Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis

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Peige Song, Diana Rudan, Yajie Zhu, Freya J I Fowkes, Kazem Rahimi, F Gerald R Fowkes, Igor Rudan

Summary

Background Peripheral artery disease is a major cardiovascular disease that affected 202 million people worldwide in 2010. In the past decade, new epidemiological data on peripheral artery disease have emerged, enabling us to provide updated estimates of the prevalence and risk factors for peripheral artery disease globally and regionally and, for the first time, nationally.

Methods For this systematic review and analysis, we did a comprehensive literature search for studies reporting on the prevalence of peripheral artery disease in the general population that were published between Jan 1, 2011, and April 30, 2019, in PubMed, MEDLINE, Embase, the Global Health database, CINAHL, the Global Health Library, the Allied and Complementary Medicine Database, and ProQuest Dissertations and Theses Global. We also included the Global Peripheral Artery Disease Study of 2013 and the China Peripheral Artery Disease Study as sources. Peripheral artery disease had to be defined as an ankle–brachial index lower than or equal to 0·90. With a purpose-built data collection form, data on study characteristics, sample characteristics, prevalence, and risk factors were abstracted from all the included studies identified from the sources. Age-specific and sex-specific prevalence of peripheral artery disease was estimated in both high-income countries (HICs) and low-income and middle-income countries (LMICs). We also did random-effects meta-analyses to pool the odds ratios of 30 risk factors for peripheral artery disease in HICs and LMICs. UN population data were used to generate the number of people affected by the disease in 2015. Finally, we derived the regional and national numbers of people with peripheral artery disease on the basis of a risk factor-based model.

Findings We included 118 articles for systematic review and analysis. The prevalence of peripheral artery disease increased consistently with age. At younger ages, prevalence was slightly higher in LMICs than HICs (4·32%, 95% CI 3·01–6·29, *vs* 3·54%, 1·17–10·24, at 40–44 years), but the increase with age was greater in HICs than LMICs, leading to a higher prevalence in HICs than LMICs at older ages (21·24%, 15·22–28·90, *vs* 12·04%, 8·67–16·60, at 80–84 years). In HICs, prevalence was slightly higher in women than in men up to age 75 years (eg, 7·81%, 3·97–14·77, *vs* 6·60%, 3·74–11·38, at 55–59 years), whereas in LMICs little difference was found between women and men (eg, 6·40%, 5·06–8·05, *vs* 6·37%, 4·74–8·49, at 55–59 years). Overall, the global prevalence of peripheral artery disease in people aged 25 years and older was 5·56%, 3·79–8·55, and the prevalence estimate was higher in HICs than that in LMICs (7·37%, 4·35–13·66, *vs* 5·09%, 3·64–7·24). Smoking, diabetes, hypertension, and hypercholesterolaemia were major risk factors for peripheral artery disease. Globally, a total of 236·62 million people aged 25 years and older were living with peripheral artery disease in 2015, among whom 72·91% were in LMICs. The Western Pacific Region had the most peripheral artery disease cases (74·08 million), whereas the Eastern Mediterranean Region had the least (14·67 million). More than two thirds of the global peripheral artery disease cases were concentrated in 15 individual countries in 2015.

Interpretation Peripheral artery disease continues to become an increasingly serious public health problem, especially in LMICs. With the demographic trend towards ageing and projected rise in important risk factors, a larger burden of peripheral artery disease is to be expected in the foreseeable future.

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Introduction

Peripheral artery disease is characterised by debilitating atherosclerotic occlusion of arteries in the lower extremities and is a major cardiovascular disease.[1,2] Peripheral artery disease can be asymptomatic or accompanied by symptoms, such as intermittent claudication, atypical leg pain, critical limb ischaemia, and occasionally acute limb ischaemia.[3–5] Regardless of the presence of symptoms, peripheral artery disease is linked to significantly increased risk of cardiovascular morbidity and mortality, representing a considerable public health concern.[6–9] Peripheral artery disease is the

Research in context

Evidence before this study

Peripheral artery disease, defined as an ankle–brachial index lower than or equal to 0·90, is a major cardiovascular disease worldwide. We searched PubMed, MEDLINE, Embase, the Global Health database, CINAHL, the Global Health Library, AMED, and ProQuest Dissertations and Theses Global to identify studies published from Jan 1, 2011, onwards that reported the prevalence of peripheral artery disease in the general population. Search terms were a combination of peripheral-artery-disease and epidemiological search terms. No language or geographic restrictions were applied. We did the search on April 30, 2019, and identified 14 719 records, of which 51 were included. Reference lists of the included studies were checked to identify studies of interest. Additional eligible studies came from our previous systematic reviews. Finally, 118 individual articles were included in this study. We previously estimated that in 2010, 202 million people had peripheral artery disease, among whom almost 70% were in low-income and middle-income countries (LMICs). However, those estimates were based on only 34 individual articles, and no national estimates have been reported.

Added value of this study

Based on an expanded dataset (118 articles from 33 individual countries), we provided updated estimates of peripheral artery disease prevalence at global and regional levels. We estimated that 236·62 million (5·56%) people aged 25 years and older had peripheral artery disease in 2015, among whom 73% were in LMICs. For the first time, we generated the national prevalence data of peripheral artery disease and found that 15 individual countries (Bangladesh, Brazil, China, France, Germany, India, Indonesia, Italy, Japan, Mexico, Pakistan, Russia, Spain, the UK, and the USA) contained more than two thirds of the global peripheral artery disease cases in 2015.

Implications of all the available evidence

This study is expected to prompt further epidemiological studies on peripheral artery disease, especially in LMICs. On the basis of our results, many governments will need to develop effective and appropriate strategies for preventing and treating peripheral artery disease, especially in countries where peripheral artery disease is a considerable public health concern.

third most common clinical manifestation of atherosclerosis after coronary artery disease and stroke.[10] Despite its implications and comorbidities, peripheral artery disease still receives relatively less research or public attention compared with the other two diseases.[10–13]

Peripheral artery disease is age related, with its prevalence increasing significantly with advancing age.[3,4,14] Given the increases in population ageing, an upward trend of peripheral artery disease prevalence is to be expected. Accurate and up-to-date epidemiological information is imperative for guiding public health policy making and updating burden of disease estimates. In 2013, the Global Peripheral Artery Disease Study[10] established the global and regional prevalence of peripheral artery disease in the general population for the first time. According to its estimates, peripheral artery disease, as defined by an ankle–brachial index (ABI; the ratio of the systolic blood pressure at the ankle to the systolic blood pressure in the arm) of 0·90 or less, affected approximately 202 million people worldwide in 2010, among whom almost 70% were residing in low-income and middle-income countries (LMICs).[10] The Global Peripheral Artery Disease Study of 2013[10] highlighted that priority needs to be given to adequate prevention, diagnosis, and control of peripheral artery disease. Thereafter, a growing body of epidemiological studies on peripheral artery disease has become available, enabling a more accurate and contemporary estimation of peripheral artery disease prevalence based on more data points.[4,15,16] Furthermore, the inclusion of more data in the assessment of risk factors for peripheral artery disease would lead to a better understanding of the disease causes and a more effective preventive strategy.[1,7]

In our study, we did an updated systematic review of population-based studies reporting peripheral artery disease prevalence in the general population. We sought to assess the prevalence of peripheral artery disease at global, regional, and national levels. The specific aims of this study were to estimate the age-specific and sex-specific prevalence of peripheral artery disease in high-income countries (HICs) and LMICs, to investigate major risk factors for peripheral artery disease in HICs and LMICs, and to establish the number of people with peripheral artery disease worldwide, in different geographical and income regions and in different countries and territories in 2015.

