division's website,¹⁵ to derive the number of people living with peripheral artery disease every year. We added the predicted cases of peripheral artery disease across all age groups to develop the estimates of the total numbers in HIC, in LMIC, and worldwide.

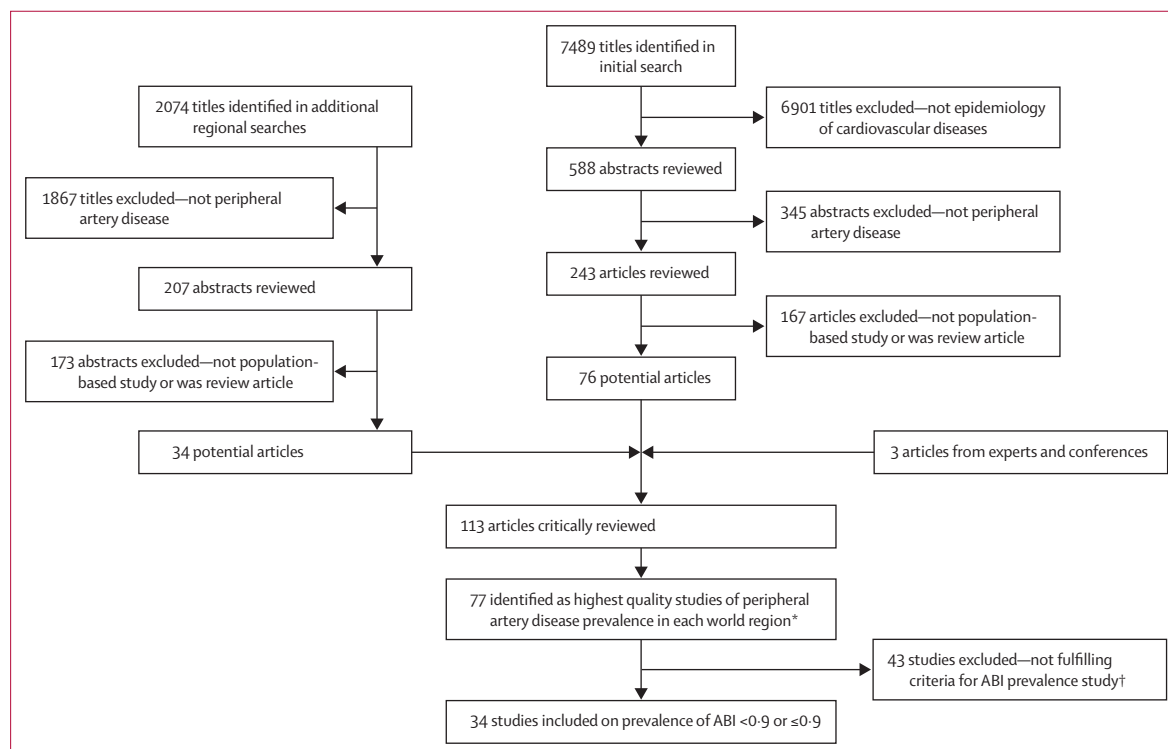


Figure 1: Literature search for studies of prevalence of peripheral artery disease, defined by a low ABI

ABI=ankle brachial index. *Peripheral artery disease studies included a broad definition: intermittent claudication or low ABI or vascular reconstruction or amputation. †Inclusion criteria were prevalence data based on ABI <0.9 or ABI ≤0.9; reliable ABI method; general population sample; data collected 1997–2011.

We then did meta-analyses on the 15 suspected risk factors to obtain meta-estimates of ORs separately for HIC and LMIC to investigate whether the role of risk factors substantially differed between the two contexts. The number of examinees used in the meta-analyses ranged from 5243 (C-reactive protein) to 60 231 (diabetes).

Estimation of population with peripheral artery disease in world regions

Finally, we combined our risk factor meta-ORs and regional prevalences of risk factors to distribute the

estimated global number of cases by regions, using a method proposed by the Child Health Epidemiology Reference Group.⁵⁵ We estimated the number of peripheral artery disease cases in different age groups in the six WHO regions: sub-Saharan Africa, eastern Mediterranean, southeast Asia, western Pacific, Europe, and the Americas.⁵⁶ We did this analysis on the basis of the differences in regional prevalence of four risk factors and the differences in their OR values in the context of HIC and LMIC. We chose the four risk factors (current smoking, hypertension, hypercholesterolaemia, and

