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Complete List of Authors:	Cea-Soriano, Lucia; Spanish Center for Pharmacoepidemioly Research CEIFE, Fowkes, FGR; University of Edinburgh, Centre for Population Health Sciences Johansson, Saga; AstraZeneca R&D, ; Gothenburg University, Institute of Medicine, Sahlgrenska Academy Allum, Alaster; AstraZeneca R&D Cambridge García Rodríguez, Luis; Spanish Centre for Pharmacoepidemiologic Research (CEIFE),
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Time trends in peripheral artery disease incidence, prevalence, and secondary preventive therapy: a cohort study in The Health Improvement Network in the UK

Lucía Cea Soriano,[1,2] F Gerry R Fowkes,[3] Saga Johansson,[4] Alaster M Allum[5] and Luis A García Rodriguez[1]

[1]Pharmacoepidemiology, Spanish Centre for Pharmacoepidemiologic Research (CEIFE), Madrid, Spain

[2]Department of Preventive Medicine and Public Health, Faculty of Medicine, Complutense University of Madrid, Madrid, Spain

[3]Centre for Population Health Sciences, University of Edinburgh, Edinburgh, UK

[4]AstraZeneca Gothenburg, Mölndal, Sweden

[5]AstraZeneca Cambridge, Cambridge, UK

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Correspondence to: Dr Lucía Cea Soriano, Centro Español de Investigación Farmacoepidemiológica (CEIFE), c/ Almirante 28-2°, Madrid 28004, Spain.
E-mail: luciaceife@gmail.com; phone: +34 (91) 531 3404; fax: +34 (91) 531 2871.

ABSTRACT

Objectives: To assess time trends in symptomatic peripheral artery disease (PAD) incidence and prevalence, and secondary preventive therapy.

Design: Cohort study using The Health Improvement Network (THIN).

Setting: UK primary care.

Participants: Individuals aged 50–89 years, annually between 2000 and 2014. Participants with symptomatic PAD were identified using Read codes.

Outcome measures: Incidence and prevalence of symptomatic PAD from 2000 to 2014, overall and by sex and age. Proportion of patients prescribed secondary preventive therapy with acetylsalicylic acid (ASA), clopidogrel, an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin-receptor blocker (ARB), and/or a statin.

Results: The incidence of symptomatic PAD per 10 000 person-years decreased over time, from 38.6 (men: 51.0; women: 28.7) in 2000 to 17.3 (men: 23.1; women: 12.4) in 2014. The prevalence of symptomatic PAD decreased from 3.4% (men: 4.5%; women: 2.5%) in 2000 to 2.4% (men: 3.1%; women: 1.7%) in 2014. Incidence and prevalence decreases were observed in all age groups. The proportions of patients prescribed ASA monotherapy, clopidogrel monotherapy, and dual antiplatelet therapy in the 2 months after PAD diagnosis were 42.7%, 2.9%, and 2.5%, respectively, during 2000–2003, and 44.7%, 11.0%, and 5.2%, respectively, during 2012–2014. For ACE inhibitor/ARB therapy and statins, proportions in the 2 months after diagnosis were 30.2% and 31.2%, respectively, during 2000–2003, and 45.1% and 65.9%, respectively, during 2012–2014.

Conclusion: The incidence and prevalence of symptomatic PAD diagnosed in UK primary care are decreasing. A large proportion of the population with PAD in clinical practice does not receive guideline-recommended secondary prevention therapy.

Word count: 254 (limit 300)

Strengths and limitations of this study

- This is, to our knowledge, the largest study to date of time trends in PAD incidence and prevalence in the UK.
- Data are from electronic medical records in THIN, which has demonstrated validity for use in pharmacoepidemiological studies.
- Patients' anonymised medical records were reviewed manually to validate the selected diagnostic Read codes used to identify symptomatic PAD in a random sample.
- Potential limitations include possible changes over time in the source population and in how PAD is diagnosed in UK primary care, which would have affected the secular incidence and prevalence trend patterns.

What this paper adds

What is already know on this subject

– Whereas rates of myocardial infarction and ischaemic stroke are declining in most countries, secular incidence and prevalence trends for peripheral artery disease (PAD) are less clear.

– An increase in the prevalence of PAD from 2000 to 2010 was reported in a recent meta-analysis of data from 10 high-income countries including from the USA and four European countries, but not the UK.

– Age-standardised PAD prevalence data from the USA show only minimal changes from 1990 to 2010.

What this study adds

– The results of this large observational study, conducted in 'real-life' clinical practice, showed a steady decline over time in the incidence and prevalence of symptomatic PAD in UK primary care from 2000 to 2014.

INTRODUCTION

Peripheral artery disease (PAD) causes leg pain or discomfort, most commonly occurring on exertion and resolving after rest (intermittent claudication), although some individuals have no obvious symptoms even when functional impairment is noticeable on testing.[1] Individuals with PAD are at increased risk of myocardial infarction (MI), ischaemic stroke, and death.[2 3] To reduce the risk of cardiovascular (CV) events, US and European guidelines recommend antiplatelet therapy and statins for all individuals with symptomatic PAD, and antihypertensive therapy for those with concomitant hypertension.[4-7] Angiotensin-converting enzyme (ACE) inhibitors may also reduce CV risk in symptomatic patients with PAD.[4-7]

The key risk factors for PAD are similar to those for other CV diseases, and include smoking, increasing age, diabetes mellitus, hypertension, and dyslipidaemia.[8 9] In recent years, the prevalence patterns of PAD risk factors have been changing substantially. Smoking prevalence is decreasing, but there is an increase in the prevalence of diabetes mellitus. Advances in treatment and in the implementation of processes of care have resulted in individuals with coronary heart disease and cerebrovascular disease now surviving to older ages, which is when PAD tends to manifest itself.

Whereas rates of MI and ischaemic stroke are declining in most countries,[10-12] secular incidence and prevalence trends for PAD are less clear. A recent meta-analysis reported an increase in the prevalence of PAD (assessed using the ankle–brachial index [ABI]) in high-income countries from 2000 to 2010.[9] The analysis included data from 10 high-income countries including the USA and four European countries, but not the UK. Age-standardised prevalence data for symptomatic PAD from the US State of Health report show only minimal changes (<0.2%) from 1990 to 2010.[13] The aim of the current study was to determine secular trends in the incidence and prevalence of symptomatic PAD and of secondary preventive therapy in a large, representative primary care population in the UK.

METHODS

Study design and data source

This was a retrospective observational cohort study. Data were collected from The Health Improvement Network (THIN) database in the UK. THIN is an electronic medical research database that contains fully anonymised data on approximately 11 million patients collected from participating primary care practices in the UK.[14] The data in THIN are from all patients in participating practices and are recorded during each consultation with the primary care

physician/nurse, leaving no scope for selective participation or reporting. Patients included in THIN are representative of the UK general population.[14] The Read classification is used to code specific diagnoses,[15] and a drug dictionary based on data from the Gemscript classification is used to code drugs.[16]

Study cohorts

Source population

Patients aged 50–89 years were identified in THIN, annually between 1 January 2000 and 31 December 2014. To be eligible for entry into the study, patients had to have been enrolled with their primary care physician for at least 2 years, to have visited their primary care physician at least once during that time, and to have a computerised prescription history for at least 2 years before study entry. These inclusion criteria helped to ensure that study participants were making use of healthcare services offered by their primary care practice and had historical information available.

Incident and prevalent symptomatic PAD

For each year during the follow up period, individuals with evidence of symptomatic PAD were identified by an automated database search using Read codes indicative of a symptomatic PAD diagnosis and/or related surgical procedures (supplementary table S1). For PAD incidence and secular trends, the date of the first entry of a PAD diagnosis in the THIN database was set as the index date. For prevalent PAD, each patient's start date was set as the date on which the study inclusion criteria (as listed above) were met.

The positive predictive value of the automated database search to identify patients with symptomatic PAD was assessed in a random validation sample of 400 of the identified patients. Patients' anonymised medical records, which included free-text comments from the primary care physicians, were reviewed manually. The diagnosis was confirmed in 97.0% of individuals (194/200) with incident PAD and in 99.0% of patients (198/200) with prevalent PAD, thereby confirming the positive predictive validity of the selected diagnostic Read codes used to identify symptomatic PAD.

Statistical analyses

Annual incidence and prevalence were determined for the years 2000–2014. The annual incidence was calculated by dividing the number of individuals with newly diagnosed PAD in a particular year by the contribution of all study participants at risk (free of PAD) in that year. To calculate the annual prevalence, the sum of the number of individuals with a history of PAD plus the number of individuals with newly diagnosed PAD in a particular year was divided by the total population meeting the study eligibility criteria. The time trends in the proportions of patients prescribed therapy with acetylsalicylic acid (ASA), clopidogrel, an ACE inhibitor, an angiotensin-receptor blocker (ARB), and/or a statin in the 12 months before and 12 months after an incident PAD diagnosis were also assessed.