Methods

We did an updated systematic review and analysis in accordance with the Guidelines for Accurate and Transparent Health Estimates Reporting.[17] The review protocol was not registered in any database.

Study approach

Similar to the Global Peripheral Artery Disease Study of 2013,[10] our study approach can be classified into seven stages: identification of studies that reported peripheral artery disease prevalence in the general population using multiple sources; extraction of data on peripheral artery disease prevalence and risk factors for peripheral artery disease; modelling age-specific and sex-specific prevalence of peripheral artery disease in HICs and LMICs on the basis of the extracted prevalence data; estimation of the number of people with peripheral artery disease in HICs and LMICs in 2015 by multiplying

the age-specific and sex-specific prevalence estimates according to the corresponding demographic data derived from the UN Population Division (UNPD);[18] assessment of the associations of major risk factors with peripheral artery disease in HICs and LMICs on the basis of the extracted data on risk factors; distribution of the number of people with peripheral artery disease into different world regions using a risk factor-based model; and generation of the number of people living with peripheral artery disease in 201 countries and territories by the aforementioned risk factor-based model. The study approach is detailed in the appendix (pp 3–8).

Data sources

The articles included in the present study were collected from four types of sources. First, for the updated systematic review, we did a literature search in PubMed, MEDLINE, Embase, the Global Health database, CINAHL, the Global Health Library, the Allied and Complementary Medicine Database, and ProQuest Dissertations and Theses Global for articles and grey literature published between Jan 1, 2011, and April 30, 2019. The search strategy was a combination of terms related to peripheral artery disease and epidemiology. No language or geographical restrictions were applied. The specific search strategies for each bibliographic database and the detailed search terms for each database are presented in the appendix (pp 9–10). We did not make attempts to contact authors for further information. All non-English documents were translated into English by use of Google Translate before reviewing.

Only population-based studies that quantified prevalence estimates of peripheral artery disease in the general population were included. Studies that were hospital based or done in a sample with special characteristics (eg, patients with diabetes and people with a high risk of cardiovacular diseases) were excluded because they would not be representative of the general population. To capture the most accurate estimation of peripheral artery disease prevalence, peripheral artery disease had to be established by the presence of a lower ABI value rather than on the basis of typical symptoms or self-reporting; therefore, studies were only eligible for inclusion when defining peripheral artery disease as having an ABI of less than 0·90 or of 0·90 or less. Several publications from the same study were carefully compared and those with the largest sample size or contributing the most comprehensive results were included for further analysis. For the purpose of evaluating risk factors for peripheral artery disease, odds ratios (ORs) in the included studies had to be based on a multivariable analysis.

The second source was the Global Peripheral Artery Disease Study of 2013;[10] all the 34 included articles in the study were retained.

The third source was the China Peripheral Artery Disease Study;[19] we incorporated all the 37 included articles in the study.

Lastly, we did an additional search in which we identified studies of interest by screening the reference lists of included studies and related systematic reviews.

Data extraction

With a purpose-built data collection form, data on study characteristics, sample characteristics, prevalence, and risk factors were abstracted from all the included studies identified from the aforementioned four sources. When available, stratified prevalence data by age group and sex were extracted within the same study. For studies that were done in more than one geographical location (eg, prevalence estimates of peripheral artery disease in different countries reported in a single study), we extracted the data for each location separately (if available). In case of censoring age groups (eg, people older than 80 years), we imputed the missing age band

See Online for appendix

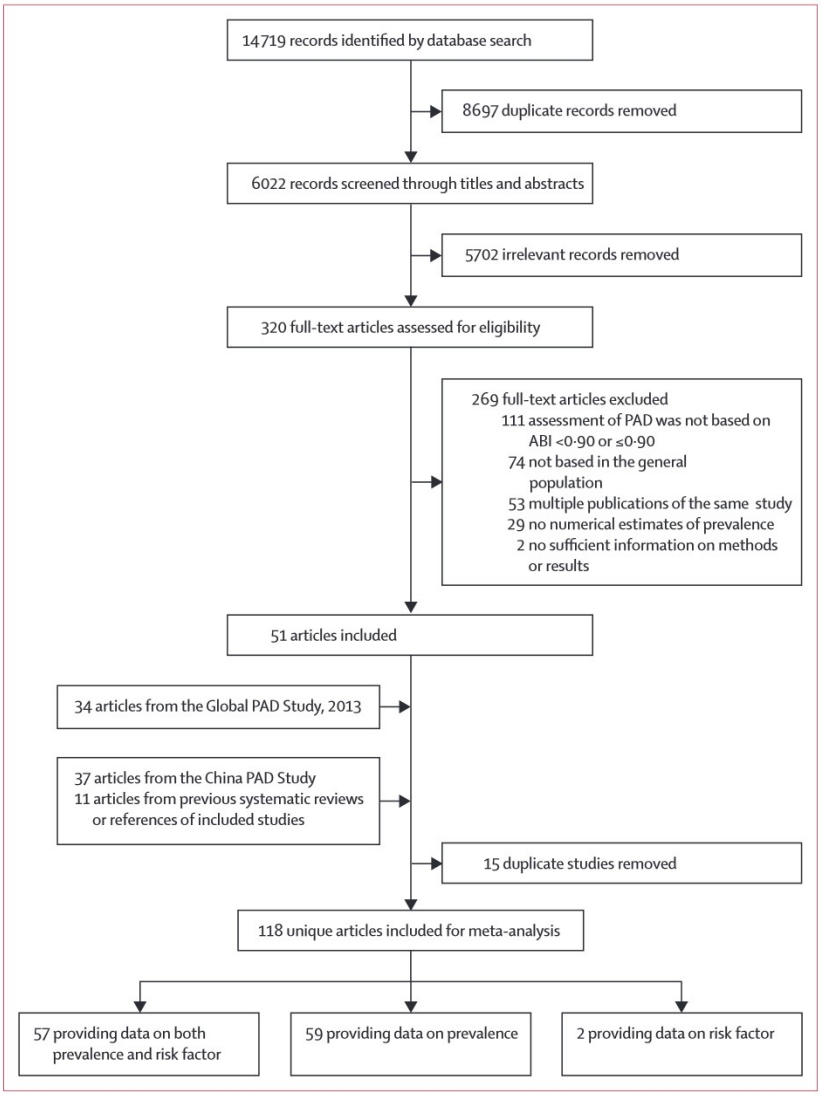

Figure 1: **Study selection**
ABI=ankle–brachial index. PAD=peripheral artery disease.