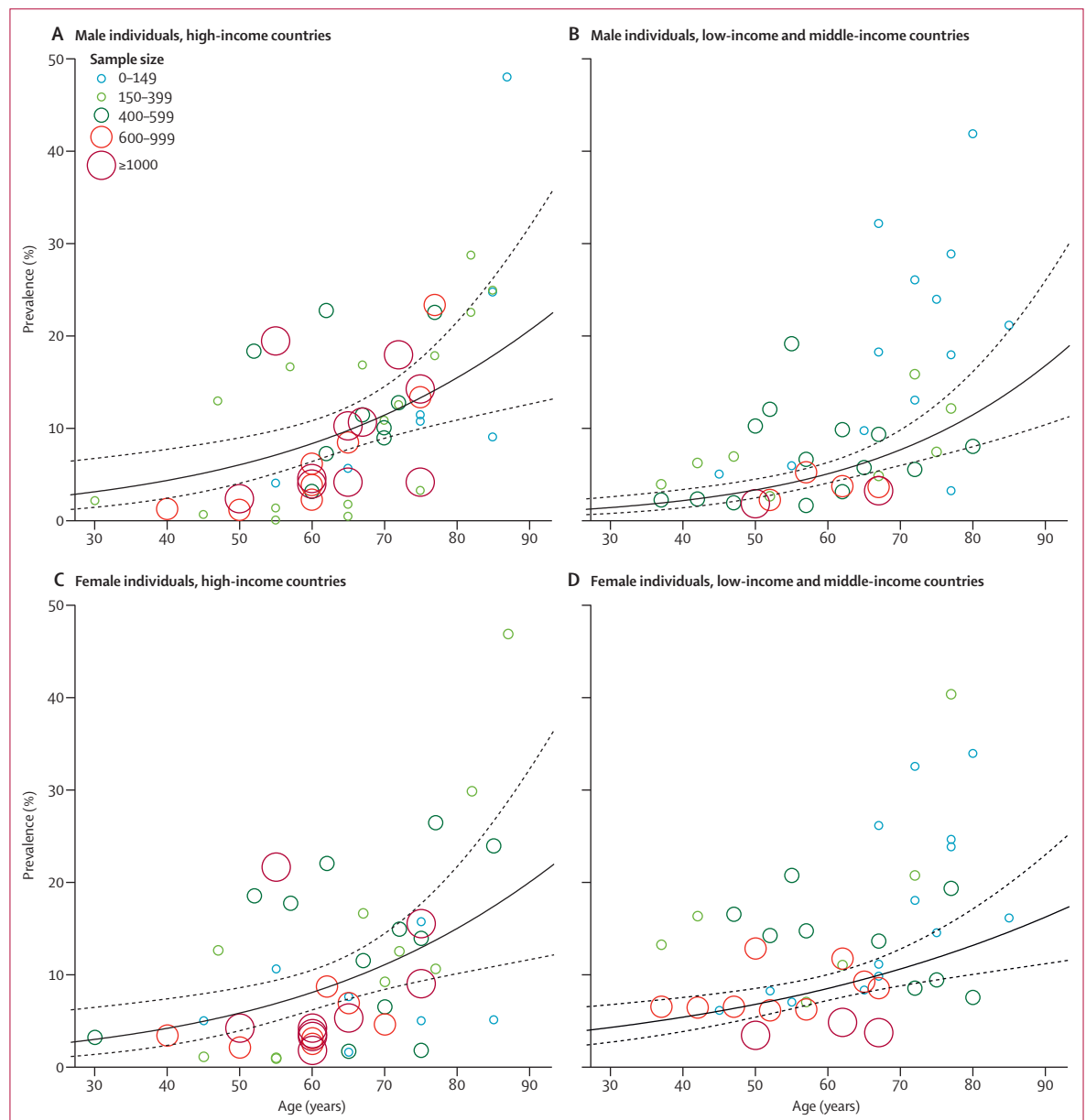


Figure 2: Prevalence of peripheral artery disease by age in men and women in high-income countries and low-income or middle-income countries
 Size and colour of circles equivalent to sample size of population from which datapoint was derived. Note that at younger (<40 years) and older (>80 years) ages, regression lines are based on projection only or very few datapoints. Akaike Information Criterion for model goodness of fit: male high-income countries 1974-72; male low-income or middle-income countries 838-36; female high-income countries 1971-59; female low-income or middle-income countries 1115-09.

diabetes) because they had significantly increased meta-ORs in HIC and LMIC, and regional prevalence data were available. We used crude prevalence of exposure for all four risk factors, and obtained the data from the WHO global health observatory.¹⁶ We further split two WHO regions (Americas and western Pacific) into high-income and low-income and middle-income populations, because the ORs relevant to the four retained risk factors had different values in the HIC and LMIC contexts. Moreover, we ensured that the definitions of risk factors were similar in the studies estimating ORs, as well as in the surveys that measured prevalence of exposure to these risk factors.

