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Global epidemiology of lower extremity artery disease in the 21st century (2000–21): a systematic review and meta-analysis

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Aims

The epidemiology of lower extremity artery disease (LEAD) is evolving. This meta-analysis of aggregate data aimed to (i) determine the global prevalence of LEAD and by regions in the 21st century and (ii) update the associated risk factors in this period.

Methods and results

A systematic literature review was performed through PubMed, Cochrane, Scopus, Science Direct, and Google Scholar databases, restricted to general population studies between January 2000 and September 2021, with LEAD defined by a low ($</\leq 0.90$) ankle–brachial index. The Newcastle–Ottawa Scale was used to evaluate the quality of the articles before data extraction. Due to high heterogeneity, the random effect model was applied to this meta-analysis. Among 1418 references, 38 studies (127 961 participants) were retained. The global prevalence in adults, mostly ≥ 40 years, was estimated at 9.7% [95% confidence interval (CI): 7.1–12.4], higher in women (10.2%) than in men (8.8%), increasing sharply with age. The highest prevalence was found in South–Central Asia (14.5%) and the lowest in North America (5.6%). Significant associations were found between LEAD and current [odds ratio (OR) = 1.9, 95% CI: 1.4–2.5] and past smoking (OR = 1.6, 95% CI: 1.3–1.9) and between LEAD and diabetes (OR = 2.3, 95% CI: 2.0–2.8). Hypertension was significantly associated with LEAD (OR = 2.3, 95% CI: 1.9–2.8) and in particular in South America (OR = 4.0). Obesity (OR = 1.5, 95% CI: 1.2–1.8) and hypercholesterolaemia ≥ 200 mg/dL (OR = 1.9, 95% CI: 1.3–2.8) were also significantly associated with LEAD.

Conclusion

This meta-analysis highlights a currently high prevalence of LEAD worldwide, with substantial differences in global regions and between sexes. The strongest associations were found with metabolic risk factors.

Lay summary

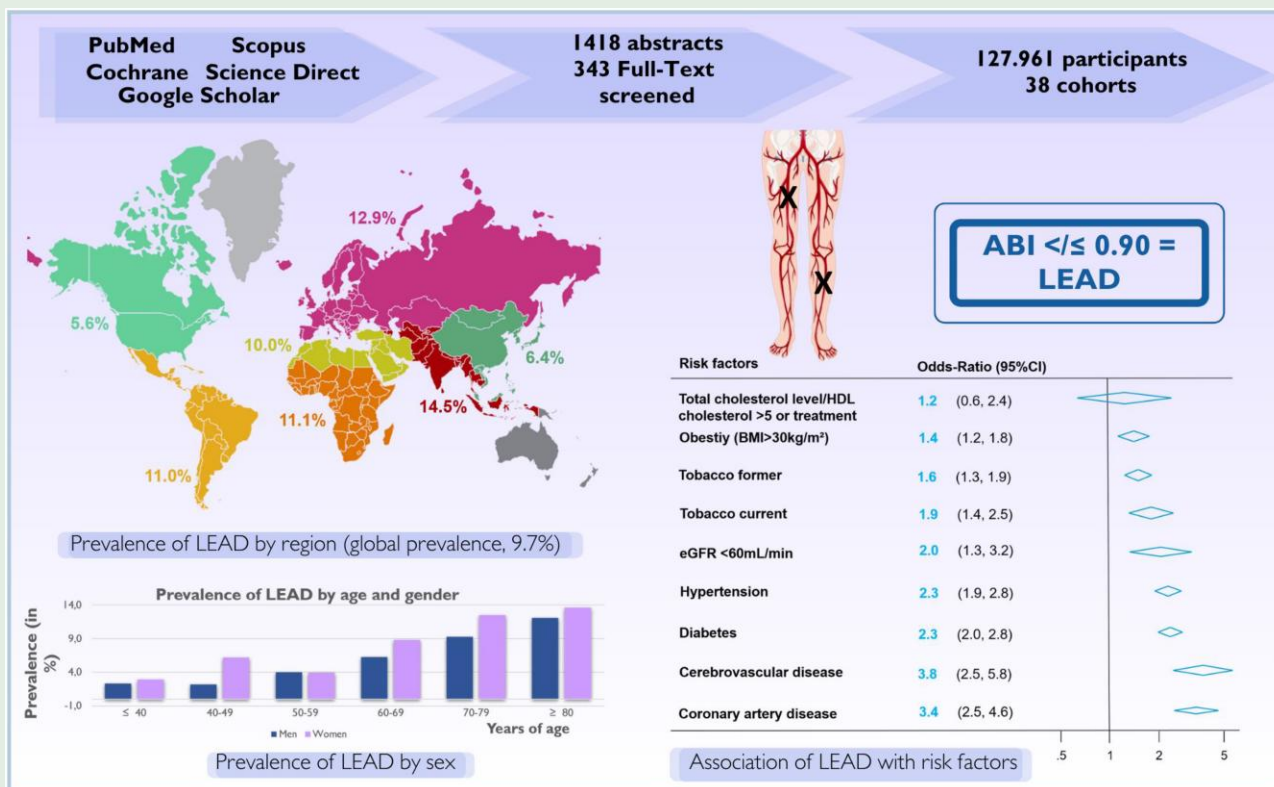
- The global epidemiology of lower extremity artery disease has evolved since the 21st century as has its association with cardiovascular risk factors.
- High overall prevalence (9.7%) in men and women, increasing with age.
- It is associated with traditional risk factors (tobacco, dyslipidaemia) but also diabetes, hypertension, and obesity in all regions of the world.