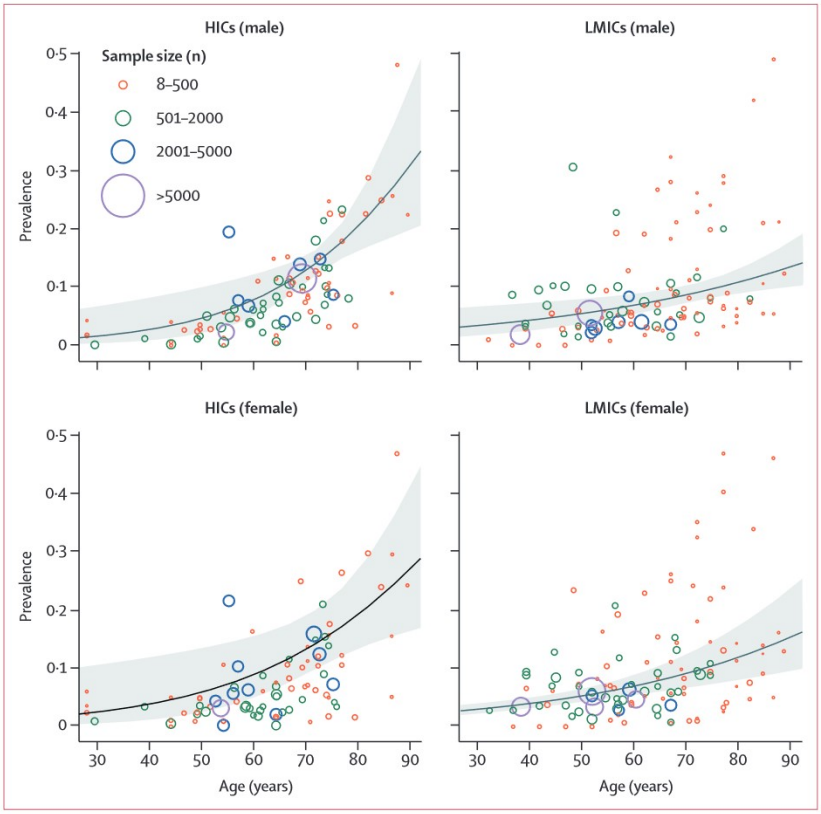

Figure 2: **Prevalence of peripheral artery disease in high-income countries and low-income and middle-income countries, by age and sex group**
The size of the bubble is proportional to the number of individuals in the sample. In LMICs, the regression lines for men and women in younger (<35 years) and older (>85 years) age groups are based on few data points or projections only. HICs=high-income countries. LMICs=low-income and middle-income countries.

by taking the same width as reported in other age groups in the same study. To enable the inclusion of zero prevalent cases as reported in some specific subgroups, a value of 0·0005 was adopted to replace zero cells. The systematic review was done by PS, DR, and FJIF and data extraction by PS and DR independently, and all discrepancies in study selection and data extraction were resolved by consensus.

Modelling age-specific and sex-specific prevalence of peripheral artery disease

To best describe and fit the hierarchical data structure (ie, several data points from the same study), a multilevel mixed-effects logistic regression was modelled to establish the relation between age and peripheral artery disease prevalence.[10,20,21] This modelling was done for men and women in HICs and LMICs. Among all the included studies from HICs, many studies were done in the USA. A similar phenomenon was found for China among studies from LMICs. Therefore, we controlled the effect of studies from the same study country by adding the study country identification number as the random effect.[21] Age was fitted as a fixed effect given that it was the covariate of interest (appendix, pp 5–6).

Estimation of the global number of peripheral artery disease cases in 2015

The number of people with peripheral artery disease in HICs (the HIC envelope) and LMICs (the LMIC envelope) were generated by multiplying the age-specific and sex-specific prevalence of peripheral artery disease derived by corresponding population data obtained from the UNPD.[18] This estimation was done for the year 2015 and in people older than 25 years, by every 5-year age group. The global number of peripheral artery disease cases was then calculated by adding the cases in HICs and LMICs together.

Meta-analysis of risk factors for peripheral artery disease

Because of the intrinsic heterogeneity between epidemiological studies, we chose a random-effects (DerSimonian Laird method) meta-analysis a priori to explore the effects of major risk factors for peripheral artery disease.[22] As a rule, we analysed only risk factors that shared similar definitions and had been investigated in at least three individual studies on the basis of a multivariable analysis. When available, the effects of suspected risk factors in HICs and LMICs were separately evaluated to assess whether a difference existed in the role of risk factors in these two contexts. The detailed process of meta-analysis is provided in the appendix (pp 6–7).

Estimation of the regional number of peripheral artery disease cases in 2015

To address both the features of geography (as designated by WHO) and income (as designated by the World Bank), we classified the world into ten different regions (the so-called WHO–World Bank regions across this study). The global number of people with peripheral artery disease in 2015 was distributed into different regions using a risk factor-based model. This model was initially proposed by the Child Health Epidemiology Reference Group and has been widely adopted in global burden of disease studies.[10,19,23] In brief, the HIC envelope and LMIC envelope were split by taking into account the regional prevalence of major risk factors and their meta-ORs. In line with the Global Peripheral Artery Disease Study of 2013, four major risk factors, including current smoking, hypertension, diabetes, and hypercholesterolaemia were selected for the risk factor-based model. The prevalence of current smoking (in 2015) was obtained from the WHO report on the global tobacco epidemic,[24,25] and those of hypertension (in 2015), diabetes (in 2014), and hypercholesterolaemia (in 2008) from the WHO Global Health Observatory data repository (appendix, pp 7–8).[26,27]

Estimation of the national number of peripheral artery disease cases in 2015

Using the same risk factor-based model approach as in the regional estimation of affected people, we estimated

the number of peripheral artery disease cases in 201 countries and territories in 2015. All analyses were done with STATA version 14.0 and R version 3.3.0.

Role of the funding source

There was no funding source for this study. 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

In the updated literature search, we identified a total of 14719 records from bibliographic databases. After removal of duplicates and an initial screening of titles and abstracts, 320 articles were assessed in full text, of which 51 met the inclusion criteria. We additionally included 34 articles from the Global Peripheral Artery Disease Study of 2013, 37 from the China Peripheral Artery Disease Study, and 11 from previous systematic reviews and reference screening. Finally, 118 individual articles covering 33 countries were included, among which 57 articles provided information on both peripheral artery disease prevalence and risk factors for peripheral artery disease, 59 contributed data only on peripheral artery disease prevalence, and two explored only the potential risk factors for peripheral artery disease. The study selection process is summarised in figure 1 and a full list of the included studies is shown in the appendix (pp 12–18).