Then, we calculated the number of cases of peripheral artery disease for every WHO region (five LMIC and three HIC) using a model based on the epidemiological concept of potential impact fraction (appendix B).⁵⁷ We distributed the eight regional estimates of the number of peripheral artery disease cases by 10-year age groups by computing the proportional contribution of every age group, starting from 25 to 34 years onwards, to the total numbers with peripheral artery disease in HIC and LMIC based on the above model.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The initial screening retrieved 7489 titles of articles, 588 of which indicated a possible population-based study of cardiovascular disease (figure 1), and 243 had any mention of peripheral artery disease. These 243 full-text articles were then reviewed independently by two assessors and retained after discussion and agreement. We identified 2074 articles in the additional regional search. Of the 113 articles critically reviewed, 34 were included in this study.

The 34 retained studies on prevalence included 112 027 participants (9347 patients with peripheral artery disease). 22 studies were from HIC (Australia, Denmark, Germany, Hong Kong, Japan, Singapore, South Korea, Spain, Sweden, and USA), and 12 studies from LMIC (Brazil, Central African Republic, China, India, Mexico, Republic of Congo, South Africa, and Thailand). The appendix B shows characteristics of every study. Figure 2 shows the four models of prevalence by age for each sex in HIC and LMIC. In every model, a substantial number of datapoints and large sample sizes, which were spread across most of the age spectrum, resulted in rather narrow 95% CIs, except at old ages where there were fewer available data. In both HIC and LMIC the prevalence of peripheral artery disease increased across all ages.

The prevalence of peripheral artery disease in HIC did not differ meaningfully between men and women (table 1). In LMIC the prevalence up to 85–89 years was consistently higher in women than men, although the difference narrowed with age. When comparing HIC with LMIC, the prevalence of women with peripheral artery disease was slightly higher in LMIC at all ages up to 60–64 years, above which the prevalence was slightly higher in HIC. The prevalence of men with the disorder was consistently higher in HIC than in LMIC.

The prevalence rates when applied to the populations of HIC and LMIC in 2000 and 2010 provided an estimate of the number of people living with peripheral artery disease (table 2). Because of world population ageing during 2000–10, the number of people with peripheral artery disease increased by 23·5% globally, from 164 million cases in the year 2000 to 202 million in 2010. The age groups in which the increase was particularly striking were those at older ages: the increase over 2000–10 in all age groups older than

	Prevalence (women)		Prevalence (men)	
	High-income countries	Low-income and middle-income countries	High-income countries	Low-income and middle-income countries
25–29 years	2·70% (1·15–6·20)	3·96% (2·39–6·51)	2·76% (1·17–6·41)	1·21% (0·62–2·34)
30–34 years	3·20% (1·52–6·62)	4·46% (2·86–6·87)	3·27% (1·53–6·85)	1·50% (0·84–2·68)
35–39 years	3·78% (1·99–7·07)	5·01% (3·43–7·25)	3·88% (2·01–7·34)	1·87% (1·14–3·07)
40–44 years	4·47% (2·60–7·58)	5·62% (4·10–7·68)	4·58% (2·63–7·88)	2·33% (1·53–3·52)
45–49 years	5·28% (3·38–8·17)	6·31% (4·86–8·15)	5·41% (3·41–8·49)	2·89% (2·04–4·07)
50–54 years	6·23% (4·33–8·87)	7·08% (5·72–8·72)	6·38% (4·38–9·20)	3·58% (2·70–4·73)
55–59 years	7·33% (5·45–9·77)	7·92% (6·64–9·44)	7·51% (5·55–10·08)	4·43% (3·50–5·59)
60–64 years	8·60% (6·65–11·05)	8·87% (7·53–10·41)	8·82% (6·85–11·28)	5·47% (4·40–6·48)
65–69 years	10·08% (7·78–12·95)	9·91% (8·33–11·75)	10·33% (8·14–13·03)	6·74% (5·35–8·46)
70–74 years	11·77% (8·76–15·63)	11·05% (9·02–13·48)	12·07% (9·28–15·55)	8·28% (6·32–10·77)
75–79 years	13·71% (9·62–19·17)	12·32% (9·64–15·62)	14·05% (10·26–18·94)	10·13% (7·33–13·83)
80–84 years	15·91% (10·40–23·56)	13·70% (10·22–18·13)	16·30% (11·16–23·18)	12·33% (8·41–17·74)
85–89 years	18·38% (11·16–28·76)	15·22% (10·80–21·02)	18·83% (12·03–28·25)	14·94% (9·58–22·56)
90–94 years	21·14% (11·91–34·71)	16·87% (11·38–24·28)	21·65% (12·88–34·06)	17·99% (10·86–28·30)
95–99 years	24·20% (12·68–41·24)	18·65% (11·96–27·90)	24·77% (13·75–40·47)	21·50% (12·27–34·90)