Results

Time trends in incidence and prevalence

Time trends in the incidence and prevalence of PAD from 2000 to 2014, overall and separately by sex and age group, are shown in figure 1. The incidence of PAD decreased steadily over time, from 38.55 per 10 000 person-years in 2000 to 17.33 per 10 000 person-years in 2014 (figure 1a). The incidence was higher in men than in women: in 2000 it was 50.96 per 10 000 person-years in men and 28.70 per 10 000 person-years in women, and in 2014 it was 23.05 per 10 000 person-years and 12.37 per 10 000 person-years, respectively. Decreases in incidence over time were observed in all age groups (figure 1b).

The incidence of PAD was higher in patients with a history of ischaemic heart disease at the study start date than in those with no such history (supplementary table S2). The incidence of PAD decreased over time at a similar rate in patients with a history of ischaemic heart disease (from 93.5 per 10 000 person-years in 2000 to 43.5 per 10 000 person-years in 2014) and those without a history of ischaemic heart disease (from 30.7 per 10 000 person-years in 2000 to 14.5 per 10 000 person-years in 2014).

The overall decrease in incidence of PAD from 2000 to 2014 was paralleled by a decrease in prevalence of the disease (figure 1c). The prevalence of PAD decreased from 3.42% (men: 4.53%; women: 2.52%) in 2000 to 2.37% (men: 3.12%; women: 1.70%) in 2014. Decreases in prevalence over time were observed in all age groups (figure 1d).

Time trends in demographics and comorbidities

Noticeable changes over time among patients with incident PAD diagnosed in 2000, 2005, 2010, or 2014 included increases in the proportions of patients who were obese (body mass index ≥30 kg/m^2), patients who were former smokers (paralleled by a decrease in those who never smoked, with the proportion of current smokers remaining relatively constant), and individuals who had prescriptions for five or more medications (supplementary table S3). Regarding comorbidity patterns, ischaemic heart disease prevalence without MI declined over time, with rates of 34.0%, 32.8%, 29.5%, and 26.4% in the years 2000, 2005, 2010, and 2014, respectively. However, increases in prevalence over time were observed for diagnoses of diabetes mellitus, chronic obstructive pulmonary disease, asthma, cancer, depression, and dementia. The age and sex distributions were similar over time.

Time trends in treatment patterns

Time trends in treatment patterns in the 12 months before and 12 months after an incident diagnosis of PAD are shown in figure 2. Prescription rates increased at the time of the incident PAD diagnosis. ASA monotherapy was the most commonly prescribed antiplatelet therapy during the study period. Prescription rates for antiplatelet therapy in the 2 months after diagnosis in the years 2000–2003, 2004–2007, 2008–2011, and 2012–2014 were 42.7%, 47.4%, 48.4%, and 44.7% for ASA, 2.9%, 4.6%, 4.7%, and 11.0% for clopidogrel, and 2.5%, 3.2%, 4.6%, and 5.2% for dual antiplatelet therapy, respectively.

For ACE inhibitor or ARB therapy, prescription rates in the 2 months after diagnosis in the years 2000–2003, 2004–2007, 2008–2011, and 2012–2014 were 30.2%, 41.9%, 46.5%, and 45.1%, and for statin therapy they were 31.2%, 56.5%, 63.6%, and 65.9%, respectively. The proportion of patients with a prescription for an ACE inhibitor or ARB remained relatively similar before PAD diagnosis compared with after diagnosis in the earlier three study periods, but decreased after diagnosis in the most recent (2012–2014) study period. The proportion of patients with a statin prescription increased after an incident PAD diagnosis. In the most recent study period it decreased again in the months after the diagnosis, although this trend was less pronounced when the analysis was restricted to practices with at least 1 year of data collection after the start date in the 2012–2014 subgroup (supplementary figure S1), suggesting differences between practices in their end of year data collection rather than an actual decline in statin prescriptions.

Although the proportion of patients with prescriptions for all three therapies (an antiplatelet agent, plus an ACE inhibitor or ARB, plus a statin) in the 12 months before and

12 months after an incident diagnosis increased after 2000–2003 and also rose at PAD diagnosis, it remained below 30% at all times. Prescription rates for the three therapies combined in the 2 months after diagnosis in the years 2000–2003, 2004–2007, 2008–2011, and 2012–2014 were 9.7%, 22.6%, 27.3%, and 27.6%, respectively.

DISCUSSION

The results of this large observational study, conducted in 'real-life' clinical practice, showed a steady decline over time in the incidence and prevalence of symptomatic PAD in UK primary care. The incidence in patients with ischaemic heart disease was approximately three times higher than in those without ischaemic heart disease, but both groups showed similar rates of decline. Ischaemic heart disease prevalence declined over time, potentially underlying the parallel secular trend in PAD prevalence, and suggesting general improvements in overall CV health over time in the UK.

Results of a recent meta-analysis indicated that the prevalence of PAD increased from 2000 to 2010 in high-income countries.[9] Data on temporal trends in PAD prevalence suggest that any observed prevalence increases over time may be due to an ageing population, with age-standardised prevalence data for symptomatic PAD reporting only minimal changes over time.[13]

The current study, which included only patients aged 50 years or older, observed a symptomatic PAD prevalence that ranged from 3.42% in 2000 to 2.37% in 2014. These rates are similar to those reported in other population-based studies in the USA and Europe that include a minimum age cut-off. In both the US Life Line Screening programme (participants aged ≥40 years; study years 2003–2008)[17] and the Spanish HERMEX study (participants aged ≥50 years; study years: 2007–2009),[18] PAD prevalence was 3.7%. Slightly higher prevalences of 7.6% and 5.8%, respectively, were reported in a Spanish primary healthcare study (participants aged ≥50 years; study years 2006–2008)[19] and the German Heinz Nixdorf Recall study (participants aged ≥45 years; study years 2000–2003).[20]

There is a paucity of published data regarding the incidence of PAD.[8] Long-term results from a German study conducted in primary care (the 'getABI' study), which enrolled patients aged 65 years and older, found a PAD incidence of 203 per 10 000 person-years. In our study, a lower PAD incidence than in the German study was observed in the older age groups, ranging from approximately 30 per 10 000 person-years to 70 per 10 000 person-years (figure 1).

The reported incidence and prevalence across studies will depend on whether they are obtained using recorded diagnoses, as in the current study, or by assessing all study patients for PAD symptoms and signs (e.g. via the ABI). The latter approach will tend to result in higher observed incidence and prevalence. When assessing secular trends, it is essential to ensure that the methodology for identifying patients with PAD is similar across all time points, as was the case in the current study.

Guidelines on the management of PAD were first published by the European Society of Cardiology (ESC) in August 2011[5] and by the UK National Institute of Health and Care Excellence (NICE) in August 2012.[21] Both recommend antiplatelet therapy in all individuals with symptomatic PAD. Antiplatelet therapy for the prevention of vascular events has also been included in the NICE PAD management pathway. Additional recommendations from the ESC and NICE include smoking cessation, and management of diabetes mellitus, hypertension, and hyperlipidaemia.

Although the proportion of patients with PAD prescribed antiplatelet therapy increased over time in the current study, more than one-third of patients were not prescribed antiplatelet therapy with ASA, clopidogrel, or combination therapy following an incident PAD diagnosis between 2012 and 2014. The proportion of patients with incident PAD who were prescribed a statin increased to approximately 66% at the time of PAD diagnosis during 2012–2014. The proportion prescribed an ACE inhibitor or ARB decreased slightly after diagnosis in 2012–2014. Prescribing for secondary preventive therapies tended to be highest following PAD diagnosis.

Our study has several key strengths. It is, to our knowledge, the largest study to date of time trends in PAD incidence and prevalence in the UK. Data are from electronic medical records in THIN. Patients included in THIN are representative of the UK general population in terms of age, sex, and geographical location.[14] THIN has demonstrated validity for use in pharmacoepidemiological studies.[22] Patients' anonymised medical records, which included free-text comments from the primary care physicians, were reviewed manually to validate the selected diagnostic Read codes used to identify symptomatic PAD in a random sample. Potential limitations include possible changes over time in the source population and in how PAD is diagnosed in UK primary care, which would have affected the secular incidence and prevalence trend patterns.