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Graphical Abstract



Keywords

Lower extremity artery disease • Epidemiology • Prevalence • Risk factors • Meta-analysis • General population

Introduction

Along with coronary arteries and cerebrovascular diseases, lower extremity artery disease (LEAD) is one of the most frequent presentations of atherosclerosis. It encompasses for all arteries affected by atherosclerosis, from the termination of the aorta to the feet arteries.¹ This condition has a long period of subclinical progression prior to its clinical presentations, from intermittent claudication or atypical pains up to chronic limb-threatening ischaemia, which can lead to amputation. As soon as its subclinical period, patients affected by this condition are at increased risk of cardiovascular events and death.¹ On top of its vital prognosis, LEAD is a source of disability, loss of autonomy, and alteration of quality of life.

The easiest way to detect LEAD (symptomatic or not) is to measure the ankle-brachial index (ABI). This is a non-invasive and inexpensive method widely available and hence highly favourable for population studies.^{2,3} An ABI < 0.90 is diagnostic for LEAD with reasonably high specificity (83–99%) and acceptable sensitivity (69–79%).²

With the population aging and evolution of several cardiovascular risk factors [e.g. tobacco smoking decreases especially among men in high-income countries (HICs) and the development of obesity and metabolic syndrome worldwide], it is expected to observe some evolutions in the epidemiology of LEAD. Through data collection along with modelling, the Global Burden Disease estimated that 202 million individuals were living with LEAD in 2010⁴ with a new estimation in 2015 rising to 236 million.⁵ These estimations are of paramount importance as they have underscored the higher burden in low-middle-income countries (LMICs) and especially in women and

surprisingly showed high numbers of young or even very young individuals with this disease. These estimations resulting from modelling can be challenged especially as the performance of ABI to detect LEAD in youth (and especially in women) is debatable⁶ and might have overestimated the prevalence of this disease. Because many studies have been performed on LEAD epidemiology these last decades including in populations in LMICs, a review of available data and meta-analysis (without modelling) is also necessary to estimate the actual prevalence of the disease in global regions and to reassess the association between cardiovascular risk factors and LEAD in the current setting, with special attention to gender disparities.

We therefore conducted a systematic review and meta-analysis of all population-based studies on LEAD epidemiology, from 2000 to 2021. Our primary objective was to determine the prevalence of LEAD in the general population worldwide and by regions in the 21st century. Our second objective was to describe the risk factors associated with LEAD in the general population and by regions based on studies exclusively performed in the current century.

Methods

Study design

The method was carried out as follows: (i) literature search for studies of prevalence and incidence of peripheral artery disease; (ii) selection of studies according to inclusion criteria; (iii) data extraction; (iv) aggregating data of prevalence by region and then by age in men and women; and (v) identification of univariate associations between LEAD prevalence and risk factors by region.

Search strategy and inclusion criteria

We conducted a systematic review of the literature published from 1 January 2000 onward in the following databases: PubMed, Cochrane, Scopus, Science Direct, and Google Scholar with the keywords 'prevalence/epidemiology and peripheral disease/lower extremity disease or intermittent claudication/critical limb ischemia or Ankle-Brachial Index' including studies published between 2000 and 2021 in English and French. We contacted the authors of articles that were not in full text and searched the references of the articles found.

The articles found in non-English languages were not available in full text, and the authors did not reply. We only included studies with data collection performed after 2000 that had a definition of LEAD based on the ABI $</\leq 0.90$. Papers published after 1 January 2000 but reporting on data before that date were excluded. The selection was performed using Zotero 5.0, and the protocol was registered on PROSPERO (CRD42022376447).

The selected reports were also included in the risk factor association analysis if any of the following criteria were met:

- Hypertension: taking anti-hypertensive treatment, history of hypertension, systolic blood pressure ≥ 140 mmHg, and diastolic blood pressure ≥ 90 mmHg.
- Diabetes: taking anti-diabetes treatment, history of disease, and fasting blood glucose ≥ 7 mmol/L (1.26 g/L).
- Obesity: body mass index (BMI) ≥ 30 kg/m².
- Dyslipidaemia: hypercholesterolaemia (≥ 200 or ≥ 240 mg/dL), hypertriglyceridaemia (≥ 150 mg/dL), or total cholesterol/HDL cholesterol ratio > 5 .
- Tobacco consumption as defined by the categories current, former, and/or never.
- Cerebrovascular disease: history of stroke and/or transient ischaemic attack.
- Coronary artery disease: history of myocardial infarction and/or angina.
- Chronic kidney disease (CKD): estimated Glomerular Filtration Rate (eGFR) < 60 mL/min/1.73 m².

The choices for the definitions of dyslipidaemia and smoking were made on the basis of the most consensual ones, given a big variety of definitions, summarized in the appendices (see [Supplementary material online, Tables S1 and S2](#), respectively).

No selection was made on the basis of sample size. A low score (< 7) on the Newcastle–Ottawa Scale (NOS) led to exclusion from the study (see [Supplementary material online, Table S3](#)).

Study selection

We first selected the studies on the basis of the titles and then abstracts. After triage of the abstracts, we read the full texts and checked which studies met the different inclusion criteria. The selection was subsequently checked by two reviewers (V.A. and J.M.). We were careful not to include studies from similar cohorts.