Data are % (95% CI). Note that at ages 25–29 years, 90–94 years, and 95–99 years, the results are estimated predictions and outwith the range of the original data.

Table 1: Estimated age-specific prevalence of women and men living with peripheral artery disease in high-income countries and in low-income and middle-income countries, by age group

	People living with peripheral artery disease in year 2000 (thousands)			People living with peripheral artery disease in 2010 (thousands)			Rate of change (2000-10)		
	High-income countries	Low-income and middle-income countries	Worldwide	High-income countries	Low-income and middle-income countries	Worldwide	High-income countries	Low-income and middle-income countries	Worldwide
25-29 years	2311	10 756	13 068	2381	12 037	14 419	3.02%	11.91%	10.34%
30-34 years	2803	11 469	14 272	2760	12 343	15 103	-1.52%	7.62%	5.82%
35-39 years	3486	11 247	14 733	3343	13 776	17 119	-4.12%	22.49%	16.19%
40-44 years	4071	11 138	15 209	3938	14 707	18 645	-3.28%	32.05%	22.59%
45-49 years	4528	11 408	15 936	4851	14 354	19 205	7.14%	25.83%	20.51%
50-54 years	4907	9902	14 808	5503	14 100	19 603	12.15%	42.40%	32.37%
55-59 years	4530	9111	13 641	5948	14 170	20 118	31.31%	55.53%	47.49%
60-64 years	5342	9074	14 416	6242	11 787	18 029	16.85%	29.90%	25.06%
65-69 years	5287	8416	13 704	5547	10 124	15 670	4.90%	20.29%	14.35%
70-74 years	5594	6953	12 547	6043	9020	15 063	8.02%	29.73%	20.05%
75-79 years	4808	4960	9768	5370	7012	12 382	11.68%	41.36%	26.75%
80-84 years	3107	3015	6123	4723	4396	9118	51.98%	45.77%	48.92%
85-89 years	2246	1411	3658	3028	2087	5115	34.80%	47.86%	39.84%
≥90 years	1174	544	1717	1611	864	2474	37.22%	58.82%	44.09%
Total	54 195	109 405	163 600	61 287	140 775	202 062	13.08%	28.67%	23.51%

Additions in the table might deviate from the world total in the last digit due to rounding.

Table 2: Estimated number of people living with peripheral artery disease in high-income countries, low-income and middle-income countries, and worldwide in the years 2000 and 2010, and the rate of change from 2000 to 2010

80 years was consistently greater than 35%. The increase was also much greater at nearly all ages in LMIC than in HIC. Moreover, in the year 2010, more than two-thirds (69.7%) of peripheral artery disease was concentrated in LMIC.

To study the risk factors associated with peripheral artery disease, we excluded 12 of the 34 studies because they did not present data for risk factors or because they reported a univariate analysis only. The remaining 22 studies reported effect size estimates for different combinations of selected risk factors. We focused on 15 risk factors that were investigated by at least three studies. One of these risk factors was history of other cardiovascular disease, which would typically not be regarded as a causal factor but more as evidence of co-existing atherosclerotic disease. The most frequently studied risk factors were hypertension and diabetes (both with reports from 19 studies), followed by current smoking (18 studies), age (14 studies), body-mass index (BMI; 13 studies), history of cardiovascular disease (12 studies), sex (11 studies), and former smoking (ten studies). Other lipid fractions and biomarkers of inflammation and haemostasis were studied by multivariate design in eight studies or fewer. We excluded the meta-analysis on alcohol because of major inconsistencies between studies in definition of overconsumption, leaving 14 risk factors in the final analysis (table 3).

In addition to age, several risk factors showed consistently significant associations with peripheral artery disease in both HIC and LMIC (table 3). Current smoking and former smoking were significant risk factors in both settings. A meta-OR greater than 2.0 was

also noted for history of another cardiovascular disease. Significant risk factors, with meta-ORs between 1.0 and 2.0, were diabetes, hypertension, and hypercholesterolaemia. The association of sex with peripheral artery disease had an inconsistent pattern in the two settings. Although significant at the global level, and with a decreased risk for men compared with that for women, men were at increased risk in HIC, whereas they were at much reduced risk in LMIC. The appendix B shows the reported results from individual studies that contributed to these meta-analyses.

