PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Time trends in peripheral artery disease incidence, prevalence, and secondary preventive therapy: a cohort study in The Health Improvement Network in the UK
AUTHORS	Cea-Soriano, Lucia; Fowkes, FGR; Johansson, Saga; Allum, Alaster; García Rodríguez, Luis

VERSION 1 – REVIEW

REVIEWER	Marco De Carlo Azienda Ospedaliero-Universitaria Pisana Pisa, Italy
REVIEW RETURNED	04-Aug-2017

GENERAL COMMENTS	The present paper describes the time trends in peripheral artery disease (PAD) incidence, prevalence, and drug therapy in the UK from year 2000 to 2014. The study fills a major gap in currently available epidemiologic data on PAD and offers an evidence-based argument against the common perception that PAD prevalence in high-income countries is steadily increasing because of ageing of the population and because of the increased prevalence of diabetes. The authors should be commended for their work. They offer interesting data also on the correlation between PAD incidence and prevalence and the prevalence of ischaemic heart disease (with or without MI) and of diabetes. Importantly, data on drug prescription in patients with incident PAD diagnosis are also reported, highlighting the need for a widespread campaign to increase adherence to current PAD guidelines among general practitioners. The paper is very well written. The methodology is appropriate and clearly described. The discussion is well structured and balanced. My only comment is to ask the authors to provide deeper insight on the potential reasons for the decline in PAD incidence in the UK notwithstanding the increased prevalence of diabetes.

REVIEWER	Dr Alena Shantsila
	University of Birmingham, UK
REVIEW RETURNED	17-Aug-2017

GENERAL COMMENTS	In this manuscript, Soriano and colleagues show that in the incidence and prevalence of patients diagnosed with the peripheral artery disease (PAD) in the UK primary care settings are decreasing. The topic is of particular importance as the majority of the published literature reports an increased prevalence of PAD over the recent decades, whilst this study's results oppose this.
	There are important ethnic differences in the PAD and this topic has not been addressed in the study. What was the distribution of ethnicities in the catchment area of the participating practices and did this distribution change over the course of the study?
	Please consider including into the Discussion the need to identify high-risk individuals in Primary Care for the PAD screening and adequate secondary prevention. Natural history of asymptomatic and symptomatic PAD both results in the critical limb ischaemia.
	The results of this study apply only to patients diagnosed in Primary Care settings, please reflect this in your conclusion in the main text.
	Do you have information on dyslipidaemia? Please provide a reference for decreasing in smoking in your introduction. Unfortunately, the proportion of smokers did not decline in the study population, with the decreased number of patients who never smoked. This leads to the conclusion that the smoking reduction is an unlikely explanation for the decrease in the PAD, please comment.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

Comment 1.1

The present paper describes the time trends in peripheral artery disease (PAD) incidence, prevalence, and drug therapy in the UK from year 2000 to 2014. The study fills a major gap in currently available epidemiologic data on PAD and offers an evidence-based argument against the common perception that PAD prevalence in high-income countries is steadily increasing because of ageing of the population and because of the increased prevalence of diabetes. The authors should be commended for their work. They offer interesting data also on the correlation between PAD incidence and prevalence and the prevalence of ischaemic heart disease (with or without MI) and of diabetes. Importantly, data on drug prescription in patients with incident PAD diagnosis are also reported, highlighting the need for a widespread campaign to increase adherence to current PAD guidelines among general practitioners. The paper is very well written. The methodology is appropriate and clearly described. The discussion is well structured and balanced. My only comment is to ask the authors to provide deeper insight on the potential reasons for the decline in PAD incidence in the UK notwithstanding the increased prevalence of diabetes.

Response 1.1

We thank the reviewer for such a positive response. We have now added the following text after the first paragraph of the Discussion section: "The decline in incidence of PAD between 2000 and 2014 was observed across all age groups except the 50–59-year group, in which the incidence remained

largely similar over time. An important factor in the decrease in PAD incidence could be an increased uptake over time of secondary CV prevention strategies. In the current study, when assessing the 12 months either side of PAD diagnosis, an increase over time was observed in the prescription rate for antiplatelet, ACE inhibitor, ARB and/or statin therapy, which may have delayed or prevented the onset of PAD in at-risk patients. Declining rates of smoking and increasing rates of diabetes in recent years in the UK may have influenced trends in the incidence of PAD but it should be recognised that there is likely to be a considerable lag effect with these risk factors affecting the development of chronic atherosclerotic diseases, including PAD, over many years of an individual's life. Thus, short term changes in risk factor prevalence from 2000 to 2014 in our study might have only a limited impact on incidence of PAD during that period."