In conclusion, results from this study suggest that the incidence and prevalence of symptomatic PAD are decreasing in the UK. Although prescription rates have increased over

time, a large proportion of individuals with PAD in clinical practice do not receive guideline-recommended secondary prevention therapy.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare the following. L Cea Soriano and LA García Rodriguez are employees of CEIFE, which has received research funding from AstraZeneca Gothenburg, Mölndal, Sweden and Bayer Pharma AG, Berlin, Germany; LA García Rodriguez has also received honoraria for serving on scientific advisory boards for AstraZeneca and Bayer. FGR Fowkes has received honoraria for serving on scientific advisory boards for AstraZeneca, Bayer, and Merck. S Johansson is an employee of AstraZeneca Gothenburg, Mölndal, Sweden. AM Allum is an employee of AstraZeneca Cambridge, Cambridge, UK.

Data sharing statement

All relevant source data are shown in the manuscript and supplementary files.

Exclusive licence

Author contributions

Lucía Cea Soriano: conception and design of the work, data collection, data analysis, data interpretation, critical revision of the article, approval of final draft. F Gerry R Fowkes: data interpretation, critical revision of the article, approval of final draft. Saga Johansson: conception and design of the work, data interpretation, critical revision of the article, approval of final draft. Alaster M Allum: conception and design of the work, data interpretation, critical revision of the article, approval of final draft. Luis A García Rodriguez: conception and design of the work, data collection, data analysis, data interpretation, critical revision of the article, approval of final draft.

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Figure legends

Figure 1 Trends from 2000 to 2014 in peripheral artery disease: a) incidence, overall and according to sex; b) incidence according to age group; c) prevalence, overall and according to sex; d) prevalence according to age group.

Figure 2 Time trends in the proportions of patients prescribed a) acetylsalicylic acid monotherapy, b) clopidogrel monotherapy, c) dual antiplatelet therapy, d) an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker, e) a statin, or f) combined therapy with an antiplatelet, plus an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker, plus a statin in the 12 months before and 12 months after an incident diagnosis of PAD.

Shaded area highlights the 2 months before and 2 months after the PAD diagnosis.

PAD, peripheral artery disease.

Supplementary Figure S1 Time trends in the proportions of patients prescribed statin therapy in the 12 months before and 12 months after an incident diagnosis of PAD, with data for 2012–2014 restricted to primary care practices with at least 1 year of follow-up from the start date

Shaded area highlights the 2 months before and after the PAD diagnosis.

PAD, peripheral artery disease.

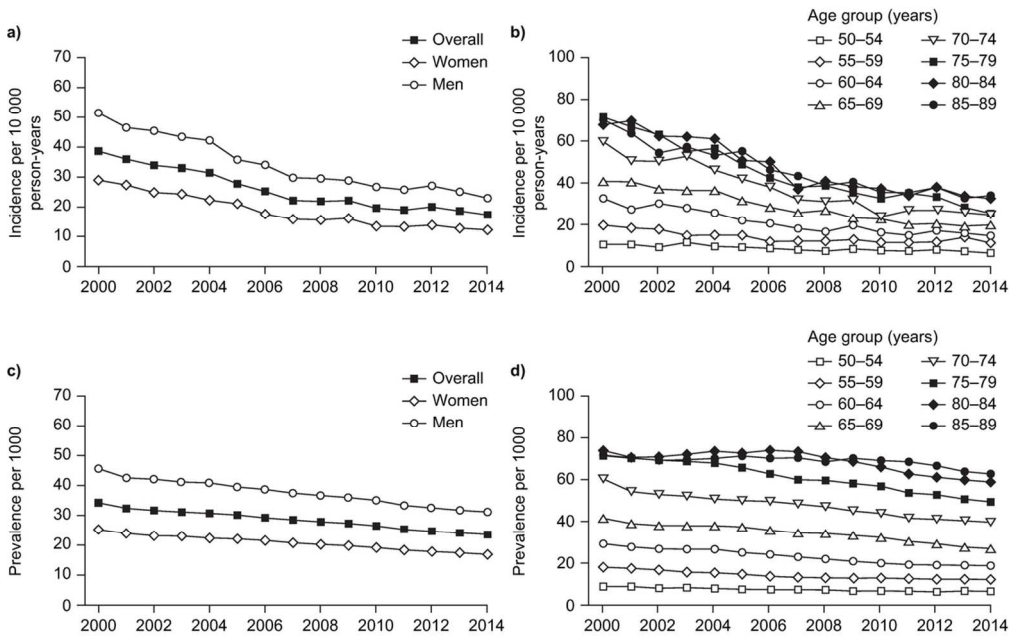


Figure 1 Trends from 2000 to 2014 in peripheral artery disease: a) incidence, overall and according to sex; b) incidence according to age group; c) prevalence, overall and according to sex; d) prevalence according to age group.

109x68mm (300 x 300 DPI)

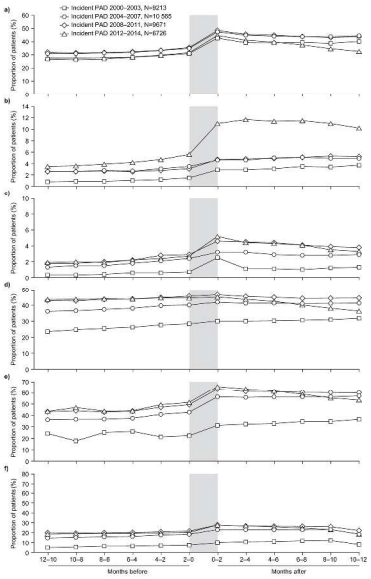


Figure 2 Time trends in the proportions of patients prescribed a) acetylsalicylic acid monotherapy, b) clopidogrel monotherapy, c) dual antiplatelet therapy, d) an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker, e) a statin, or f) combined therapy with an antiplatelet, plus an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker, plus a statin in the 12 months before and 12 months after an incident diagnosis of PAD.
Shaded area highlights the 2 months before and 2 months after the PAD diagnosis.
PAD, peripheral artery disease.

355x279mm (300 x 300 DPI)

Time trends in peripheral artery disease incidence, prevalence, and secondary preventive therapy: a cohort study in The Health Improvement Network in the UK

Lucía Cea Soriano et al.

Supplementary materials

Supplementary Table S1 Read codes indicative of a symptomatic PAD diagnosis and/or related surgical procedures

Read code	Descriptor
G700.11	Aorto-iliac disease
G702.00	Extremity artery atheroma
G702z00	Extremity artery atheroma NOS
G73..11	Peripheral ischaemic vascular disease
G73..12	Ischaemia of legs
G73..13	Peripheral ischaemia
G730100	Raynaud's phenomenon
G731000	Buerger's disease
G731100	Presenile gangrene
G732.00	Peripheral gangrene
G732000	Gangrene of toe
G732100	Gangrene of foot
G733.00	Ischaemic foot
G734.00	Peripheral arterial disease
G73y.00	Other specified peripheral vascular disease
G73y000	Diabetic peripheral angiopathy
G73y100	Peripheral angiopathic disease EC NOS
G73yz00	Other specified peripheral vascular disease NOS
G73z.00	Peripheral vascular disease NOS
G73z000	Intermittent claudication
G73z011	Claudication
G73z012	Vascular claudication

G73z100	Spasm of peripheral artery
G73zz00	Peripheral vascular disease NOS
G74..00	Arterial embolism and thrombosis
G74..11	Arterial embolus and thrombosis
G74..12	Thrombosis – arterial
G74..13	Arterial embolic and thrombotic occlusion
G740.12	Aortoiliac obstruction
G740.13	Leriche's syndrome
G742400	Embolism and thrombosis of the femoral artery
G742500	Embolism and thrombosis of the popliteal artery
G742600	Embolism and thrombosis of the anterior tibial artery
G742700	Embolism and thrombosis of the dorsalis pedis artery
G742800	Embolism and thrombosis of the posterior tibial artery
G742900	Embolism and thrombosis of a leg artery NOS
G742B00	Post radiological embolism of lower limb artery
G742z00	Peripheral arterial embolism and thrombosis NOS
G74y000	Embolism and/or thrombosis of the common iliac artery
G74y100	Embolism and/or thrombosis of the internal iliac artery
G74y200	Embolism and/or thrombosis of the external iliac artery
G74y300	Embolism and thrombosis of the iliac artery unspecified
G74z.00	Arterial embolism and thrombosis NOS
G761.00	Stricture of artery
G765.00	Necrosis of artery
G76A.00	Arterial insufficiency
G76z.00	Disorders of arteries and arterioles NOS
G76z000	Iliac artery occlusion
G76z100	Femoral artery occlusion
G76z200	Popliteal artery occlusion
G7y..00	Other specified arterial, arteriole or capillary disease
G7z..00	Arterial, arteriole and capillary diseases NOS
14NB.00	H/O: Peripheral vascular disease procedure
2I16.00	O/E - gangrene
R054.00	[D]Gangrene

R054200	[D]Gangrene of toe in diabetic
R054300	[D]Widespread diabetic foot gangrene
8HlP.00	Referred for peripheral artery disease assessment

D, diagnosis; EC, elsewhere classified; H/O, history of; O/E, on examination; NOS, not otherwise specified; PAD, peripheral artery disease.