We distributed the total number of estimated cases in HIC and LMIC to more specific WHO regions according to regional differences in the prevalence of exposure to the four major risk factors: current smoking, hypertension, hypercholesterolaemia, and diabetes (appendix B). Figure 3 shows that in the year 2010 about 140.8 million people with peripheral artery disease were living in LMIC regions: 54.8 million in southeast Asia and 45.9 million in the western Pacific, 15.5 million in Latin America, 14.2 million in sub-Saharan Africa, and 10.3 million in the eastern Mediterranean. The remaining 61.3 million were living in Europe (40.5 million), HIC of western Pacific (6.5 million) and of the Americas (14.3 million). Whereas the age groups that contributed most cases of peripheral artery disease in high-income regions (notably Europe and North America) were over 55 years of age, in western Pacific (LMIC) and southeast Asia regions, most cases in the population were noted in people younger than 55 years. This finding portrays the younger age structure of the LMIC in comparison to HIC.

	Number of studies	Sample size	OR (95% CI)	p value	HIC vs LMIC p values
Age (per 10 year increase)					
All countries	14	43 799	1.39 (1.34-1.44)	<0.0001	<0.0001
HIC	10	20 902	1.75 (1.64-1.87)	<0.0001	
LMIC	4	22 897	1.25 (1.20-1.30)	<0.0001	
Sex (male sex)					
All countries	11	36 461	0.83 (0.74-0.93)	0.001	<0.0001
HIC	6	11 500	1.43 (1.18-1.73)	0.0002	
LMIC	5	24 961	0.50 (0.43-0.57)	<0.0001	
Body-mass index (binary [>25 kg/m ²] or continuous [per 1 kg/m ² increase])					
All countries (binary)	6	31 775	0.83 (0.75-0.91)	<0.0001	Binary p=0.002; continuous p=0.74
HIC (binary)	4	13 517	0.96 (0.84-1.10)	0.56	
LMIC (binary)	2	18 258	0.72 (0.63-0.81)	<0.0001	
All countries (continuous)	7	10 067	0.87 (0.76-1.01)	0.07	
HIC (continuous)	4	5 310	0.95 (0.57-1.58)	0.84	
LMIC (continuous)	3	4 757	0.87 (0.75-1.01)	0.06	
Hypertension ($\geq 140/90$ mm Hg)					
All countries	19	54 532	1.47 (1.37-1.57)	<0.0001	0.06
HIC	11	27 447	1.55 (1.42-1.71)	<0.0001	
LMIC	8	26 985	1.36 (1.24-1.50)	<0.0001	
Diabetes (fasting glucose >7 mmol/L or diabetes medication or doctor's diagnosis)					
All countries	19	60 231	1.68 (1.53-1.84)	<0.0001	0.009
HIC	12	30 887	1.88 (1.66-2.14)	<0.0001	
LMIC	7	29 344	1.47 (1.29-1.68)	<0.0001	
Smoking (current smoker)					
All countries	18	58 147	2.09 (1.91-2.29)	<0.0001	<0.0001
HIC	11	29 844	2.72 (2.39-3.09)	<0.0001	
LMIC	7	28 303	1.42 (1.25-1.62)	<0.0001	
Smoking (former smoker)					
All countries	10	24 368	1.87 (1.64-2.18)	<0.0001	0.04
HIC	6	16 935	2.03 (1.71-2.41)	<0.0001	
LMIC	4	7 433	1.47 (1.13-1.91)	0.005	
Hypercholesterolaemia (>240 mg/dL or >200 mg/dL)					
All countries	11	41 017	1.16 (1.08-1.25)	<0.0001	0.54
HIC	6	19 046	1.19 (1.07-1.33)	0.002	
LMIC	5	21 971	1.14 (1.03-1.25)	0.009	
Hypertriglyceridaemia (>150 mg/dL)					
All countries	6	16 850	1.22 (1.10-1.35)	0.0002	0.38
HIC	3	13 137	1.26 (1.11-1.42)	0.0003	
LMIC	3	3 713	1.13 (0.94-1.37)	0.19	
Elevated LDL cholesterol (>130 mg/dL)					
All countries	5	11 437	1.03 (0.94-1.13)	0.47	0.84
HIC	4	9 132	1.03 (0.92-1.14)	0.62	
LMIC	1	2 305	0.99 (0.81-1.20)	0.58	
Low HDL cholesterol (binary [<40 mg/dL] or continuous [per 5 mg/dL increase in HDL])					
All countries (binary)	4	6 744	0.92 (0.83-1.01)	0.09	Binary p=0.46; continuous N/A
HIC (binary)	1	3 313	0.90 (0.80-1.01)	0.06	
HIC (continuous)	4	9 132	0.99 (0.89-1.09)	0.73	
LMIC (binary)	3	3 431	0.92 (0.80-1.20)	0.86	