Data extraction

We extracted the prevalence data by age and gender from each study as well as the socio-demographic data and the study information (inclusion period, duration of the study, name of the cohort, country, etc.) and entered them in an Excel sheet. For the studies included in the analysis of risk factor associations, we extracted the prevalence of people with or without LEAD and with or without these risk factors. We also extracted the diagnostic criteria for each of the risk factors according to the study.

Statistical analyses

We have described continuous variables as mean/median and standard deviation (SD) or interquartile range (IQR) and categorical variables as number and percentages. We first examined potential publication bias using funnel plot (Begg's) and Egger's test. We conducted a meta-analysis based on prevalence and odds ratio (OR) and calculated pooled summary estimates by using random effects to further explore heterogeneity among studies, and we calculated I^2 statistics and used forest plots visualizing study-specific estimates and the pooled random effect estimators. If sufficient studies were available, we conducted subgroup analyses by regions or age. The results were presented as stratified forest plot, and a $P \leq 0.05$

was considered significant. All statistical analyses were performed using Stata 11.1 and R Studio 4.1.1.

Results

From the 1418 original hits, we finally included 38 studies^{7–44} in this meta-analysis ([Figure 1](#)). Overall, the studies represent 127 961 individuals (48.1% being women) with an average age of 60.4 ± 8.5 years. Among these studies, 25 included exclusively individuals ≥ 40 years of age, among whom 10 included exclusively individuals ≥ 60 years. All continents were represented except Oceania. The characteristics of the studies are summarized in [Supplementary material online, Table S4](#). Publication bias was assessed using Begg's funnel plot and Egger's test and was found to be high ($P < 0.001$). Heterogeneity due to continent was evaluated via meta-regression and was found to be not significant.

The overall prevalence of LEAD was 9.7% [95% confidence interval (CI): 7.1–12.4], $P < 0.001$, for all sexes combined. The prevalence was higher among women than in men (10.2%, 95% CI: 7.0–13.5 vs. 8.8%, 95% CI: 6.3–11.3). The highest prevalence (in men and women combined) was found in South–Central Asia (14.5%, 95% CI: 0.0–159.8, $P < 0.01$) and the lowest in North America (5.6%, 95% CI: 2.5–8.6, $P < 0.01$; see [Supplementary material online, Figure S1](#)). While in men the prevalence of LEAD raised with age, this prevalence appeared to decrease between 50 and 59 years in women prior to increasing steadily at older ages ([Figure 2A and B](#)). Ultimately, when considering prevalence rates separately for men and women based on LMICs and HICs, we found a higher prevalence among women in LMICs (11.7%, 95% CI: 7.7–15.7) and a higher prevalence among men in HICs (9.5%, 95% CI: 5.5–13.4; see [Supplementary material online, Figure S2A and B](#)).

Association with risk factors

Diabetes was found significantly associated with LEAD (29 studies, $n = 111\ 175$, OR = 2.3; 95% CI: 2.0–2.8). This association was the strongest in South–Central Asia (one study, $n = 2779$, OR = 12.7, 95% CI: 7.5, 19.4) and South America (three studies, $n = 11\ 420$, OR = 3.0, 95% CI: 1.0–9.0) and the weakest in sub-Saharan Africa (three studies, $n = 5022$, OR = 1.3, 95% CI: 1.0–1.7; [Figure 3](#)).

We found similar strength of association between hypertension and LEAD (29 studies, $n = 111\ 175$, OR = 2.3, 95% CI: 1.9–2.8). Similarly, the highest associations were found in South America (three studies, $n = 11\ 420$, OR = 4.0, 95% CI: 0.9–18.0) and even more so in South–Central Asia (one study, $n = 2779$, OR = 14.6, 95% CI: 8.7–24.4) and the lowest in sub-Saharan Africa (three studies, $n = 5022$, OR = 1.4, 95% CI: 1.2–1.7; [Figure 4](#)).

In terms of the association of LEAD with CKD, a statistically significant association was observed overall (10 studies, $n = 18\ 161$, OR = 2.0, 95% CI: 1.3–3.2). The strongest association was found in Eastern Asia (two studies, $n = 4446$, OR = 3.6, 95% CI: 1.8–6.9), while the weakest association was observed in sub-Saharan Africa (one study, $n = 771$, OR = 0.6, 95% CI: 0.3–1.2; see [Supplementary material online, Figure S3](#)).

[Figure 5](#) shows the association between tobacco smoking and LEAD, according to smoking status. The association between LEAD and current and past smokers was close (15 studies, $n = 51\ 280$, OR = 1.9, 95% CI: 1.4–2.5 for current smokers and OR = 1.6, 95% CI: 1.3–1.9 for past smokers). However, it should be underscored considerable heterogeneity among studies.

The association of LEAD with obesity was significant (10 studies, $n = 27\ 873$, OR = 1.5; 95% CI: 1.2–1.8). Heterogeneity between studies was more moderate compared with other risk factors ($I^2 = 75.2\%$), but some regions were not included (East and South–Central Asia and North America). The strongest association was found in a single study in sub-Saharan Africa ($n = 1815$, OR = 2.0, 95% CI: 1.2–3.4) while