Supplementary Table S2 Trends from 2000 to 2014 in peripheral artery disease incidence, overall and according to history of IHD at baseline

Year	Overall	IHD	No IHD
2000			
Population, n	540 918	67 713	473 205
Cases, n	1891	575	1316
Person-years	490 553	61 463	429 089
Incidence (95% CI)*	38.5 (36.8–40.3)	93.5 (86.2–101.5)	30.7 (29.0–32.4)
2005			
Population, n	1 008 929	121 781	887 148
Cases, n	2635	789	1846
Person-years	949 911	114 885	835 026
Incidence (95% CI)*	27.7 (26.7–28.8)	68.7 (64.0–73.6)	22.1(21.1–23.1)
2010			
Population, n	1 219 901	132 092	1 087 809
Cases, n	2211	592	1619
Person-years	1 135 809	122 635	1 013 174
Incidence (95% CI)*	19.5 (18.7–20.3)	48.3 (44.5–52.3)	16.0 (15.2–16.8)
2014			
Population, n	1 306 192	126 031	1 180 161
Cases, n	2050	499	1551
Person-years	1 182 588	114 760	1 067 828
Incidence (95% CI)*	17.3 (16.7–18.1)	43.5 (39.8–47.5)	14.5 (13.8–15.3)

*Incidence per 10 000 person–years.

CI, confidence interval; IHD, ischaemic heart disease.

Supplementary Table S3 Characteristics of patients with incident peripheral artery disease diagnosed in the years 2000, 2005, 2010, and 2014

Characteristic	Year 2000 (n=1891) n (%)	Year 2005 (n=2635) n (%)	Year 2010 (n=2211) n (%)	Year 2014 (n=2050) n (%)
Sex				
Male	1106 (58.5)	1542 (58.5)	1393 (63.0)	1267 (61.8)
Female	785 (41.5)	1093 (41.5)	818 (37.0)	783 (38.2)
Age, years				
50–59	260 (13.7)	412 (15.6)	368 (16.6)	361 (17.6)
60–69	537 (28.4)	762 (28.9)	708 (32.0)	636 (31.0)
70–79	745 (39.4)	950 (36.1)	688 (31.1)	631 (30.8)
80–89	349 (18.5)	511 (19.4)	447 (20.2)	422 (20.6)
Body mass index,* kg/m^2				
15–19	87 (5.8)	150 (6.5)	142 (6.8)	132 (6.7)
20–24	539 (36.1)	718 (31.0)	626 (30.2)	559 (28.5)
25–29	581 (38.9)	919 (39.7)	761 (36.7)	705 (35.9)
≥30	286 (19.2)	527 (22.8)	546 (26.3)	567 (28.9)
Smoking status*				
Current smoker	672 (39.5)	922 (35.4)	771 (35.0)	731 (35.7)
Former smoker	454 (26.7)	1095 (42.0)	1033 (46.8)	930 (45.4)
Never smoked	575 (33.8)	588 (22.6)	402 (18.2)	388 (18.9)
Alcohol use, units/week*				
None	310 (20.7)	490 (21.7)	403 (20.7)	344 (18.7)
1–4	799 (53.3)	1113 (49.2)	913 (46.8)	895 (48.7)
5–9	243 (16.2)	401 (17.7)	385 (19.7)	329 (17.9)
10–15	95 (6.3)	159 (7.0)	143 (7.3)	177 (9.6)
≥20	53 (3.5)	98 (4.3)	107 (5.5)	94 (5.1)
Number of prescription medications				
≤1	773 (40.9)	910 (34.5)	711 (32.2)	624 (30.4)

Characteristic	Year 2000 (n=1891) n (%)	Year 2005 (n=2635) n (%)	Year 2010 (n=2211) n (%)	Year 2014 (n=2050) n (%)
2–4	635 (33.6)	746 (28.3)	568 (25.7)	520 (25.4)
≥5	483 (25.5)	979 (37.2)	932 (42.2)	906 (44.2)
Comorbidities				
MI	261 (13.8)	375 (14.2)	281 (12.7)	262 (12.8)
IHD without MI	483 (25.5)	638 (24.1)	470 (21.3)	386 (18.8)
Heart failure	204 (10.8)	243 (9.2)	161 (7.3)	178 (8.7)
Atrial fibrillation	175 (9.3)	276 (10.5)	297 (13.4)	250 (12.2)
Ischaemic stroke	145 (7.7)	182 (6.9)	177 (8.0)	184 (9.0)
TIA	173 (9.1)	190 (7.2)	158 (7.1)	147 (7.2)
Diabetes mellitus	383 (20.3)	677 (25.7)	593 (26.8)	589 (28.7)
COPD	193 (10.2)	300 (11.4)	318 (14.4)	352 (17.2)
Asthma	237 (12.5)	400 (15.2)	422 (19.1)	424 (20.7)
Cancer	199 (10.5)	343 (13.0)	349 (15.8)	370 (18.0)
Depression	366 (19.4)	602 (22.8)	563 (25.5)	582 (28.4)
Dementia	256 (13.5)	439 (16.7)	464 (21.0)	495 (24.1)

*Excluding patients for whom this information was not known.

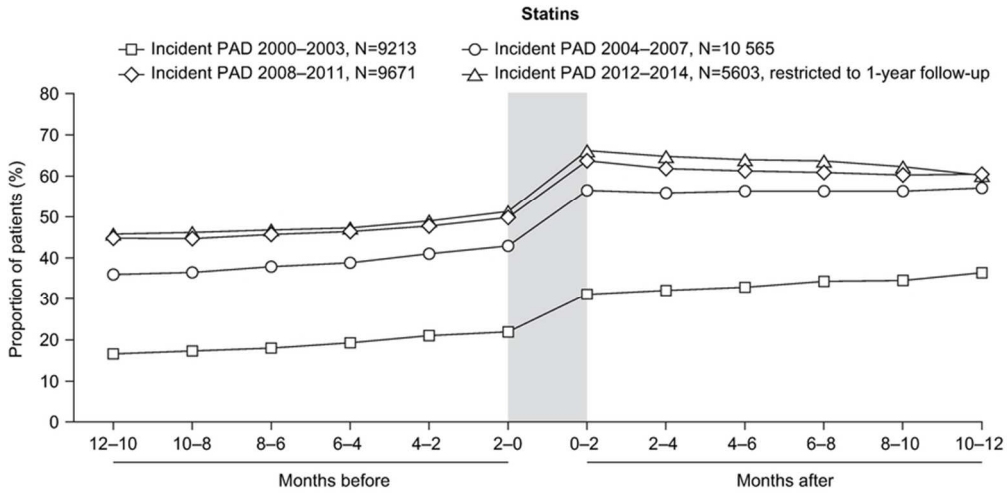
COPD, chronic obstructive pulmonary disease; IHD, ischaemic heart disease; MI, myocardial infarction; TIA, transient ischaemic attack.

Figure legend

Supplementary Figure S1 Time trends in the proportions of patients prescribed statin therapy in the 12 months before and 12 months after an incident diagnosis of PAD, with data for 2012–2014 restricted to primary care practices with at least 1 year of follow-up from the start date

Shaded area highlights the 2 months before and after the PAD diagnosis.

PAD, peripheral artery disease.



Supplementary Figure S1 Time trends in the proportions of patients prescribed statin therapy in the 12 months before and 12 months after an incident diagnosis of PAD, with data for 2012–2014 restricted to primary care practices with at least 1 year of follow-up from the start date
Shaded area highlights the 2 months before and after the PAD diagnosis.
PAD, peripheral artery disease.