Among the 118 articles included for analysis, 61 were from HICs (Australia, China, Denmark, Germany, Greece, Italy, Japan, the Netherlands, Poland, Saudi Arabia, Singapore, South Korea, Spain, Sweden, the UK, and the USA) and 57 from LMICs (Central African Republic, Ethiopia, Republic of Congo, Senegal, South Africa, Tanzania, Brazil, Colombia, Ecuador, Grenada, Mexico, India, Sri Lanka, Thailand, Turkey, China, and Benin). The geographical locations and detailed characteristics of every included article are shown in the appendix (pp 19–40).

The relationship between age and peripheral artery disease prevalence was constructed on the basis of a substantial number of data points (410 in total). The age ranges covered by informative data points were not consistent in HICs and LMICs, but the majority of estimates were between age 40 years to 80 years (figure 2). We also provide the age-specific and sex-specific prevalence of peripheral artery disease in HICs and LMICs (figure 2, table 1). Generally, the prevalence of peripheral artery disease increased with increasing age. This increasing trend was similar between sexes, but more pronounced in HICs than in LMICs. In HICs, the prevalence of peripheral artery disease was lower in men than in women up until age 75 years, at which point it became greater than in women. However, in LMICs, little differences were found between women and men. After being adjusted by the demographic profile in 2015, the prevalence of peripheral artery disease in people aged 25 years and older

	Prevalence of peripheral artery disease in men			Prevalence of peripheral artery disease in women			Overall prevalence of peripheral artery disease		
	HICs	LMICs	Worldwide	HICs	LMICs	Worldwide	HICs	LMICs	Worldwide
25–29 years	1·30 (0·26–6·24)	3·10 (1·47–6·41)	2·85 (1·31–6·38)	2·16 (0·43–10·17)	2·72 (1·98–3·73)	2·65 (1·77–4·59)	1·72 (0·34–8·13)	2·91 (1·72–5·10)	2·75 (1·54–5·51)
30–34 years	1·72 (0·41–6·90)	3·50 (1·80–6·70)	3·22 (1·58–6·73)	2·69 (0·63–10·78)	3·15 (2·38–4·14)	3·08 (2·12–5·15)	2·19 (0·52–8·78)	3·32 (2·09–5·44)	3·15 (1·85–5·95)
35–39 years	2·26 (0·64–7·63)	3·95 (2·20–7·00)	3·66 (1·93–7·11)	3·34 (0·92–11·43)	3·63 (2·84–4·63)	3·58 (2·52–5·77)	2·79 (0·78–9·47)	3·79 (2·52–5·83)	3·62 (2·22–6·45)
40–44 years	2·97 (1·00–8·43)	4·46 (2·68–7·33)	4·19 (2·37–7·53)	4·15 (1·34–12·13)	4·19 (3·35–5·22)	4·18 (3·00–6·45)	3·54 (1·17–10·24)	4·32 (3·01–6·29)	4·18 (2·68–6·99)
45–49 years	3·88 (1·56–9·32)	5·02 (3·25–7·68)	4·80 (2·93–7·99)	5·13 (1·94–12·90)	4·83 (3·91–5·96)	4·89 (3·54–7·26)	4·50 (1·75–11·08)	4·93 (3·58–6·82)	4·85 (3·23–7·63)
50–54 years	5·07 (2·43–10·29)	5·66 (3·94–8·06)	5·53 (3·62–8·54)	6·34 (2·79–13·77)	5·56 (4·48–6·89)	5·73 (4·12–8·33)	5·70 (2·61–12·02)	5·61 (4·21–7·47)	5·63 (3·87–8·44)
55–59 years	6·60 (3·74–11·38)	6·37 (4·74–8·49)	6·42 (4·51–9·17)	7·81 (3·97–14·77)	6·40 (5·06–8·05)	6·73 (4·81–9·62)	7·21 (3·86–13·09)	6·38 (4·91–8·27)	6·57 (4·66–9·39)
60–64 years	8·55 (5·70–12·62)	7·16 (5·66–9·01)	7·49 (5·67–9·88)	9·58 (5·56–15·99)	7·35 (5·66–9·49)	7·89 (5·64–11·07)	9·08 (5·63–14·35)	7·26 (5·66–9·25)	7·70 (5·66–10·49)
65–69 years	11·00 (8·50–14·11)	8·04 (6·66–9·67)	8·91 (7·20–10·97)	11·70 (7·58–17·61)	8·43 (6·28–11·23)	9·39 (6·66–13·10)	11·36 (8·02–15·94)	8·24 (6·46–10·48)	9·16 (6·92–12·08)
70–74 years	14·04 (12·01–16·36)	9·02 (7·63–10·62)	10·58 (8·99–12·41)	14·21 (9·90–20·00)	9·65 (6·93–13·29)	11·09 (7·87–15·41)	14·14 (10·87–18·32)	9·36 (7·26–12·05)	10·85 (8·39–14·01)
75–79 years	17·77 (14·93–21·01)	10·10 (8·47–12·01)	12·68 (10·64–15·04)	17·17 (12·15–23·69)	11·03 (7·61–15·72)	13·11 (9·15–18·43)	17·43 (13·37–22·51)	10·62 (7·99–14·08)	12·92 (9·81–16·93)
80–84 years	22·22 (16·94–28·58)	11·30 (9·14–13·90)	15·52 (12·16–19·57)	20·59 (14·06–29·12)	12·58 (8·34–18·54)	15·81 (10·65–22·81)	21·24 (15·22–28·90)	12·04 (8·67–16·60)	15·69 (11·27–21·48)
85–89 years	27·42 (18·75–38·22)	12·62 (9·71–16·25)	19·29 (13·78–26·14)	24·48 (15·61–36·24)	14·31 (9·11–21·76)	19·28 (12·29–28·84)	25·52 (16·71–36·93)	13·66 (9·34–19·63)	19·28 (12·84–27·84)
≥90 years	34·48 (20·90–51·05)	14·38 (10·33–19·68)	24·61 (15·71–35·65)	30·06 (17·24–46·91)	16·73 (10·14–26·33)	24·65 (14·36–38·55)	31·25 (18·23–48·03)	15·93 (10·21–24·05)	24·64 (14·77–37·68)
Total (>25 years)	6·50 (4·14–11·42)	5·07 (3·38–7·78)	5·36 (3·54–8·51)	8·21 (4·55–15·82)	5·12 (3·90–6·70)	5·75 (4·03–8·58)	7·37 (4·35–13·66)	5·09 (3·64–7·24)	5·56 (3·79–8·55)

Data are % (95% CI). Prevalence estimates in age groups 25–29 years, 30–34 years, 85–89 years, and ≥90 years are estimated predictions, in which original data points are relatively few. The overall prevalence in people older than 25 years was adjusted by the demographic structure in 2015. HICs=high-income countries. LMICs=low-income and middle-income countries.