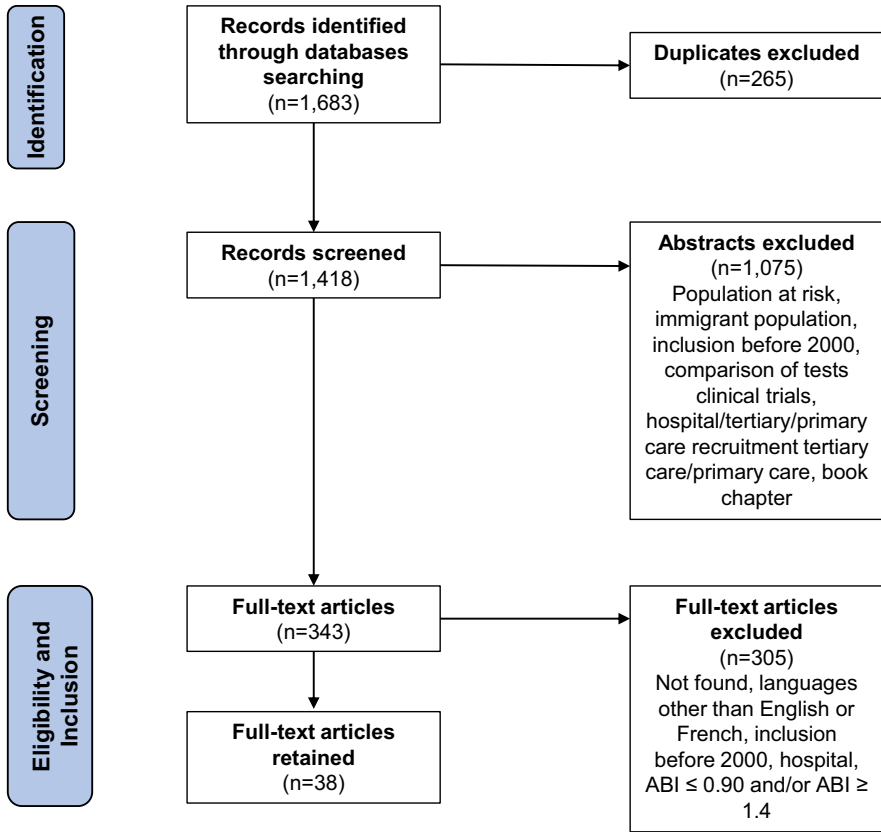


Figure 1 Flowchart of the literature review.

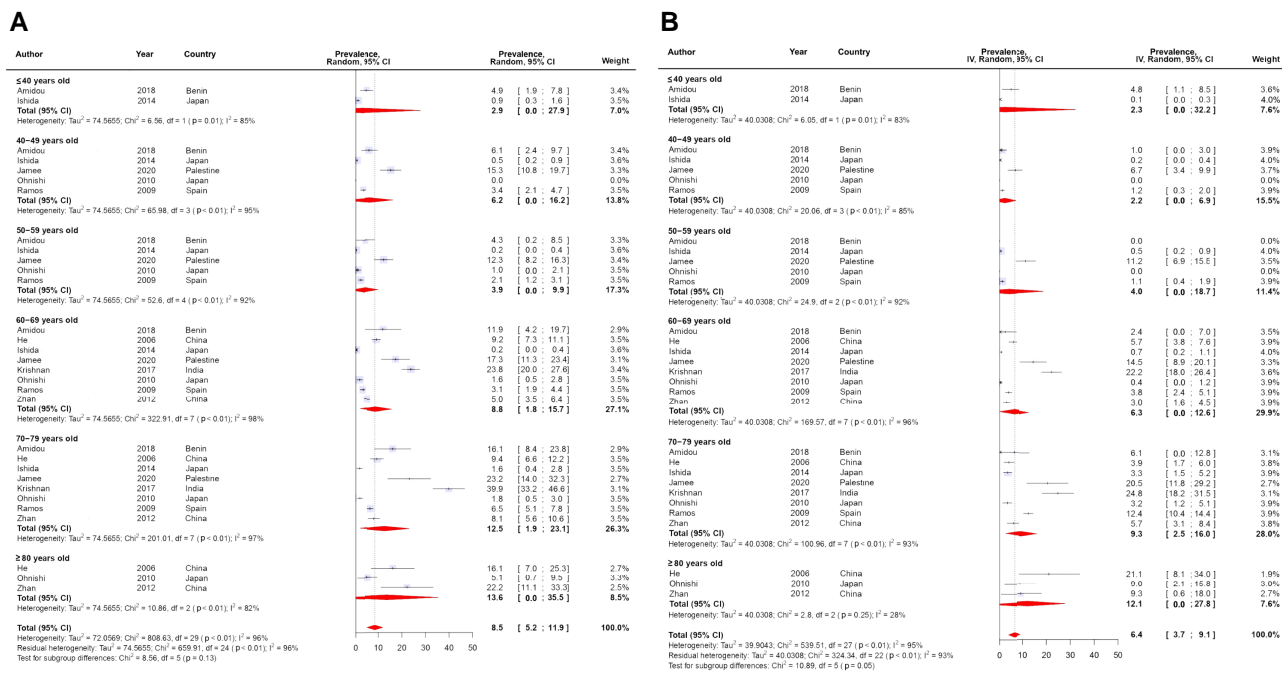


Figure 2 (A) Prevalence of lower extremity artery disease in women according to age. (B) Prevalence of lower extremity artery disease in men according to age.