78x38mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	*Page in manuscript*
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	*Pages 1 and 2*
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	*Page 2*
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	*Page 5*
Objectives	3	State specific objectives, including any prespecified hypotheses	*Page 5*
Methods			
Study design	4	Present key elements of study design early in the paper	*Pages 5–6*
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	*Pages 5–6*
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	*Pages 5–7*
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	*Not applicable*
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	*Pages 6–7*
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*Pages 6–7*
Bias	9	Describe any efforts to address potential sources of bias	*Not applicable*
Study size	10	Explain how the study size was arrived at	*Page 6*
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	*Page 7*
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	*Page 7*
		(*b*) Describe any methods used to examine subgroups and interactions	*Not applicable*
		(*c*) Explain how missing data were addressed	*Not applicable*
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	*Not applicable*
		(*e*) Describe any sensitivity analyses	

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	*Supplementary Table S3*
		(b) Give reasons for non-participation at each stage	*Not applicable*
		(c) Consider use of a flow diagram	*Not applicable*
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	*Supplementary Table S3*
		(b) Indicate number of participants with missing data for each variable of interest	*Footnote, Supplementary Table S3*
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	*Methods, Results*
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*Pages 7–9, Figures, Tables*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*Not applicable*
		Cross-sectional study—Report numbers of outcome events or summary measures	*Pages 7–9, Figures, Tables*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	*Supplementary Table S2*
		(*b*) Report category boundaries when continuous variables were categorized	*Not applicable*
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	*Not applicable*
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	*Not applicable*
Discussion			
Key results	18	Summarise key results with reference to study objectives	*Pages 9–11*
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	*Page 10*
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	*Pages 9–10*
Generalisability	21	Discuss the generalisability (external validity) of the study results	*Pages 9–10*
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	*Page 11*

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at

http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Time trends in peripheral artery disease incidence, prevalence, and secondary preventive therapy: a cohort study in The Health Improvement Network in the UK

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Time trends in peripheral artery disease incidence, prevalence, and secondary preventive therapy: a cohort study in The Health Improvement Network in the UK

Lucía Cea Soriano,[1,2] F Gerry R Fowkes,[3] Saga Johansson,[4] Alaster M Allum[5] and Luis A García Rodriguez[1]

[1]Pharmacoepidemiology, Spanish Centre for Pharmacoepidemiologic Research (CEIFE), Madrid, Spain

[2]Department of Preventive Medicine and Public Health, Faculty of Medicine, Complutense University of Madrid, Madrid, Spain

[3]Centre for Population Health Sciences, University of Edinburgh, Edinburgh, UK

[4]AstraZeneca Gothenburg, Mölndal, Sweden

[5]AstraZeneca Cambridge, Cambridge, UK

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Correspondence to: Dr Lucía Cea Soriano, Centro Español de Investigación Farmacoepidemiológica (CEIFE), c/ Almirante 28-2°, Madrid 28004, Spain.
E-mail: luciaceife@gmail.com; phone: +34 (91) 531 3404; fax: +34 (91) 531 2871.

ABSTRACT

Objectives: To assess time trends in symptomatic peripheral artery disease (PAD) incidence and prevalence, and secondary preventive therapy.

Design: Cohort study using The Health Improvement Network (THIN).

Setting: UK primary care.

Participants: Individuals aged 50–89 years, annually between 2000 and 2014. Participants with symptomatic PAD were identified using Read codes.

Outcome measures: Incidence and prevalence of symptomatic PAD from 2000 to 2014, overall and by sex and age. Proportion of patients prescribed secondary preventive therapy with acetylsalicylic acid (ASA), clopidogrel, an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin-receptor blocker (ARB), and/or a statin.

Results: The incidence of symptomatic PAD per 10 000 person-years decreased over time, from 38.6 (men: 51.0; women: 28.7) in 2000 to 17.3 (men: 23.1; women: 12.4) in 2014. The prevalence of symptomatic PAD decreased from 3.4% (men: 4.5%; women: 2.5%) in 2000 to 2.4% (men: 3.1%; women: 1.7%) in 2014. Incidence and prevalence decreases were observed in all age groups. The proportions of patients prescribed ASA monotherapy, clopidogrel monotherapy, and dual antiplatelet therapy in the 2 months after PAD diagnosis were 42.7%, 2.9%, and 2.5%, respectively, during 2000–2003, and 44.7%, 11.0%, and 5.2%, respectively, during 2012–2014. For ACE inhibitor/ARB therapy and statins, proportions in the 2 months after diagnosis were 30.2% and 31.2%, respectively, during 2000–2003, and 45.1% and 65.9%, respectively, during 2012–2014.

Conclusion: The incidence and prevalence of symptomatic PAD diagnosed in UK primary care are decreasing. A large proportion of the population with PAD in clinical practice does not receive guideline-recommended secondary prevention therapy.

Word count: 254 (limit 300)

Strengths and limitations of this study

- This is, to our knowledge, the largest study to date of time trends in PAD incidence and prevalence in the UK.
- Data are from electronic medical records in THIN, which has demonstrated validity for use in pharmacoepidemiological studies.
- Patients' anonymised medical records were reviewed manually to validate the selected diagnostic Read codes used to identify symptomatic PAD in a random sample.
- Potential limitations include possible changes over time in the source population and in how PAD is diagnosed in UK primary care, which would have affected the secular incidence and prevalence trend patterns.

INTRODUCTION

Peripheral artery disease (PAD) causes leg pain or discomfort, most commonly occurring on exertion and resolving after rest (intermittent claudication), although some individuals have no obvious symptoms even when functional impairment is noticeable on testing.[1] Individuals with PAD are at increased risk of myocardial infarction (MI), ischaemic stroke, and death.[2 3] To reduce the risk of cardiovascular (CV) events, US and European guidelines recommend antiplatelet therapy and statins for all individuals with symptomatic PAD, and antihypertensive therapy for those with concomitant hypertension.[4-7] Angiotensin-converting enzyme (ACE) inhibitors may also reduce CV risk in symptomatic patients with PAD.[4-7]

The key risk factors for PAD are similar to those for other CV diseases, and include smoking, increasing age, diabetes mellitus, hypertension, and dyslipidaemia.[8 9] In recent years, the prevalence patterns of PAD risk factors have been changing substantially. Smoking prevalence is decreasing,[10] but there is an increase in the prevalence of diabetes mellitus. Advances in treatment and in the implementation of processes of care have resulted in individuals with coronary heart disease and cerebrovascular disease now surviving to older ages, which is when PAD tends to manifest itself.

Whereas rates of MI and ischaemic stroke are declining in most countries,[11-13] secular incidence and prevalence trends for PAD are less clear. A recent meta-analysis reported an increase in the prevalence of PAD (assessed using the ankle–brachial index [ABI]) in high-income countries from 2000 to 2010.[9] The analysis included data from 10 high-income countries including the USA and four European countries, but not the UK. Age-standardised prevalence data for symptomatic PAD from the US State of Health report show only minimal changes (<0.2%) from 1990 to 2010.[14] The aim of the current study was to determine secular trends in the incidence and prevalence of symptomatic PAD and of secondary preventive therapy in a large, representative primary care population in the UK.

METHODS

Study design and data source

This was a retrospective observational cohort study. Data were collected from The Health Improvement Network (THIN) database in the UK. THIN is an electronic medical research database that contains fully anonymised data on approximately 11 million patients collected from participating primary care practices in the UK.[15] The data in THIN are from all patients in participating practices and are recorded during each consultation with the primary care

physician/nurse, leaving no scope for selective participation or reporting. Patients included in THIN are representative of the UK general population.[15] The Read classification is used to code specific diagnoses,[16] and a drug dictionary based on data from the Gemscript classification is used to code drugs.[17]

Study cohorts

Source population

Patients aged 50–89 years were identified in THIN, annually between 1 January 2000 and 31 December 2014. To be eligible for entry into the study, patients had to have been enrolled with their primary care physician for at least 2 years, to have visited their primary care physician at least once during that time, and to have a computerised prescription history for at least 2 years before study entry. These inclusion criteria helped to ensure that study participants were making use of healthcare services offered by their primary care practice and had historical information available.

Incident and prevalent symptomatic PAD

For each year during the follow up period, individuals with evidence of symptomatic PAD were identified by an automated database search using Read codes indicative of a symptomatic PAD diagnosis and/or related surgical procedures (supplementary table S1). For PAD incidence and secular trends, the date of the first entry of a PAD diagnosis in the THIN database was set as the index date. For prevalent PAD, each patient's start date was set as the date on which the study inclusion criteria (as listed above) were met.

The positive predictive value of the automated database search to identify patients with symptomatic PAD was assessed in a random validation sample of 400 of the identified patients. Patients' anonymised medical records, which included free-text comments from the primary care physicians, were reviewed manually. The diagnosis was confirmed in 97.0% of individuals (194/200) with incident PAD and in 99.0% of patients (198/200) with prevalent PAD, thereby confirming the positive predictive validity of the selected diagnostic Read codes used to identify symptomatic PAD.

Statistical analyses

Annual incidence and prevalence were determined for the years 2000–2014. The annual incidence was calculated by dividing the number of individuals with newly diagnosed PAD in a particular year by the contribution of all study participants at risk (free of PAD) in that year. To calculate the annual prevalence, the sum of the number of individuals with a history of PAD plus the number of individuals with newly diagnosed PAD in a particular year was divided by the total population meeting the study eligibility criteria. The time trends in the proportions of patients prescribed therapy with acetylsalicylic acid (ASA), clopidogrel, an ACE inhibitor, an angiotensin-receptor blocker (ARB), and/or a statin in the 12 months before and 12 months after an incident PAD diagnosis were also assessed.