Table 1: **Estimated prevalence of peripheral artery disease in high-income countries and in low-income and middle-income countries, by age and sex group**

	Men with peripheral artery disease in 2015 (millions)			Women with peripheral artery disease in 2015 (millions)			Overall number of people with peripheral artery disease in 2015 (millions)		
	HICs	LMICs	Worldwide	HICs	LMICs	Worldwide	HICs	LMICs	Worldwide
25–29 years	0·56 (0·11–2·67)	8·37 (3·98–17·29)	8·93 (4·09–19·97)	0·86 (0·17–4·05)	7·07 (5·14–9·70)	7·93 (5·31–13·75)	1·42 (0·28–6·73)	15·44 (9·12–26·99)	16·86 (9·40–33·72)
30–34 years	0·76 (0·18–3·04)	8·29 (4·26–15·86)	9·05 (4·45–18·90)	1·11 (0·26–4·44)	7·27 (5·50–9·58)	8·38 (5·76–14·02)	1·86 (0·44–7·48)	15·56 (9·77–25·44)	17·43 (10·21–32·92)
35–39 years	0·99 (0·28–3·35)	8·28 (4·61–14·68)	9·28 (4·89–18·04)	1·39 (0·38–4·74)	7·47 (5·84–9·53)	8·86 (6·22–14·27)	2·38 (0·66–8·10)	15·75 (10·45–24·21)	18·13 (11·11–32·31)
40–44 years	1·32 (0·45–3·77)	8·97 (5·39–14·75)	10·30 (5·84–18·52)	1·76 (0·57–5·16)	8·28 (6·63–10·32)	10·05 (7·20–15·48)	3·09 (1·02–8·93)	17·25 (12·02–25·08)	20·34 (13·04–34·00)
45–49 years	1·71 (0·69–4·10)	9·30 (6·02–14·22)	11·01 (6·71–18·32)	2·18 (0·82–5·48)	8·90 (7·20–10·99)	11·08 (8·02–16·46)	3·89 (1·51–9·57)	18·20 (13·22–25·20)	22·09 (14·73–34·78)
50–54 years	2·19 (1·05–4·43)	8·97 (6·25–12·78)	11·15 (7·29–17·22)	2·68 (1·18–5·83)	8·86 (7·13–10·97)	11·54 (8·31–16·80)	4·87 (2·23–10·26)	17·83 (13·38–23·75)	22·70 (15·60–34·02)
55–59 years	2·60 (1·48–4·49)	8·20 (6·11–10·94)	10·80 (7·59–15·43)	3·12 (1·59–5·91)	8·44 (6·68–10·63)	11·57 (8·27–16·54)	5·72 (3·06–10·39)	16·65 (12·79–21·57)	22·37 (15·86–31·96)
60–64 years	2·96 (1·97–4·36)	7·80 (6·17–9·81)	10·75 (8·14–14·18)	3·50 (2·03–5·84)	8·38 (6·46–10·82)	11·88 (8·49–16·66)	6·46 (4·01–10·21)	16·18 (12·63–20·63)	22·63 (16·63–30·84)
65–69 years	3·33 (2·58–4·28)	5·87 (4·87–7·07)	9·21 (7·44–11·34)	3·88 (2·52–5·85)	6·74 (5·02–8·97)	10·62 (7·54–14·82)	7·22 (5·10–10·12)	12·61 (9·89–16·04)	19·83 (14·98–26·16)
70–74 years	3·13 (2·67–3·64)	4·45 (3·77–5·25)	7·58 (6·44–8·89)	3·69 (2·57–5·19)	5·43 (3·90–7·48)	9·13 (6·47–12·68)	6·82 (5·24–8·84)	9·89 (7·67–12·73)	16·70 (12·91–21·56)
75–79 years	3·05 (2·57–3·61)	3·42 (2·87–4·07)	6·47 (5·43–7·68)	3·76 (2·66–5·18)	4·70 (3·24–6·70)	8·46 (5·90–11·88)	6·81 (5·22–8·79)	8·12 (6·11–10·77)	14·93 (11·33–19·56)
80–84 years	2·54 (1·94–3·27)	2·05 (1·66–2·52)	4·59 (3·60–5·79)	3·51 (2·40–4·97)	3·17 (2·10–4·67)	6·68 (4·50–9·64)	6·05 (4·34–8·24)	5·22 (3·76–7·19)	11·27 (8·09–15·43)
85–89 years	1·71 (1·17–2·38)	0·96 (0·74–1·23)	2·66 (1·90–3·61)	2·81 (1·79–4·16)	1·72 (1·09–2·61)	4·53 (2·88–6·77)	4·52 (2·96–6·54)	2·68 (1·83–3·85)	7·19 (4·79–10·38)
≥90 years	0·89 (0·54–1·32)	0·36 (0·26–0·49)	1·25 (0·80–1·81)	2·10 (1·20–3·28)	0·80 (0·48–1·26)	2·90 (1·69–4·53)	2·99 (1·74–4·59)	1·16 (0·74–1·75)	4·15 (2·48–6·34)
Total (>25 years)	27·73 (17·67–48·71)	85·30 (56·94–130·98)	113·03 (74·61–179·68)	36·36 (20·15–70·08)	87·23 (66·43–114·22)	123·59 (86·58–184·30)	64·09 (37·81–118·78)	172·53 (123·37–245·20)	236·62 (161·19–363·98)

Data are n (95% CI). HICs=high-income countries. LMICs=low-income and middle-income countries.

Table 2: **Estimated number of people with peripheral artery disease in high-income countries and in low-income and middle-income countries in 2015, by age and sex group**

was 5·56% (95% CI 3·79–8·55) worldwide, and the prevalence estimate was higher in HICs than LMICs (7·37%, 4·35–13·66 *vs* 5·09%, 3·64–7·24), although the prevalence was higher in LMICs than in HICs in younger men (<55 years) and women (<45 years; figure 2, table 1).

A total of 236·62 million (95% CI 161·19–363·98) people aged 25 years and older were living with peripheral artery disease worldwide in 2015, among whom 72·91% were in LMICs (table 2). The age groups that contributed the largest share of cases were aged 65–69 years in HICs and aged 45–49 years in LMICs, implying a relatively younger demographic structure in LMICs than in HICs. Worldwide, 52·23% of people with peripheral artery disease were women.