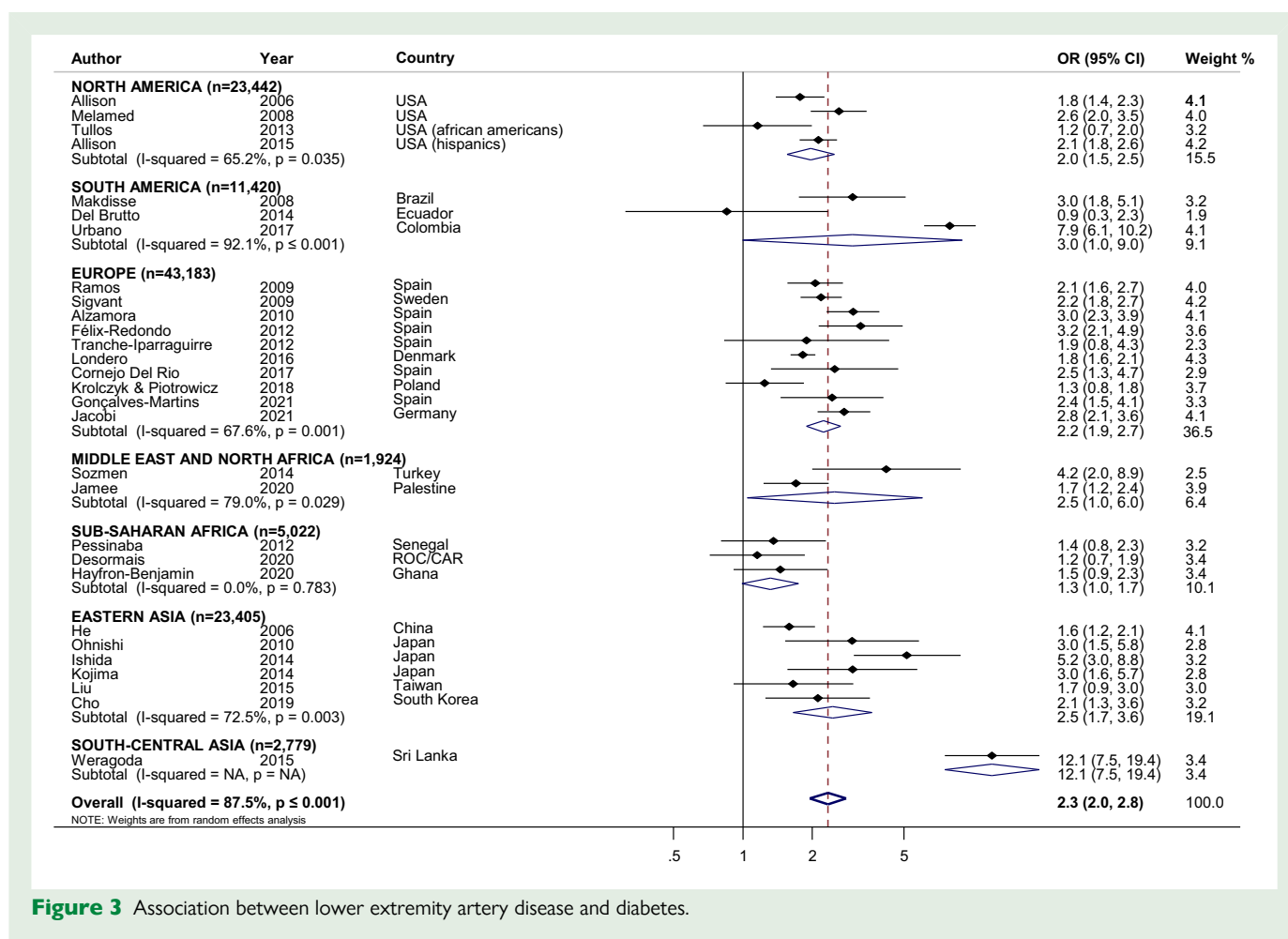


Figure 3 Association between lower extremity artery disease and diabetes.

the strength of association was the lowest in Europe (four studies, $n = 12\,894$, OR = 1.3, 95% CI: 0.9–1.8, $P = 0.002$; see [Supplementary material online, Figure S4](#)).

Regarding dyslipidaemia, the association with LEAD varied according to different definitions. If we considered hypercholesterolaemia as a total cholesterol ≥ 200 mg/dL, the association was significant (one study, $n = 1815$, OR = 1.9, 95% CI: 1.3–2.8). The association was slightly the same for cholesterol above 240 mg/dL (one study, $n = 261$, OR = 1.4, 95% CI: 0.7–2.8) but not significant. When dyslipidaemia was defined as a total cholesterol/HDL cholesterol ratio > 5 , the OR for the association with LEAD was 1.2 (two studies, $n = 16\,301$, 95% CI: 0.6–2.4). Regarding hypertriglyceridaemia (≥ 150 mg/dL), only one study assessed its association with LEAD distinctly from high cholesterol ($n = 3,551$, OR = 1.8, 95% CI: 1.4–2.3; see [Supplementary material online, Figure S5](#)).

The association between a history of cerebrovascular diseases and LEAD was found to be globally significant, with an OR of 3.8 (95% CI: 2.5–5.8). Concerning the history of coronary artery disease, the OR was 3.4 (95% CI: 2.5–4.6). For both disease histories, the weakest association was observed in Eastern Asia.

Discussion

To our knowledge, this is the first meta-analysis assessing the global epidemiology of LEAD. Because the risk factor profiles and management are evolving, we decided to limit our review to studies performed in the 21st century. Also, more studies have also been performed in

LMICs these last 20 years. Our meta-analysis confirms the high prevalence of LEAD globally, with almost 1 in 10 adults >20 years of age affected by this condition. It also highlights remarkable disparities among global regions. Our data support a higher prevalence of LEAD among women than in men. We found strong association with many known cardiovascular risk factors, with similar results in both genders but substantial disparities among global regions associated with high heterogeneity, even sometimes among studies in a similar global region.