(Continues on next page)

	Number of studies	Sample size	OR (95% CI)	p value	HIC vs LMIC p values
(Continued from previous page)					
C-reactive protein (binary [1.0–2.9 mg/dL] or continuous [per 1 mg/dL increase])					Binary p=0.11; continuous p=0.95
All countries (binary)	3	5243	1.69 (1.13–2.54)	0.01	
HIC (binary)	2	5123	1.82 (1.19–2.80)	0.006	
LMIC (binary)	1	118	0.62 (0.18–2.15)	0.45	
All countries (continuous)	5	9250	1.11 (1.04–1.18)	0.001	
HIC (continuous)	4	9132	1.10 (1.03–1.18)	0.003	
LMIC (continuous)	1	118	1.11 (0.94–1.31)	0.21	
Fibrinogen (>400 mg/dL or per 50 mg/dL increase)					
HIC only	3	9097	1.07 (1.00–1.14)	0.06	
Cardiovascular disease (history of other cardiovascular disease such as CHD or stroke)					0.01
All countries	12	42799	2.27 (1.98–2.59)	<0.0001	
HIC	10	23500	2.55 (2.16–3.02)	<0.0001	
LMIC	2	19299	1.77 (1.42–2.21)	<0.0001	
HIC=high-income countries. LMIC=low-income and middle-income countries. OR=odds ratio. LDL=low-density lipoprotein. HDL=high-density lipoprotein. CHD=coronary heart disease. NA=not available. Some definitions for risk factors varied slightly between studies. ORs for binary variable risk factor indicate risk of peripheral artery disease compared with all others without the risk factor, except for current smokers and former smokers, who are compared with never smokers, and high HDL, which is compared with low HDL cholesterol.					
Table 3: Meta-analyses of the effect size of 14 risk factors that were investigated in at least three retained studies using multivariate design					

Discussion

This study presents the first comprehensive, data-driven estimates of the global epidemiology of peripheral artery disease, and the differences between HIC and LMIC. As expected, prevalence of peripheral artery disease increased with age in both settings, from a relatively uncommon disorder in people younger than 40 years to a common problem affecting one in ten people aged 70 years, and one in six people older than 80 years. We retrieved sufficient information from both HIC and LMIC to conclude that age-specific prevalences of peripheral artery disease did not differ substantially between the two settings. Thus, one of the most important findings of our study is that it should not be assumed that peripheral artery disease is a smaller public health problem in LMIC than in HIC, because the evidence indicates that peripheral artery disease is similarly important in both settings.

The most striking differences in prevalence were higher rates in HIC than in LMIC for men, and, the higher prevalence of women with the disease than men in LMIC. The excess in women was unlikely to be due to differential effects of risk factors, given our finding of an independent association of sex with peripheral artery disease (table 3). Furthermore, in LMIC the prevalence of smoking, a major risk factor, was higher in men than in women (appendix B). However, these sex differences could be related to unidentified risk factors or represent a survival advantage for women, with men being more likely to experience death from concomitant coronary heart disease. Also, the higher rates noted in women might be due partly to the apparently lower normal distribution of the ABI in women than in men.^{58,59} The

sex difference may be reduced slightly on adjusting for height,¹⁷ but the adjustment was not feasible in our study. Although these sex differences are small,^{58,59} we cannot conclude with certainty that the prevalence of peripheral artery disease in LMIC is higher in women than men.