Reviewer #2
In this manuscript, Soriano and colleagues show that in the incidence and prevalence of patients diagnosed with the peripheral artery disease (PAD) in the UK primary care settings are decreasing. The topic is of particular importance as the majority of the published literature reports an increased prevalence of PAD over the recent decades, whilst this study's results oppose this.

Comment 2.1
There are important ethnic differences in the PAD and this topic has not been addressed in the study. What was the distribution of ethnicities in the catchment area of the participating practices and did this distribution change over the course of the study?

Response 2.1
Unfortunately, information on patients' race is not systematically available in the database. This drawback has now been added to the limitations section in the Discussion.

Comment 2.2
Please consider including into the Discussion the need to identify high-risk individuals in Primary Care for the PAD screening and adequate secondary prevention. Natural history of asymptomatic and symptomatic PAD both results in the critical limb ischaemia.

Response 2.2
The following text has now been added to the Discussion section: "Risk factors for PAD should be carefully managed in primary care. Patients with PAD are at risk of progressing to critical limb ischaemia, irrespective of whether their PAD is symptomatic or asymptomatic. Patients who are at high risk for PAD need to be identified and screened, and adequate secondary prevention strategies implemented where appropriate. In the real world this is often not the case as is manifest by, for example, continuing high rates of smoking. There is a need to take an aggressive approach to dealing with factors to reduce the risk of PAD and of future serious outcomes."

Comment 2.3
The results of this study apply only to patients diagnosed in Primary Care settings, please reflect this in your conclusion in the main text.

Response 2.3
The last sentence of the Conclusion has been amended to the following: "Although prescription rates have increased over time, a large proportion of individuals diagnosed with PAD in the primary care setting do not receive guideline-recommended secondary prevention therapy.
Comment 2.4
Do you have information on dyslipidaemia?
Response 2.4

We have now added the following information to supplementary table S3 (under the "Comorbidities" subheading): "Hyperlipidaemia, n (%), 2000: 204 (10.8%); 2005: 243 (9.2%); 2010: 161 (7.3%); 2014: 178 (8.7%)".

Comment 2.5
Please provide a reference for decreasing in smoking in your introduction. Unfortunately, the proportion of smokers did not decline in the study population, with the decreased number of patients who never smoked. This leads to the conclusion that the smoking reduction is an unlikely explanation for the decrease in the PAD, please comment.

Response 2.5
A reference to data from the UK Office for National Statistics is now cited in the Introduction with respect to the decrease in smoking prevalence. We have also now added the following text to the Discussion section: "Declining rates of smoking and increasing rates of diabetes in recent years in the UK may have influenced trends in the incidence of PAD but it should be recognized that there is likely to be a considerable lag effect with these risk factors affecting the development of chronic atherosclerotic diseases, including PAD, over many years of an individual's life. Thus, short term changes in risk factor prevalence from 2000 to 2014 in our study might have only a limited impact on incidence of PAD during that period."
In addition, we have added the following text to the Results section: "The proportion of current smokers decreased initially, from 39.5% among patients diagnosed in 2000 to 35.4% among those diagnosed in 2004, and then remained relatively constant thereafter. In the general population in THIN (i.e. the study source population), a decline in the proportion who were current smokers was observed over time, from 22.0% in the year 2000 to 14.8% in 2014 (note: these data exclude patients for whom information on smoking status was not known, which in 2000 and 2014 equalled 10.1% and 0.1%, respectively, among those diagnosed with incident PAD, and 14.0% and 0.3%, respectively, among the study source population)." Note that we also added the following additional information to the footnote of supplementary table S3: "Overall, data on smoking status and alcohol use were missing for 2.6% and 14.1% of patients, respectively."

VERSION 2 – REVIEW

REVIEWER	Marco De Carlo Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy
REVIEW RETURNED	02-Oct-2017

GENERAL COMMENTS	The authors need to be commended again for their work. I am satisfied with the answer to my comment to the original paper.

REVIEWER	Dr Alena Shantsila University of Birmingham
REVIEW RETURNED	01-Oct-2017

GENERAL COMMENTS	Thank you for the changes. Please make sure the abstract reflects the changes as well.