We found an overall prevalence of 9.7% of LEAD in a population on average at age of 60. Overall, the sex ratio was balanced with an average age of study participants comparable in women and men, but this result needs to be split by sex because of significant differences, with a prevalence of 10.2% in women and 8.8% in men, which cannot be explained by difference on age. Besides potential differences in risk factors in both sexes, this difference in prevalence could partly be explained by an intrinsically lower ABI in women in the absence of any traditional risk factor.⁴⁵ The 'J-shaped' curve of LEAD prevalence according to age bands in women has been observed in several other studies⁴⁶ and suggests an overestimation of LEAD in younger women who could naturally have lower ABI without being related to occlusive disease. This highlights a drawback of ABI when used as the sole diagnostic criterion for LEAD at a similar threshold in both sexes and different ages.

Our results are consistent with estimates provided in global burden of disease reports (1401.8 per 100,000, 95% CI: 1228.5–1589.4)^{47,48} of LEAD. The prevalence of LEAD was found more than double in Europe (12.9%) as compared with North America (5.6%). These differences may be related to different study characteristics but more plausibly related to risk factor expositions and genetic factors.

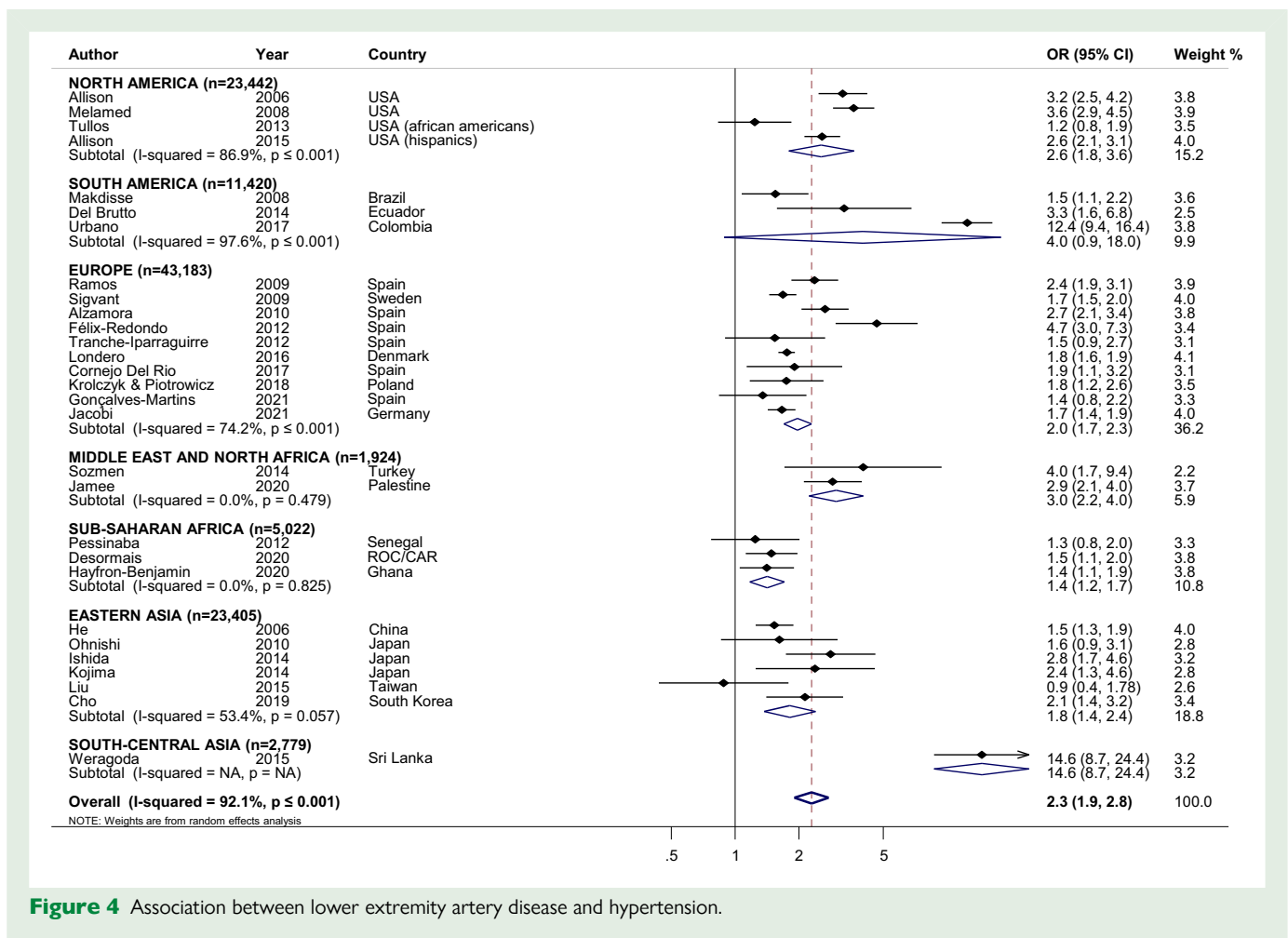


Figure 4 Association between lower extremity artery disease and hypertension.