Results

Time trends in incidence and prevalence

Time trends in the incidence and prevalence of PAD from 2000 to 2014, overall and separately by sex and age group, are shown in figure 1. The incidence of PAD decreased steadily over time, from 38.55 per 10 000 person-years in 2000 to 17.33 per 10 000 person-years in 2014 (figure 1a). The incidence was higher in men than in women: in 2000 it was 50.96 per 10 000 person-years in men and 28.70 per 10 000 person-years in women, and in 2014 it was 23.05 per 10 000 person-years and 12.37 per 10 000 person-years, respectively. Decreases in incidence over time were observed in all age groups (figure 1b).

The incidence of PAD was higher in patients with a history of ischaemic heart disease at the study start date than in those with no such history (supplementary table S2). The incidence of PAD decreased over time at a similar rate in patients with a history of ischaemic heart disease (from 93.5 per 10 000 person-years in 2000 to 43.5 per 10 000 person-years in 2014) and those without a history of ischaemic heart disease (from 30.7 per 10 000 person-years in 2000 to 14.5 per 10 000 person-years in 2014).

The overall decrease in incidence of PAD from 2000 to 2014 was paralleled by a decrease in prevalence of the disease (figure 1c). The prevalence of PAD decreased from 3.42% (men: 4.53%; women: 2.52%) in 2000 to 2.37% (men: 3.12%; women: 1.70%) in 2014. Decreases in prevalence over time were observed in all age groups (figure 1d).

Time trends in demographics and comorbidities

Noticeable changes over time among patients with incident PAD diagnosed in 2000, 2005, 2010, or 2014 included increases in the proportions of patients who were obese (body mass index ≥30 kg/m^2) and individuals who had prescriptions for five or more medications (supplementary table S3). 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).

Regarding comorbidity patterns, ischaemic heart disease prevalence without MI declined over time, with rates of 34.0%, 32.8%, 29.5%, and 26.4% in the years 2000, 2005, 2010, and 2014, respectively. However, increases in prevalence over time were observed for diagnoses of diabetes mellitus, chronic obstructive pulmonary disease, asthma, cancer, depression, and dementia. The age and sex distributions were similar over time.

Time trends in treatment patterns

Time trends in treatment patterns in the 12 months before and 12 months after an incident diagnosis of PAD are shown in figure 2. Prescription rates increased at the time of the incident PAD diagnosis. ASA monotherapy was the most commonly prescribed antiplatelet therapy during the study period. Prescription rates for antiplatelet therapy in the 2 months after diagnosis in the years 2000–2003, 2004–2007, 2008–2011, and 2012–2014 were 42.7%, 47.4%, 48.4%, and 44.7% for ASA, 2.9%, 4.6%, 4.7%, and 11.0% for clopidogrel, and 2.5%, 3.2%, 4.6%, and 5.2% for dual antiplatelet therapy, respectively.

For ACE inhibitor or ARB therapy, prescription rates in the 2 months after diagnosis in the years 2000–2003, 2004–2007, 2008–2011, and 2012–2014 were 30.2%, 41.9%, 46.5%, and 45.1%, and for statin therapy they were 31.2%, 56.5%, 63.6%, and 65.9%, respectively. The proportion of patients with a prescription for an ACE inhibitor or ARB remained relatively similar before PAD diagnosis compared with after diagnosis in the earlier three study periods, but decreased after diagnosis in the most recent (2012–2014) study period. The proportion of patients with a statin prescription increased after an incident PAD diagnosis. In the most recent study period it decreased again in the months after the diagnosis, although

this trend was less pronounced when the analysis was restricted to practices with at least 1 year of data collection after the start date in the 2012–2014 subgroup (supplementary figure S1), suggesting differences between practices in their end of year data collection rather than an actual decline in statin prescriptions.

Although the proportion of patients with prescriptions for all three therapies (an antiplatelet agent, plus an ACE inhibitor or ARB, plus a statin) in the 12 months before and 12 months after an incident diagnosis increased after 2000–2003 and also rose at PAD diagnosis, it remained below 30% at all times. Prescription rates for the three therapies combined in the 2 months after diagnosis in the years 2000–2003, 2004–2007, 2008–2011, and 2012–2014 were 9.7%, 22.6%, 27.3%, and 27.6%, respectively.

DISCUSSION

The results of this large observational study, conducted in 'real-life' clinical practice, showed a steady decline over time in the incidence and prevalence of symptomatic PAD in UK primary care. The incidence in patients with ischaemic heart disease was approximately three times higher than in those without ischaemic heart disease, but both groups showed similar rates of decline. Ischaemic heart disease prevalence declined over time, potentially underlying the parallel secular trend in PAD prevalence, and suggesting general improvements in overall CV health over time in the UK.

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 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.

Results of a recent meta-analysis indicated that the prevalence of PAD increased from 2000 to 2010 in high-income countries.[9] Data on temporal trends in PAD prevalence suggest that any observed prevalence increases over time may be due to an ageing population, with age-standardised prevalence data for symptomatic PAD reporting only minimal changes over time.[14] The current study, which included only patients aged 50 years or older, observed a symptomatic PAD prevalence that ranged from 3.42% in 2000 to 2.37% in 2014. These rates are similar to those reported in other population-based studies in the USA and Europe that include a minimum age cut-off. In both the US Life Line Screening programme (participants aged ≥40 years; study years 2003–2008)[18] and the Spanish HERMEX study (participants aged ≥50 years; study years: 2007–2009),[19] PAD prevalence was 3.7%. Slightly higher prevalences of 7.6% and 5.8%, respectively, were reported in a Spanish primary healthcare study (participants aged ≥50 years; study years 2006–2008)[20] and the German Heinz Nixdorf Recall study (participants aged ≥45 years; study years 2000–2003).[21]

There is a paucity of published data regarding the incidence of PAD.[8] Long-term results from a German study conducted in primary care (the 'getABI' study), which enrolled patients aged 65 years and older, found a PAD incidence of 203 per 10 000 person-years. In our study, a lower PAD incidence than in the German study was observed in the older age groups, ranging from approximately 30 per 10 000 person-years to 70 per 10 000 person-years (figure 1).

The reported incidence and prevalence across studies will depend on whether they are obtained using recorded diagnoses, as in the current study, or by assessing all study patients for PAD symptoms and signs (e.g. via the ABI). The latter approach will tend to result in higher observed incidence and prevalence. When assessing secular trends, it is essential to ensure that the methodology for identifying patients with PAD is similar across all time points, as was the case in the current study.

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.

Guidelines on the management of PAD were first published by the European Society of Cardiology (ESC) in August 2011[5] and by the UK National Institute of Health and Care

Excellence (NICE) in August 2012.[22] Both recommend antiplatelet therapy in all individuals with symptomatic PAD. Antiplatelet therapy for the prevention of vascular events has also been included in the NICE PAD management pathway. Additional recommendations from the ESC and NICE include smoking cessation, and management of diabetes mellitus, hypertension, and hyperlipidaemia.

Although the proportion of patients with PAD prescribed antiplatelet therapy increased over time in the current study, more than one-third of patients were not prescribed antiplatelet therapy with ASA, clopidogrel, or combination therapy following an incident PAD diagnosis between 2012 and 2014. The proportion of patients with incident PAD who were prescribed a statin increased to approximately 66% at the time of PAD diagnosis during 2012–2014. The proportion prescribed an ACE inhibitor or ARB decreased slightly after diagnosis in 2012–2014. Prescribing for secondary preventive therapies tended to be highest following PAD diagnosis.

Our study has several key strengths. It is, to our knowledge, the largest study to date of time trends in PAD incidence and prevalence in the UK. Data are from electronic medical records in THIN. Patients included in THIN are representative of the UK general population in terms of age, sex, and geographical location.[15] THIN has demonstrated validity for use in pharmacoepidemiological studies.[23] Patients' anonymised medical records, which included free-text comments from the primary care physicians, were reviewed manually to validate the selected diagnostic Read codes used to identify symptomatic PAD in a random sample. Potential limitations include possible changes over time in the source population and in how PAD is diagnosed in UK primary care, which would have affected the secular incidence and prevalence trend patterns. PAD data were not assessed by race because patients' race is not systematically captured in THIN.

In conclusion, results from this study suggest that the incidence and prevalence of symptomatic PAD are decreasing in the UK. 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.

Funding

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare the following. L Cea Soriano and LA García Rodriguez are employees of CEIFE, which has received research funding from AstraZeneca Gothenburg, Mölndal, Sweden and Bayer Pharma AG, Berlin, Germany; LA García Rodriguez has also received honoraria for serving on scientific advisory boards for AstraZeneca and Bayer. FGR Fowkes has received honoraria for serving on scientific advisory boards for AstraZeneca, Bayer, and Merck. S Johansson is an employee of AstraZeneca Gothenburg, Mölndal, Sweden. AM Allum is an employee of AstraZeneca Cambridge, Cambridge, UK.