After clustering all reported risk factors for peripheral artery disease by their definitions, we found that 30 individual factors were investigated in at least three studies and therefore included in the meta-analysis. Those 30 factors were further grouped into 13 broad categories according to their causal pathways. Apart from age, other risk factors for peripheral artery disease in both HICs and LMICs included smoking (former, current, and having ever smoked), hypertension, diabetes, and a history of concomitant cardiovascular diseases (table 3). We estimated the number of people with peripheral artery disease in each WHO–World Bank region by taking into account the different exposures to four major risk factors for peripheral artery disease (current smoking, hypertension, diabetes, and hypercholesterolaemia) based on a risk factor-based model (figure 3; appendix, pp 71–73). In 2015, the Western Pacific region (WPR) had the largest share of global peripheral artery disease cases (74·08 million, 95% CI 51·84–109·30), whereas the Eastern Mediterranean Region (EMR) had the least (14·67 million, 10·04–22·48). The prevalence of peripheral artery disease was highest in the European Region (7·99%, 5·10–13·41) and lowest in the African Region (4·06%, 2·90–5·91). The age group that contributed the most peripheral artery disease cases was that aged 55–64 years in the Region of the Americas, 65–74 years in the European Region, and 45–54 years in the South-East Asia Region and WPR (figure 3). In the African Region and EMR, however, the most peripheral artery disease cases were noted in people

aged 25–34 years. We estimated the national prevalence of peripheral artery disease and the number of affected people for 201 countries and territories (appendix, pp 80–84). The 15 countries with the highest number of people with peripheral artery disease accounted for 160·90 million, or more than two thirds (68%) of the estimated 236·62 million global peripheral artery disease cases. China, India, and the USA had the largest numbers of cases (figure 3).

Discussion

This systematic review and modelling analysis, based on a total of 118 articles covering 33 individual countries, provides the most up-to-date and comprehensive overview of the prevalence and number of people with peripheral artery disease at global, regional, and national levels. In 2015, the global prevalence of peripheral artery disease in individuals aged 25 years and older was 5·56% (95% CI 3·79–8·55), equivalent to 236·62 million (161·19–363·98) people with peripheral artery disease worldwide. Advanced age, smoking, hypertension, diabetes, and concomitant cardiovascular diseases were confirmed to be associated with a higher risk of peripheral artery disease in both HICs and LMICs. Substantial variations were highlighted in the distribution of peripheral artery disease cases across regions, where LMICs contributed almost 73% of the global cases. Among all the WHO regions, the share of peripheral artery disease cases was the largest in WPR (74·08 million, 95% CI 51·84–109·30), whereas the smallest was in EMR (14·67 million, 10·04–22·48) in 2015. More than two thirds of the global peripheral artery disease cases were concentrated in 15 individual countries.

The search strategies in this study were designed to obtain as much population-based data on peripheral artery disease prevalence as possible, while ensuring the quality and comparability of the results. During the selection process, we limited the inclusion of studies to those that confirmed the presence of peripheral artery disease with an ABI value of less than 0·90 or 0·90 or less. This is of both clinical and public health importance, because even patients with asymptomatic peripheral artery disease have an elevated risk of cardiovascular morbidity and mortality.[6,11] As such, the estimation of peripheral artery disease prevalence and cases presented in our study serves to inform stakeholders of the magnitude of this public health problem. The 236·62 million peripheral artery disease cases in 2015 as revealed in this study represent a relative increase of 17·10% from 202·06 million in 2010. However, this increase did not occur evenly in HICs and LMICs, where the increasing prevalence were higher in LMICs than in HICs across those 5 years (22·56% *vs* 4·48%). This disparity of increasing prevalence rates between HICs and LMICs has been observed in the Global Peripheral Artery Disease Study of 2013, and collectively resulted in an increased proportion of LMICs cases among all the

	Number of studies	Sample size	OR (95% CI)	HICs *vs* LMICs
Risk factor 1: age (per 10-year increase)				
Worldwide	26	117 428	1·55 (1·38–1·75)	..
HICs	17	32 609	1·65 (1·37–1·97)	Ref
LMICs	9	84 819	1·28 (1·17–1·41)	0·86 (0·62–1·19)
Risk factor 2: male sex				
Worldwide	29	119 743	0·74 (0·61–0·91)	..
HICs	12	16 897	0·94 (0·67–1·32)	Ref
LMICs	17	102 846	0·65 (0·51–0·83)	0·69 (0·43–1·11)
Risk factor 3: smoking				
Former smoker				
Worldwide	17	70 222	1·70 (1·39–2·09)	..
HICs	11	31 009	1·94 (1·62–2·32)	Ref
LMICs	6	39 213	1·36 (1·01–1·83)	0·68 (0·48–0·99)
Current smoker				
Worldwide	28	136 424	2·82 (2·00–3·98)	..
HICs	16	53 559	3·43 (2·58–4·58)	Ref
LMICs	12	82 865	2·15 (1·55–2·97)	0·62 (0·40–0·95)
Former smoker				
Worldwide	15	35 742	1·88 (1·39–2·54)	..
HICs	7	18 275	1·95 (1·33–2·85)	Ref
LMICs	8	17 467	1·83 (1·18–2·83)	0·92 (0·47–1·82)
Per ten pack-year increase of smoking in HICs	3	6440	1·33 (1·24–1·44)	..
Risk factor 4: current alcohol drinker				
Worldwide	7	37 857	0·84 (0·67–1·05)	..
HICs	1	2831	0·53 (0·31–0·90)	Ref
LMICs	6	35 026	0·89 (0·72–1·11)	1·69 (0·64–4·48)
Risk factor 5: hypertension				
Hypertension				
Worldwide	34	127 522	1·67 (1·50–1·86)	..
HICs	17	49 018	1·59 (1·46–1·74)	Ref
LMICs	17	78 504	1·76 (1·42–2·19)	1·05 (0·79–1·41)
SBP (per 10 mm Hg increase)				
Worldwide	9	28 709	1·15 (0·95–1·39)	..
HICs	4	8513	1·31 (1·20–1·42)	Ref
LMICs	5	20 196	1·07 (0·78–1·48)	0·85 (0·54–1·33)
DBP (per 10 mm Hg increase)				
Worldwide	3	10 917	1·19 (0·68–2·10)	..
HICs	1	1036	0·78 (0·61–0·99)	Ref
LMICs	2	9881	1·52 (0·79–2·95)	1·96 (0–2252·01)
Risk factor 6: diabetes				
Worldwide	40	167 096	1·89 (1·68–2·13)	..
HICs	19	48 873	1·98 (1·77–2·22)	Ref
LMICs	21	118 223	1·82 (1·49–2·23)	0·87 (0·64–1·18)
Risk factor 7: dyslipidaemia				
Dyslipidaemia				
Worldwide	7	68 645	1·51 (1·02–2·24)	..
HICs	1	1502	2·57 (0·95–6·97)	Ref
LMICs	6	67 143	1·44 (0·95–2·17)	0·56 (0·09–3·41)

(Table 3 continues on next page)