Our study included 25 studies from HICs (Europe, North America, and Eastern Asia) and 13 from LMICs (sub-Saharan Africa, Middle East and North Africa, South America, and South–Central Asia). The prevalence was diverse in these two groups, ranging from 5.6 to 12.9% in HICs and 11.0 to 14.5% in LMICs. These results were in agreement with those found in the study by Lin et al.,⁴⁹ where, although the percentage change between 1990 and 2019 in the overall number of cases was 72.5%, it ranged from 126.3 to 160.8% in LMICs and only 20.4 to 70.8% in HICs. Thus, even though low prevalence was found in LMICs, the increase in prevalence in these regions has been and is likely to continue to be much higher than in HICs, highlighting the importance of studying LEAD prevalence considering inter-regional differences.

Our data confirm the association between LEAD and diabetes, with an OR = 2.3 as compared with a two- to four-fold risk increase in studies performed in the previous century.⁵⁰ This global result is in agreement with the Global Burden Study.⁵¹ The weakest association between diabetes and LEAD was found in Africa (OR = 1.3), and interestingly, a similar result was reported in African-Americans in the Jackson Heart Study.⁴⁰ Data regarding different susceptibility of diabetic Blacks to present LEAD are debated with contradictory results: while in a previous multiethnic study in the USA,⁵² stronger association was found in African-Americans as compared with other ethnicities, another US study found no interaction regarding the association between diabetes and LEAD according ethnicity.⁵³ However, major differences in socio-economic status, including access to care, are underlying confounders when comparing different ethnic groups in different countries,

and the results found in Africa cannot be transposable to African-Americans. In turn, the strongest association (OR = 12.1) in Sri Lanka appears as an outlier and requires confirmation. Finally, it should be born in mind that the performances of ABI to detect LEAD are poorer in diabetic vs. non-diabetic subjects because of increased arterial stiffening in the former, so the actual association between diabetes and LEAD might be under-estimated when ABI is used as the sole diagnostic criteria.⁵⁴

With regard to hypertension, our results also point to a similar strength of association than in diabetes. Given the much higher prevalence of hypertension, the population attributable risk (PAR) of hypertension in the global LEAD prevalence is substantial. This observation has been supported by a population study in the USA where the PAR related to hypertension has been estimated at 41%.⁵⁵

The observed associations between LEAD and CKD in our study, indicating an OR of ~2.0, align with the findings from O'Hare's study,⁵⁶ where they reported an association of around 3.0. Despite the disparity in associations between the two studies, both reveal a consistent and noteworthy positive association between lead exposure and the risk of CKD. The findings across these studies reinforce the concept that CKD might serve as a significant risk factor contributing to the development or exacerbation of LEAD.

Several factors might explain the divergence in the reported effect sizes. Variances in sample characteristics, methodologies employed for CKD assessment, different population demographics (US vs. global), and adjustments made for potential confounding variables could contribute to these slight discrepancies in effect magnitude.