Data sharing statement

All relevant source data are shown in the manuscript and supplementary files.

Exclusive licence

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Author contributions

Lucía Cea Soriano: conception and design of the work, data collection, data analysis, data interpretation, critical revision of the article, approval of final draft. F Gerry R Fowkes: data interpretation, critical revision of the article, approval of final draft. Saga Johansson: conception and design of the work, data interpretation, critical revision of the article, approval of final draft. Alaster M Allum: conception and design of the work, data interpretation, critical revision of the article, approval of final draft. Luis A García Rodriguez: conception and design of the work, data collection, data analysis, data interpretation, critical revision of the article, approval of final draft.

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Figure legends

Figure 1 Trends from 2000 to 2014 in peripheral artery disease: a) incidence, overall and according to sex; b) incidence according to age group; c) prevalence, overall and according to sex; d) prevalence according to age group.

Figure 2 Time trends in the proportions of patients prescribed a) acetylsalicylic acid monotherapy, b) clopidogrel monotherapy, c) dual antiplatelet therapy, d) an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker, e) a statin, or f) combined therapy with an antiplatelet, plus an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker, plus a statin in the 12 months before and 12 months after an incident diagnosis of PAD.

Shaded area highlights the 2 months before and 2 months after the PAD diagnosis.

PAD, peripheral artery disease.

Supplementary Figure S1 Time trends in the proportions of patients prescribed statin therapy in the 12 months before and 12 months after an incident diagnosis of PAD, with data for 2012–2014 restricted to primary care practices with at least 1 year of follow-up from the start date

Shaded area highlights the 2 months before and after the PAD diagnosis.

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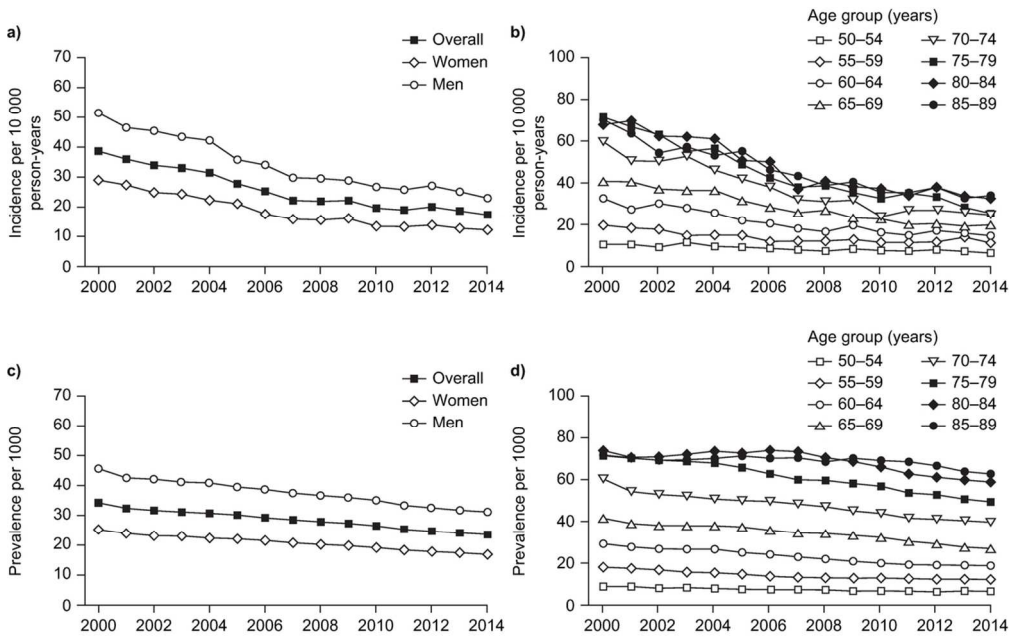

Figure 1 Trends from 2000 to 2014 in peripheral artery disease: a) incidence, overall and according to sex; b) incidence according to age group; c) prevalence, overall and according to sex; d) prevalence according to age group.

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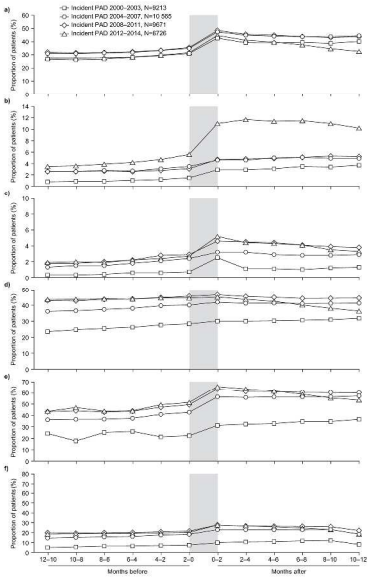

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Shaded area highlights the 2 months before and 2 months after the PAD diagnosis.
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355x279mm (300 x 300 DPI)

Time trends in peripheral artery disease incidence, prevalence, and secondary preventive therapy: a cohort study in The Health Improvement Network in the UK

Lucía Cea Soriano et al.

Supplementary materials

Supplementary Table S1 Read codes indicative of a symptomatic PAD diagnosis and/or related surgical procedures

Read code	Descriptor
G700.11	Aorto-iliac disease
G702.00	Extremity artery atheroma
G702z00	Extremity artery atheroma NOS
G73..11	Peripheral ischaemic vascular disease
G73..12	Ischaemia of legs
G73..13	Peripheral ischaemia
G730100	Raynaud's phenomenon
G731000	Buerger's disease
G731100	Presenile gangrene
G732.00	Peripheral gangrene
G732000	Gangrene of toe
G732100	Gangrene of foot
G733.00	Ischaemic foot
G734.00	Peripheral arterial disease
G73y.00	Other specified peripheral vascular disease
G73y000	Diabetic peripheral angiopathy
G73y100	Peripheral angiopathic disease EC NOS
G73yz00	Other specified peripheral vascular disease NOS
G73z.00	Peripheral vascular disease NOS
G73z000	Intermittent claudication
G73z011	Claudication
G73z012	Vascular claudication

G73z100	Spasm of peripheral artery
G73zz00	Peripheral vascular disease NOS
G74..00	Arterial embolism and thrombosis
G74..11	Arterial embolus and thrombosis
G74..12	Thrombosis – arterial
G74..13	Arterial embolic and thrombotic occlusion
G740.12	Aortoiliac obstruction
G740.13	Leriche's syndrome
G742400	Embolism and thrombosis of the femoral artery
G742500	Embolism and thrombosis of the popliteal artery
G742600	Embolism and thrombosis of the anterior tibial artery
G742700	Embolism and thrombosis of the dorsalis pedis artery
G742800	Embolism and thrombosis of the posterior tibial artery
G742900	Embolism and thrombosis of a leg artery NOS
G742B00	Post radiological embolism of lower limb artery
G742z00	Peripheral arterial embolism and thrombosis NOS
G74y000	Embolism and/or thrombosis of the common iliac artery
G74y100	Embolism and/or thrombosis of the internal iliac artery
G74y200	Embolism and/or thrombosis of the external iliac artery
G74y300	Embolism and thrombosis of the iliac artery unspecified
G74z.00	Arterial embolism and thrombosis NOS
G761.00	Stricture of artery
G765.00	Necrosis of artery
G76A.00	Arterial insufficiency
G76z.00	Disorders of arteries and arterioles NOS
G76z000	Iliac artery occlusion
G76z100	Femoral artery occlusion
G76z200	Popliteal artery occlusion
G7y..00	Other specified arterial, arteriole or capillary disease
G7z..00	Arterial, arteriole and capillary diseases NOS
14NB.00	H/O: Peripheral vascular disease procedure
2I16.00	O/E - gangrene
R054.00	[D]Gangrene

R054200	[D]Gangrene of toe in diabetic
R054300	[D]Widespread diabetic foot gangrene
8HlP.00	Referred for peripheral artery disease assessment

D, diagnosis; EC, elsewhere classified; H/O, history of; O/E, on examination; NOS, not otherwise specified; PAD, peripheral artery disease.