	Number of studies	Sample size	OR (95% CI)	HICs vs LMICs
(Continued from previous page)				
Hypercholesterolaemia				
Worldwide	16	63225	1·34 (1·17–1·53)	..
HICs	10	32221	1·43 (1·18–1·74)	Ref
LMICs	6	31004	1·20 (0·88–1·63)	0·85 (0·59–1·24)
Low HDL				
Worldwide	8	37342	1·67 (1·19–2·36)	..
HICs	3	16119	1·84 (0·98–3·44)	Ref
LMICs	5	21223	1·60 (1·01–2·56)	0·88 (0·32–2·43)
High LDL				
Worldwide	5	33235	1·78 (1·41–2·25)	..
HICs	2	15173	1·56 (0·79–3·10)	Ref
LMICs	3	18062	1·93 (1·57–2·38)	1·34 (0·54–3·35)
High triglycerides				
Worldwide	8	34409	1·41 (1·16–1·72)	..
HICs	4	23429	1·48 (1·17–1·87)	Ref
LMICs	4	10980	1·31 (0·89–1·91)	0·89 (0·50–1·57)
Risk factor 8: cardiovascular diseases				
Cardiovascular diseases				
Worldwide	11	39837	2·31 (1·89–2·83)	..
HICs	7	19036	2·41 (1·98–2·92)	Ref
LMICs	4	20801	2·45 (1·40–4·29)	0·85 (0·53–1·35)
Coronary heart disease				
Worldwide	13	77239	1·72 (1·48–1·99)	..
HICs	9	13675	2·18 (1·65–2·86)	Ref
LMICs	4	63564	1·56 (1·31–1·86)	0·72 (0·50–1·03)
Stroke				
Worldwide	6	28790	2·35 (1·74–3·16)	..
HICs	4	6650	2·78 (1·48–5·22)	Ref
LMICs	2	22140	2·23 (1·59–3·14)	0·80 (0·29–2·22)
Risk factor 9: obesity				
Overweight (BMI 25–30 kg/m^2)				
Worldwide	6	20099	0·96 (0·82–1·13)	..
HICs	2	4731	0·92 (0·61–1·37)	Ref
LMICs	4	15368	0·96 (0·80–1·17)	1·03 (0·59–1·79)
Obesity (BMI ≥30 kg/m^2)				
Worldwide	9	36474	1·55 (1·23–1·96)	..
HICs	2	4731	1·07 (0·64–1·79)	Ref
LMICs	7	31743	1·76 (1·42–2·18)	1·53 (0·93–2·51)
BMI (per 1 kg/m^2 increase)				
Worldwide	13	24475	0·92 (0·87–0·97)	..
HICs	8	10600	0·92 (0·86–0·99)	Ref
LMICs	5	13875	0·92 (0·84–1·00)	1·00 (0·88–1·14)
Waist circumference (per 1 cm increase)				
Worldwide	3	24101	1·03 (1·00–1·06)	..
HICs	1	1502	1·07 (1·03–1·12)	Ref
LMICs	2	22599	1·01 (1·00–1·03)	0·95 (0·68–1·32)
Risk factor 10: renal impairment				
HICs only	5	9661	1·79 (1·03–3·12)	..

(Table 3 continues on next page)

peripheral artery disease cases worldwide in 2015 compared with 2010 (73% *vs* 69%).[10] The age-specific and sex-specific prevalence of peripheral artery disease in the Global Peripheral Artery Disease Study of 2013 and in this present study differed slightly. Given that our age-specific and sex-specific prevalence modelling and risk-factor assessment were based on more informative data points than in the previous study, the precision of our estimation has been improved.

Several limitations of our study should also be acknowledged. First, although we collected more than 347 (90%) of 410 data points for constructing the age-specific and sex-specific prevalence in HICs and LMICs from 2005 onwards, the accuracy of our models in reflecting the situation in 2015 is still questionable because the time trends of peripheral artery disease prevalence and its influencing factors were not fully understood. Second, the estimation of regional and national peripheral artery disease cases is likely to be biased given that it was driven by the demographic structure (age and sex) in every region and a risk factor-based model that only included four major risk factors (current smoking, hypertension, diabetes, and hypercholesterolaemia) for peripheral artery disease, and other explanatory variables were not accounted for. Moreover, the regional distribution of peripheral artery disease prevalence might also be a result of the different mean ABIs across ethnic groups.[28,29] Although this ethnic variation deserves further exploration, we could not do such an analysis because of the absence of relevant data from included studies. Third, because of the scarcity of the data, the regional and national prevalence of hypercholesterolaemia adopted in our risk factor-based model was based on a WHO estimation for the year 2008. Although the relative magnitudes of hypercholesterolaemia prevalence across regions and countries have probably not changed substantially within a decade, this data source still represented a considerable time lag, which needs to be improved in further study.

We found that the prevalence of peripheral artery disease was relatively higher in LMICs than in HICs in young people, but became lower from the age of 50 years, which might be related to a relatively lower life expectancy in LMICs than in HICs.[18] In line with previous epidemiological evidence from the Global Peripheral Artery Disease Study of 2013, the prevalence of peripheral artery disease was age related in both sexes and across regions.[10,19]

The positive relation between increasing age and the development of peripheral artery disease was also supported in our separate meta-analysis of risk factors for peripheral artery disease. In our risk factor estimation, women in LMICs were at a statistically higher risk of peripheral artery disease than men in LMICs, which was concordant with the results in the Global Peripheral Artery Disease Study of 2013.[10] Given that the prevalence of three major risk factors,

comprising current smoking, hypertension, and diabetes, were all higher in men in LMICs than in women in LMICs, this paradoxical female preponderance of peripheral artery disease might be inherent to the disease mechanism or a combined effect of other potential risk factors in LMICs settings, such as obesity and socioeconomic inequality.[26,27,30–32] A striking new finding in the present study is that the prevalence of peripheral artery disease in HICs did not statistically differ between men and women, as revealed by our meta-analysis of sex as a risk factor for peripheral artery disease in HICs settings. In the research field of peripheral artery disease, this epidemiological phenomenon has already attracted attention and experts have made calls for more attention on peripheral artery disease in women.[33–36]

Another key feature of our study is that the effects of 30 individual risk factors were investigated by meta-analysis. We only included studies that reported ORs based on a multivariable analysis to avoid suspected bias inherent to univariable analysis. On the basis of a substantial amount of existing data on risk factors for peripheral artery disease, our study showed an improved assessment of potential risk factors for peripheral artery disease, which has noteworthy clinical implications. In agreement with the Global Peripheral Artery Disease Study of 2013[10] and common clinical knowledge, smoking was again shown to be a strong risk factor for peripheral artery disease, irrespective of the status of smoking (current, former, or having ever smoked).[2,3,10] The benefits of smoking cessation in reducing the risk of peripheral artery disease have also been supported in our results, given that a lower OR was observed for former smoking than for current smoking. Another two risk factors for peripheral artery disease that have already been shown in the Global Peripheral Artery Disease Study of 2013[10] were diabetes and hypertension, implying the importance of proper control of blood sugar and blood pressure.[1–3] In the Global Peripheral Artery Disease Study of 2013,[10] a positive association between hypercholesterolaemia and peripheral artery disease was found in both HICs and LMICs settings, which, however, was not observed in LMICs in the present study. A possible reason for this result might be the relative lower total cholesterol concentrations in people living in LMICs than in those living in HICs, which might result in insufficient power for the synthesised estimation of hypercholesterolaemia as a risk factor in LMICs.[10,37] With an increasing trend of mean total cholesterol in both men and women in LMICs, the cumulative effect of elevated total cholesterol might be witnessed in the future and needs further confirmation with new data coming in.[37] Importantly, this finding does not indicate that lipid control is not necessary for peripheral artery disease management in LMICs given that the benefits of lipid-lowering treatment have long been established.[2,3]