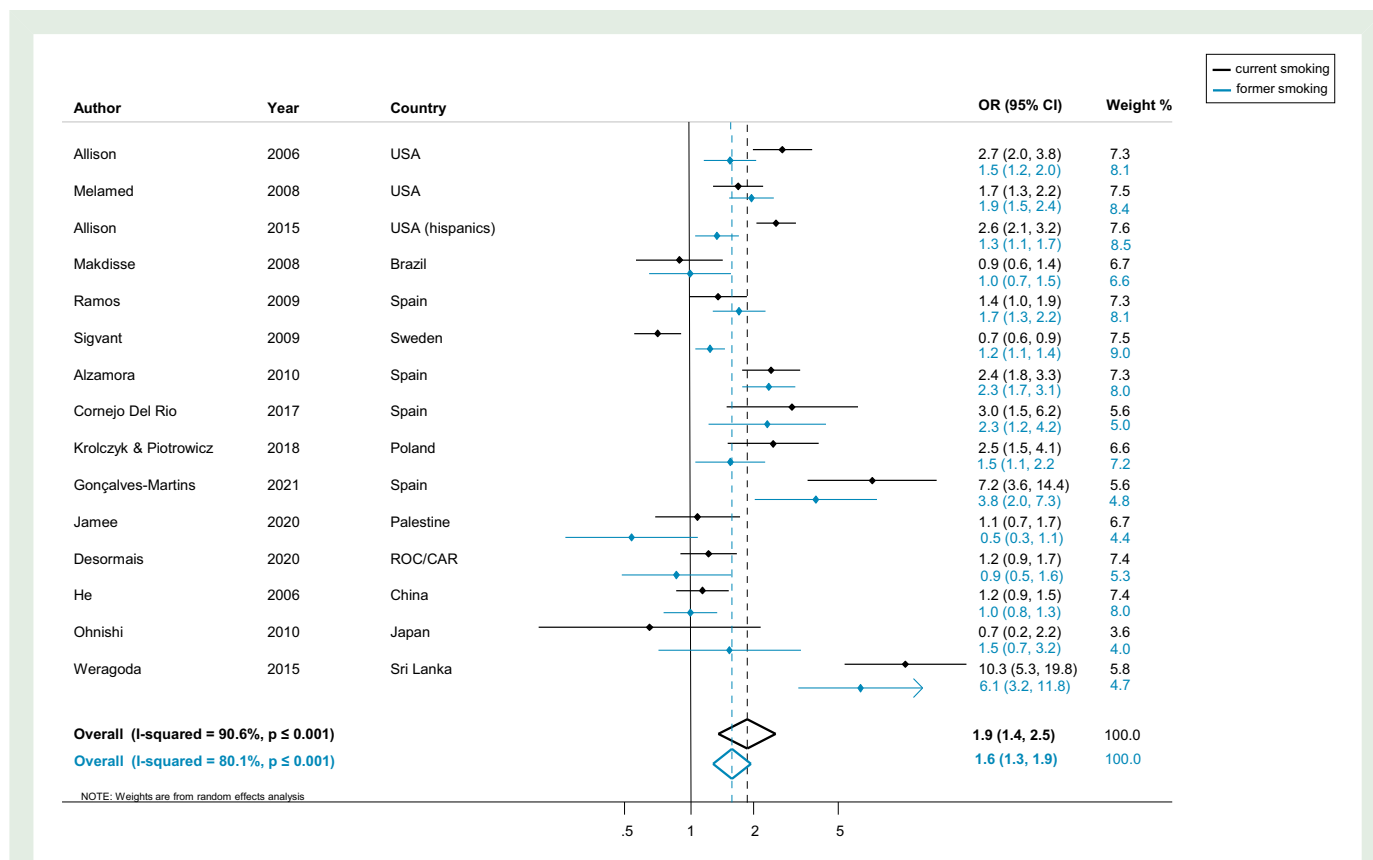


Figure 5 Association between lower extremity artery disease and smoking.

Smoking is the best known risk factor for LEAD since many decades,³ and this association is maintained in the 21st century studies globally, both for current (OR = 1.9) and former (OR = 1.6) smokers. In our review, we should underscore the high variability in categorization of smoking status (current vs. former/never or current/former vs. never) and definitions associated with smoking and smoking cessation (cessation > 1 year, <100 cigarettes per year, etc.). In the study by He *et al.*,²⁰ it was found that although the association ratio was the same as in our study when considering consumption by status (current, former, etc.), the association taking into account the number of packets smoked per year highlighted the importance of this factor with very different ORs (for example, 2.71 for >40 packets per year, i.e. approximately more than two cigarettes per day).

The association of obesity with LEAD was found to be significant in our study. Previous reviews on studies mostly performed in the 20th century were unable to draw definite conclusions on such association.³ However, data are lacking in several global regions. It is difficult to estimate the actual PAR related to obesity, which this condition is strongly associated with hypertension, diabetes, and low physical activity. Also, one study in Africa suggests that the association between BMI and LEAD is not linear, as under-nutrition was also found associated with low ABI in a Central African study.¹⁴

Among all the risk factors, we found a strong association between all definitions of dyslipidaemia and LEAD, but these analyses included only a few studies, because of a wide variety of definitions of dyslipidaemia in the different studies (see [Supplementary material online, Table S1](#)), and the necessity to exclude from this analysis study mixing hypercholesterolaemia and high triglycerides and/or high HDL or LDL level (qualified overall as dyslipidaemia).^{9,17,22,24,26,29,34,38,39,41} Despite the small number of studies included, the results of our analyses remain consistent

with the literature⁵⁰ and support the significant association between dyslipidaemia and the prevalent LEAD.

In this study, which encompasses research conducted in the 21st century, we have demonstrated a shift in the epidemiology of LEAD. Consequently, the prevalence of LEAD appears to remain consistently high or even higher when compared with the previous century (Stoffers *et al.*'s⁵⁷ study reported a prevalence of 6.9% in the Netherlands, while the European prevalence derived from our study was nearly doubled). Established risk factors for LEAD, such as gender, known since the 20th century, continue to be associated with this disease. However, whereas Fowkes *et al.*'s⁵⁸ study previously suggested a slightly higher risk of LEAD among women compared with men, the prevalence data from our 21st-century study demonstrate a greater disparity in risk between the sexes. Furthermore, when examining other atherosclerotic diseases, Fowkes *et al.*'s⁵⁸ study revealed that cardiovascular risk factors (in this case, tobacco consumption) were more strongly associated with LEAD than with angina. This underscores the importance of studying the epidemiology of LEAD in the 21st century, as its overall prevalence has been observed to increase since the early 2000s.

Limitations

This systematic review and meta-analysis provide an estimate of the overall prevalence of LEAD according to region, sex, and associated risk factors. However, all analyses showed considerable heterogeneity owing to the diversity of existing definitions of risk factors and inter-regional differences in studies.

It should also be noted that some studies could not be included because LEAD was sometimes defined as ABI < 0.90 and/or > 1.40 or by a hospitalization criterion.

In addition, we were unable to control for other risk factors that may be strongly associated with LEAD, such as a sedentary lifestyle and socioeconomic status.³

Last, we have been able to identify population studies on LEAD in all continents except for Oceania where the last population study was performed in 1996–98, only in men ≥ 65 years, with a reported crude prevalence of 16.6%, which fits within our global estimation in this age category.⁴⁷

Conclusions

This meta-analysis highlights and quantifies the high prevalence of LEAD in the 21st century in all regions in men and women and presents also the current association of LEAD with different risk factors globally. The disparity in the number of studies by region as well as in the definitions of different risk factors underlines the necessity of standardization of variables and the need for joint effort to undertake a large international study to better understand the current epidemiology of LEAD, both in its asymptomatic and symptomatic forms. Meanwhile, an individual participant data meta-analysis could overcome some of these pitfalls by attempting variable homogenization.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Author contributions

C.A., N.G., M.A., L.C., J.M., and V.A.: systematic review. C.A., J.M., and V.A.: meta-analysis on aggregated data.

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Conflict of interest: C.A., N.G., M.A., L.C., and J.M.: none. V.A.: Amarin, AstraZeneca, Bayer, Boehringer-Ingelheim, and Novo Nordisk.

Data availability

This is a review of existing literature; data related to this analysis are available upon request and after validation of the scientific committee.

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