The prevalence in HIC was consistently higher than that in LMIC in very old age groups, but information on prevalence in those groups in LMIC was scarce. Information is scarce because life expectancy is much shorter in LMIC and sample sizes in older age groups were smaller, making the estimates more uncertain. Also, the survival of patients with peripheral artery disease could be worse in LMIC than in HIC leading to a relative underestimation of the rates in LMIC. At younger ages too (<40 years), the rates were less certain due to scarce data. Furthermore, the validity of a low ABI at younger ages has not been well investigated, although no biologically plausible reasons why its significance should differ from that at older ages exist. Also, in some countries, notably in east Asia, a low ABI might be due in some younger people to Buerger's disease (thromboangiitis obliterans), which might sometimes affect medium and large arteries rather than small distal arteries.⁶⁰

Due to increased life expectancy of the world's population, our study estimated that the number of people living with peripheral artery disease increased by 23.5% in only a decade between 2000 and 2010. This great increase occurred especially in LMIC (28.7% increase) whereas in HIC, we noted a 13.1% increase. The primary drivers of this increase were longer life expectancy in HIC leading to a substantial rise in cases older than 80 years. At the same time, longer life

expectancy in LMIC is responsible for higher-than-ever numbers of people reaching the age of 55 and over, when the risk of developing peripheral artery disease is accelerated. This large cohort in LMIC, especially in the western Pacific and southeast Asia regions, will enter the exponential phase of increased risk in the coming decade (figure 3), which will further enhance the growth in the global numbers with peripheral artery disease. Despite a decrease in HIC, mortality from coronary heart disease and stroke has also shown a marked increase globally from around 10 million deaths in 1990 to 13 million in 2010¹ with more than 80% occurring in LMIC.¹³

These global and regional numbers with peripheral artery disease could, however, be an under-estimate of the true burden because the sensitivity of an ABI lower than 0·90 in the detection of atheroma in leg arteries is likely to be less than 80%.⁶¹ The relatively low sensitivity is due to several reasons: mild peripheral artery disease might not be detected by ABI at rest because severe stenosis in at least one major artery is needed to reduce ankle pressure; lesions affecting the internal iliac or the femoral profunda arteries, as well as distal peripheral artery disease in the pedal or toe arteries, do not affect the ABI; nearly 4% of individuals have an ABI higher than 1·30 often due to medial calcinosis and commonly associated with peripheral artery disease, which would be undetected using only the criterion of lower than 0·90;⁶² some population studies use the higher rather than the lower of the popliteal and dorsalis pedis pressures to calculate the ABI, which might miss some cases of peripheral artery disease. Also, patients already amputated or with critical limb ischaemia are often excluded in population studies. On the other hand, despite a high specificity of over 95% in most studies,⁶¹ the false-positive results associated with an ABI <0·90 would increase the estimates of prevalence, especially at lower rates of prevalence as observed in younger age groups.

Nevertheless, the current estimate of 202 million cases worldwide is already a very large burden, and understanding its direct and indirect contribution to overall global morbidity and mortality is a current research priority.^{1,2} Around 20–40 million are likely to have intermittent claudication and 100 million atypical leg symptoms. Pain and limited mobility lead to a diminished quality of life.⁶³ However, even asymptomatic people with peripheral artery disease have impaired lower extremity functioning, increased mobility loss, and faster functional decline than individuals without peripheral artery disease.^{64–66} These effects of peripheral artery disease might be especially profound in many LMIC where walking substantial distances is required to obtain the necessities of daily life, such as water and fuel, and more so in the 2% of claudicants who end up having an amputation.⁶⁷ Furthermore, up to 45 million of the 202 million with peripheral artery disease will die from coronary or cerebrovascular disease during a 10 year period.¹¹

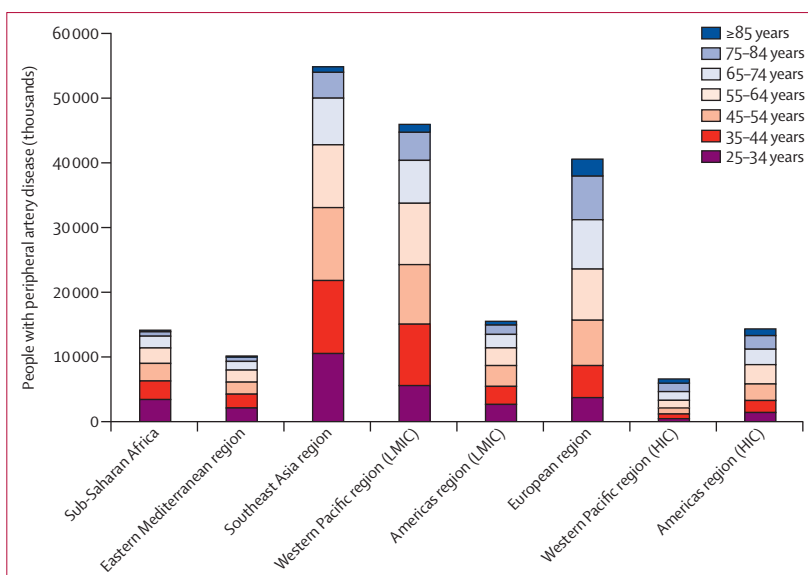


Figure 3: Estimate of the number of cases, and contributing age groups, in eight WHO regions in the year 2010. LMIC=low-income and middle-income countries. HIC=high-income countries.