Supplementary Table S2 Trends from 2000 to 2014 in peripheral artery disease incidence, overall and according to history of IHD at baseline

Year	Overall	IHD	No IHD
2000			
Population, n	540 918	67 713	473 205
Cases, n	1891	575	1316
Person-years	490 553	61 463	429 089
Incidence (95% CI)*	38.5 (36.8–40.3)	93.5 (86.2–101.5)	30.7 (29.0–32.4)
2005			
Population, n	1 008 929	121 781	887 148
Cases, n	2635	789	1846
Person-years	949 911	114 885	835 026
Incidence (95% CI)*	27.7 (26.7–28.8)	68.7 (64.0–73.6)	22.1(21.1–23.1)
2010			
Population, n	1 219 901	132 092	1 087 809
Cases, n	2211	592	1619
Person-years	1 135 809	122 635	1 013 174
Incidence (95% CI)*	19.5 (18.7–20.3)	48.3 (44.5–52.3)	16.0 (15.2–16.8)
2014			
Population, n	1 306 192	126 031	1 180 161
Cases, n	2050	499	1551
Person-years	1 182 588	114 760	1 067 828
Incidence (95% CI)*	17.3 (16.7–18.1)	43.5 (39.8–47.5)	14.5 (13.8–15.3)

*Incidence per 10 000 person–years.

CI, confidence interval; IHD, ischaemic heart disease.

Supplementary Table S3 Characteristics of patients with incident peripheral artery disease diagnosed in the years 2000, 2005, 2010, and 2014

Characteristic	Year 2000 (n=1891) n (%)	Year 2005 (n=2635) n (%)	Year 2010 (n=2211) n (%)	Year 2014 (n=2050) n (%)
Sex				
Male	1106 (58.5)	1542 (58.5)	1393 (63.0)	1267 (61.8)
Female	785 (41.5)	1093 (41.5)	818 (37.0)	783 (38.2)
Age, years				
50–59	260 (13.7)	412 (15.6)	368 (16.6)	361 (17.6)
60–69	537 (28.4)	762 (28.9)	708 (32.0)	636 (31.0)
70–79	745 (39.4)	950 (36.1)	688 (31.1)	631 (30.8)
80–89	349 (18.5)	511 (19.4)	447 (20.2)	422 (20.6)
Body mass index,* kg/m^2				
15–19	87 (5.8)	150 (6.5)	142 (6.8)	132 (6.7)
20–24	539 (36.1)	718 (31.0)	626 (30.2)	559 (28.5)
25–29	581 (38.9)	919 (39.7)	761 (36.7)	705 (35.9)
≥30	286 (19.2)	527 (22.8)	546 (26.3)	567 (28.9)
Smoking status*				
Current smoker	672 (39.5)	922 (35.4)	771 (35.0)	731 (35.7)
Former smoker	454 (26.7)	1095 (42.0)	1033 (46.8)	930 (45.4)
Never smoked	575 (33.8)	588 (22.6)	402 (18.2)	388 (18.9)
Alcohol use, units/week*				
None	310 (20.7)	490 (21.7)	403 (20.7)	344 (18.7)
1–4	799 (53.3)	1113 (49.2)	913 (46.8)	895 (48.7)
5–9	243 (16.2)	401 (17.7)	385 (19.7)	329 (17.9)
10–15	95 (6.3)	159 (7.0)	143 (7.3)	177 (9.6)
≥20	53 (3.5)	98 (4.3)	107 (5.5)	94 (5.1)
Number of prescription medications				
≤1	773 (40.9)	910 (34.5)	711 (32.2)	624 (30.4)

Characteristic	Year 2000 (n=1891) n (%)	Year 2005 (n=2635) n (%)	Year 2010 (n=2211) n (%)	Year 2014 (n=2050) n (%)
2–4	635 (33.6)	746 (28.3)	568 (25.7)	520 (25.4)
≥5	483 (25.5)	979 (37.2)	932 (42.2)	906 (44.2)
Comorbidities				
MI	261 (13.8)	375 (14.2)	281 (12.7)	262 (12.8)
IHD without MI	483 (25.5)	638 (24.1)	470 (21.3)	386 (18.8)
Heart failure	204 (10.8)	243 (9.2)	161 (7.3)	178 (8.7)
Atrial fibrillation	175 (9.3)	276 (10.5)	297 (13.4)	250 (12.2)
Ischaemic stroke	145 (7.7)	182 (6.9)	177 (8.0)	184 (9.0)
TIA	173 (9.1)	190 (7.2)	158 (7.1)	147 (7.2)
Hyperlipidaemia	204 (10.8)	243 (9.2)	161 (7.3)	178 (8.7)
Diabetes mellitus	383 (20.3)	677 (25.7)	593 (26.8)	589 (28.7)
COPD	193 (10.2)	300 (11.4)	318 (14.4)	352 (17.2)
Asthma	237 (12.5)	400 (15.2)	422 (19.1)	424 (20.7)
Cancer	199 (10.5)	343 (13.0)	349 (15.8)	370 (18.0)
Depression	366 (19.4)	602 (22.8)	563 (25.5)	582 (28.4)
Dementia	256 (13.5)	439 (16.7)	464 (21.0)	495 (24.1)

*Excluding patients for whom this information was not known (overall, data on smoking status and alcohol use were missing for 2.6% and 14.1% of patients, respectively).

COPD, chronic obstructive pulmonary disease; IHD, ischaemic heart disease; MI, myocardial infarction; TIA, transient ischaemic attack.

Figure legend

Supplementary Figure S1 Time trends in the proportions of patients prescribed statin therapy in the 12 months before and 12 months after an incident diagnosis of PAD, with data for 2012–2014 restricted to primary care practices with at least 1 year of follow-up from the start date

Shaded area highlights the 2 months before and after the PAD diagnosis.

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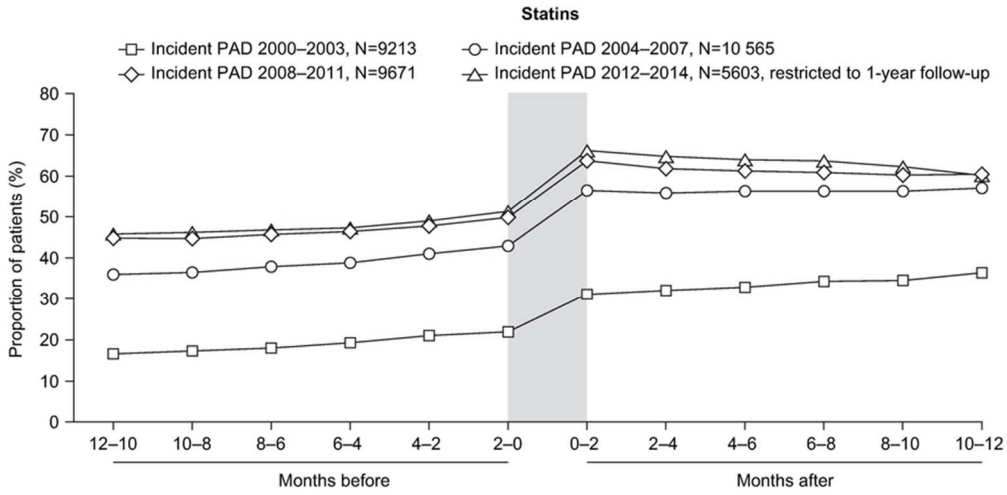

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78x38mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	*Page in manuscript*
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	*Pages 1 and 2*
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	*Page 2*
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	*Page 4*
Objectives	3	State specific objectives, including any prespecified hypotheses	*Page 4*
Methods			
Study design	4	Present key elements of study design early in the paper	*Pages 4–5*
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	*Pages 4–5*
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	*Pages 4–6*
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	*Not applicable*
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	*Pages 5–6*
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*Pages 5–6*
Bias	9	Describe any efforts to address potential sources of bias	*Not applicable*
Study size	10	Explain how the study size was arrived at	*Page 5*
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	*Page 6*
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	*Page 6*
		(*b*) Describe any methods used to examine subgroups and interactions	*Not applicable*
		(*c*) Explain how missing data were addressed	*Not applicable*
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	*Not applicable*
		(*e*) Describe any sensitivity analyses	

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	*Supplementary Table S3*
		(b) Give reasons for non-participation at each stage	*Not applicable*
		(c) Consider use of a flow diagram	*Not applicable*
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	*Supplementary Table S3*
		(b) Indicate number of participants with missing data for each variable of interest	*Footnote, Supplementary Table S3*
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	*Methods, Results*
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*Pages 6–8, Figures, Tables*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*Not applicable*
		Cross-sectional study—Report numbers of outcome events or summary measures	*Pages 6–8, Figures, Tables*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	*Supplementary Table S2*
		(*b*) Report category boundaries when continuous variables were categorized	*Not applicable*
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	*Not applicable*
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	*Not applicable*
Discussion			
Key results	18	Summarise key results with reference to study objectives	*Pages 8–10*
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	*Page 10*
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	*Pages 8–10*
Generalisability	21	Discuss the generalisability (external validity) of the study results	*Pages 8–10*
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	*Page 10–11*

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at

http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.