	Number of studies	Sample size	OR (95% CI)	HICs *vs* LMICs
(Continued from previous page)				
eGFR (ten-unit increase)				
Worldwide	3	3001	0·90 (0·84–0·96)	..
HICs	2	1509	0·90 (0·84–0·96)	Ref
LMICs	1	1492	0·90 (0·78–1·04)	1·00 (0·35–2·87)
Risk factor 11: pulse pressure (per 1 mm Hg increase)				
Worldwide	5	5647	1·02 (0·98–1·06)	..
HICs	4	4601	1·03 (1·02–1·05)	Ref
LMICs	1	1046	0·96 (0·95–0·98)	0·93 (0·91–0·96)
Risk factor 12: inflammation				
HS-CRP 1·0–3·0 mg/L				
Worldwide	3	5536	1·89 (1·31–2·72)	..
HICs	2	4893	1·80 (1·17–2·76)	Ref
LMICs	1	643	2·16 (1·08–4·33)	1·20 (0·01–239·26)
HS-CRP >3·0 mg/L				
Worldwide	4	23 914	2·16 (1·48–3·14)	..
HICs	3	23 271	2·20 (1·44–3·36)	Ref
LMICs	1	643	2·01 (0·91–4·44)	0·91 (0·13–6·57)
HS-CRP (per mg/L increase) in HICs	5	6103	1·00 (0·94–1·06)	..
Risk factor 13: hyperfibrinogenaemia in HICs	3	15 957	1·83 (1·43–2·35)	..

Hyperfibrinogenaemia referred to an elevated concentration of fibrinogen (>400 mg/dL or ≥338 mg/dL). The definitions of some risk factors varied slightly across studies. ORs for binary variable risk factors indicated risk of peripheral artery disease compared with those without the risk factor, except for former smokers (*vs* those who have never smoked), current smokers (*vs* those who have never smoked), current alcohol drinkers (*vs* those who have never drunk), individuals who were overweight (*vs* those with BMI <25 kg/m²), individuals who were obese (*vs* BMI <25 kg/m²), and those with HS-CRP of 1·0–3·0 mg/L (*vs* HS-CRP <1·0 mg/L) and HS-CRP higher than 3·0 mg/L (*vs* HS-CRP <1·0 mg/L). OR=odds ratio. HICs=high-income countries. LMICs=low-income and middle-income countries. SBP=systolic blood pressure. DBP=diastolic blood pressure. BMI=body-mass index. eGFR=estimated glomerular filtration rate. HS-CRP=high-sensitivity C-reactive protein.

Table 3: **Synthesised effect size of 13 groups of risk factors for peripheral artery disease that were investigated in at least three studies using multivariable analysis**

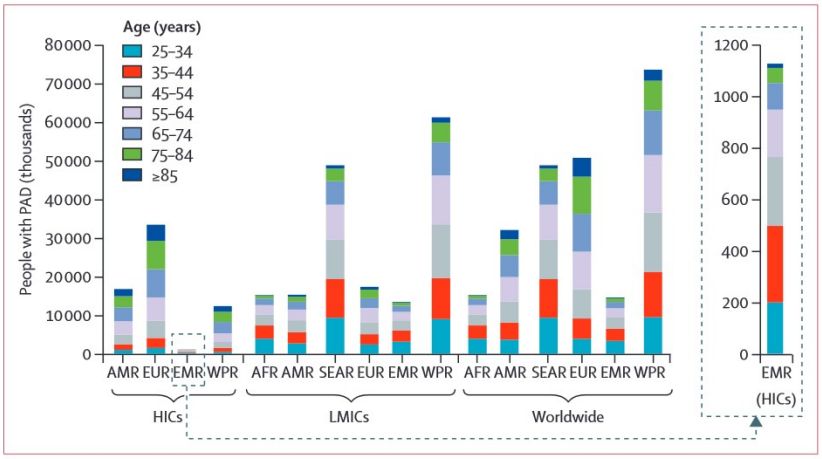

Figure 3: **Regional number of people with PAD and contributing age groups in 2015**
People with peripheral artery disease were restricted to those older than 25 years given the study context. AFR=African Region. AMR=Region of the Americas. EMR=Eastern Mediterranean Region. EUR=European Region. HICs=high-income countries. LMICs=Low-income and middle-income countries. PAD=peripheral artery disease. SEAR=South-East Asia Region. WPR=Western Pacific Region.

In this study, WPR was revealed to be the region with the largest share of peripheral artery disease cases, whereas EMR had the least. The regional disparity, as previously described in our methods section, was largely a combined result of uneven demographic structure and exposure to major risk factors. Our regional estimation of peripheral artery disease cases for different age groups implied a relatively younger age structure in affected LMICs compared with HICs. With the global ageing process continuing in the next several decades, a considerable increasing trend in the prevalence of peripheral artery disease and number of affected cases is likely to be seen, especially in LMICs. Also, the major risk factors for peripheral artery disease, especially smoking and diabetes, are projected globally to increase substantially over at least the next 10 years.[38,39] The large and increasing burden of peripheral artery disease (number of cases) in LMICs highlights that peripheral artery disease should not remain a neglected health issue in LMICs and more efforts to improve prevention, early diagnosis, and treatment of peripheral artery disease should be strengthened, as should awareness of the disease among health-care providers and the general public. In LMICs with scarce health resources, governments need to set priorities for the management of peripheral artery disease, with particular attention given to secondary prevention of acute cardiovascular events.[40] Especially, more attention should be paid to people with a high risk of peripheral artery disease, such as older women in LMICs settings, people who have a smoking habit, and those with hypertension, diabetes, or other cardiovascular diseases.

In conclusion, this study reveals that peripheral artery disease is continuing to be a major public health challenge worldwide. The majority of people with peripheral artery disease are in LMICs. Smoking, hypertension, and diabetes are positively associated with peripheral artery disease in both HICs and LMICs. With a demographic trend towards ageing and global increases in smoking and diabetes in the foreseeable future, an even larger number of peripheral artery disease cases is to be expected, especially in LMICs. More epidemiological studies and greater priority given to peripheral artery disease is required.

Contributors

IR, PS, and FGRF planned the study and IR and PS designed the methods. PS, DR, and FJIF contributed to the literature review and PS and DR extracted the data. PS, YZ, and IR did the statistical analyses. PS prepared the first draft with important contributions from KR and FGRF. All authors interpreted the results, commented on drafts of the Article, and approved the final version.

Declaration of interests

We declare no competing interests.

Data sharing

All data generated or analysed in this study are included in the appendix.

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