To our knowledge, this study has undertaken the most comprehensive global analysis of risk factors for peripheral artery disease to date. The strength of the conclusions arises from several measures that we took to derive the estimates of effect size (meta-ORs) for investigated risk factors: (1) ensuring a standardised outcome across all studies for which the risk was measured (ie, peripheral artery disease measured by ABI and defined using the same threshold); (2) using only estimates of OR from studies that applied multivariate study designs; and (3) sufficiently large numbers of observations in both HIC and LMIC contexts. This consistent approach has yielded plausible results, as ORs in multivariate analyses were consistently lower in the retained studies than ORs for the same risk factors reported in studies with univariate design (data not shown). Only well recognised risk factors, which have been consistently associated with other major cardiovascular disorders, were also confirmed as significant in this study. Moreover, these observations were typically based on meta-analyses that included 30 000–60 000 examinees, with a reasonably equal split between HIC and LMIC. Most meta-estimates of ORs fell between 1·0 and 2·0, with only a few of them between 2·0 and 3·0. This is again plausible and consistent with relatively moderate effects of individual risk factors at the population level.

We noted appreciable differences in the magnitude of associations of risk factors with peripheral artery disease. The associations of age, smoking, diabetes, and history of cardiovascular disease were significantly larger in HIC than LMIC. Hypertension and hypercholesterolaemia also had slightly stronger effects in HIC than in LMIC, although the differences were not significant. One of the possible explanations for

generally stronger associations of investigated risk factors in the HIC context is that the samples from those studies typically had a much broader age range and greater proportion of old examinees, allowing for more cases of peripheral artery disease within the sample and stronger conclusions than the studies in LMIC. Also, people living in LMIC may have had shorter lifetime exposures to risk factors, resulting in a lower risk of disease. However, our study has confirmed the importance of conventional cardiovascular risk factors for peripheral artery disease in LMIC and, given an apparent increasing trend in the prevalence of these factors^{68–71} they are likely to contribute, along with increasing numbers of elderly people, to future growth in the population with peripheral artery disease.

The estimates of global numbers with peripheral artery disease were based on the age and sex specific prevalences in HIC and LMIC. Within both settings our results were derived from studies across all WHO regions (except eastern Mediterranean), and so should be reasonably representative of the global burden. By adjusting for differences in the regional prevalence of the important risk factors, we were able to further refine the regional numbers (figure 3). These findings confirmed the very substantial numbers in southeast Asia and western Pacific regions. Some of these differences between regions could however be related to small ethnic variations in the distribution of the ABI in healthy populations.⁵⁸ Also, about a third of peripheral artery disease cases in these regions were in people aged 25–44 years and, as explained previously, there might be some uncertainty about the numbers with peripheral artery disease at younger ages. Nevertheless, even ignoring this age group, the southeast Asia region still had the largest number of people with peripheral artery disease in any region in 2010.

In conclusion, results from this study have shown that peripheral artery disease is a worldwide disease and that the known risk factors in HIC are also important in LMIC. The number of people with peripheral artery disease has increased by nearly a quarter between 2000 and 2010. In view of the association of peripheral artery disease with loss of mobility,⁶⁶ functional decline,⁶⁴ and cardiovascular events,¹¹ this dramatic increase in the number of people living with peripheral artery disease represents a major public health challenge. Interventions are urgently needed to reverse these trends both in LMIC and HIC. The numbers are likely to grow substantially in the future, especially in LMIC, where much research is required on the social and economic burden as well as strategies for optimum treatment and prevention.

Contributors

FGRF, VA, MMM, GAM, and MHC designed the study. FGRF, VA, MMM, and MHC assessed the literature. DR and JOD abstracted data and prepared databases, checked by FGRF and MHC. IR and LJW did statistical analyses. All authors interpreted results, commented on drafts

of paper, including first draft written by IR, DR, and FGRF, and approved final version.

Conflicts of interest

FGRF presented preliminary results at the World Congress of Cardiology in 2012 and had travel and accommodation costs reimbursed by Pepsico; he receives fees from AstraZeneca as co-chair of the executive committee on the EUCLID international peripheral artery disease trial. GAM was formerly employed by Pepsico. MMM has received fees as a medical editor of the Foundation for Informed Decision Making and for a consultation with Ironwood Pharmaceuticals. The other authors declare that they have no conflicts of interest.

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