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Deposited on: 27 March 2018
Peripheral arterial disease in Scottish military veterans: a retrospective cohort study of 57,000 veterans and 173,000 matched non-veterans

Short running title: PAD in veterans

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Word count (main text) 2,949
ABSTRACT

Background

While traumatic limb loss in military personnel is widely known, the threat posed by peripheral arterial disease (PAD) in those who have served is less well recognised. The aim of our study was to examine the risk of PAD in a Scotland-wide cohort of veterans who served between 1960 and 2012.

Methods

Retrospective 30-year cohort study of 56,205 veterans born 1945-1985, and 172,741 non-veterans, matched for age, sex and area of residence, using Cox proportional hazard models to examine the association between veteran status, birth cohort, length of service and risk of PAD leading to hospitalisation or death.

Results

Overall, veterans were at increased risk of PAD compared with non-veterans, unadjusted hazard ratio (HR) 1.46, 95% confidence intervals (CI) 1.33-1.60, p<0.001. The highest risk was in veterans born between 1950 and 1954, HR 1.76, 95% CI 1.50-2.07, p<0.001, and in those with the shortest service (early service leavers), HR 1.84, 95% CI 1.49-2.27, p<0.001.

Conclusions

The findings provide evidence for a hidden burden of life- and limb-threatening PAD in older veterans and are consistent with the higher rates of military smoking which have been reported previously. The study emphasises the need for vascular preventive measures in this group.
KEYWORDS

Peripheral arterial disease

Military veterans

Risk factors

Tobacco smoking

Retrospective cohort studies
INTRODUCTION

During the recent conflicts in Iraq and Afghanistan, traumatic limb loss in military personnel has attracted much public interest and concern. Between 2001 and 2016, a total of 261 people who had sustained amputations in those conflicts were medically discharged from the UK armed forces and became veterans.[1] However, data from the USA suggest that amputations in veterans due to vascular disease ultimately greatly outweigh amputations resulting from battlefield trauma.[2]

Estimates of the prevalence of peripheral arterial disease (PAD) vary widely due to differences in case ascertainment and whether early, asymptomatic disease is included.[3] However, studies suggest it affects 4.3% of middle-aged Americans, rising to 14.5% over 70 years of age.[4] The global prevalence is increasing; by 28.7% in the decade to 2010 in low- and middle-income countries and by 13.1% over the same period in high-income countries.[5] Morbidity is common, ranging from intermittent claudication in less severe cases to rest pain, ulceration, gangrene and limb loss in those with critical limb ischaemia.[6] PAD is also associated with an increased risk of ischaemic heart disease, even if asymptomatic;[3] over half of those with PAD die from coronary artery disease, with a further 10% dying from cerebrovascular disease.

Smoking is the most important, preventable risk factor for PAD. Current and former smokers, and people exposed to secondhand smoke, are all at increased risk of developing PAD.[7, 8] Smoking cessation can improve symptoms, reduce case fatality and reduces the risk of disease progression and limb loss.[9, 10] There is good evidence that serving UK military personnel smoke more than civilians, and smoke more heavily.[11, 12] Data on smoking prevalence in UK veterans are lacking, but US studies have shown that veterans smoke more than people who have never served.[13] We have also shown that Scottish veterans are at increased risk of smoking-related conditions including cancer [14] and acute myocardial infarction.[15] Few studies have examined PAD in veterans, and those that have been conducted have generally focused on ethnicity, comorbidity or amputation.[2, 16, 17] This paper uses data from the Scottish Veterans Health Study to examine the risk of PAD in veterans born between 1945 and 1985, in comparison with people with no record of military service.
METHODS

The Scottish Veterans Health Study is a retrospective cohort study of all 56,570 military veterans resident in Scotland who were born between 1 January 1945 and 31 December 1985, and a comparison group of 172,753 individuals with no record of service matched 3:1 for age, sex and postcode sector of residence (mean population 5,000). Veterans were eligible for inclusion if they were registered with National Health Service (NHS) Scotland both pre- and post-service. The study cohort and methods have been fully described elsewhere.[15] Demographic data obtained from electronic NHS registration records were linked at an individual level to routine hospital admissions data (Scottish Morbidity Record SMR01) and death certificates to provide information on first recorded diagnosis of PAD, and all-cause death. Dates of entering and leaving the Service, for veterans, were obtained from the Scottish NHS registration record. The maximum period of follow-up was from 1 January 1981 (or date of leaving the Armed Forces, for veterans, if later) to 31 December 2012. Individual-level prescribing data were obtained from the NHS Prescribing Information System for a limited range of drugs including nicotine replacement therapy (NRT). As we had no data on lifestyle risk factors, we used NRT prescribing as a proxy measure for smoking.[15] The data extract was pseudo-anonymised and approval for the study was granted by the Privacy Advisory Committee of the Information Services Division of NHS Scotland. As this was a secondary data study, individual consent was not required.

Socio-economic status

A measure of socio-economic status (SES) is provided by the Scottish Index of Multiple Deprivation (SIMD), which is based on 6505 datazones, derived from postcode of residence, each having a mean population of 800. Deprivation status is calculated from information on income, employment, health, education (including skills and training), housing, crime, and access to services. The SIMD has been used to derive quintiles of SES for the Scottish population; ranging from 1 (most deprived) to 5 (least deprived).[18] The cohort participants were categorised according to these quintiles using postcode of residence.

Statistical methods
For the purposes of the study, a diagnosis of PAD was defined as ICD-10 I73-I79 or I702, or ICD-9 443.9 or 440.2, at any position in the record. As most cases of PAD are managed in the community, only the most severe cases, requiring in-patient treatment such as invasive investigation, revascularisation or amputation, are represented in the SMR01 record and the data do not represent overall prevalence in the community. The assumption was made that there was no systematic difference between veterans and non-veterans in the likelihood of admission other than the prevalence and severity of the disease, and that any differences found would reflect the relative magnitude of cases overall. Cox proportional hazard models were used to examine the association between veteran status and cumulative risk of PAD, using age as the time dependent variable, age at first record of PAD as the failure time, and death (if no PAD) as the censor time. As PAD is rare in young people, a landmark analysis was performed using age 40 years as the starting point. We also examined comorbidity with diabetes (coded as ICD-10 E10-E14 or ICD-9 250) where this was recorded on the in-patient or death record, and with severe stress or post-traumatic stress disorder (PTSD) (ICD-10 F43 or ICD-9 308 or 309). Hazard ratios and p values were calculated and the a priori rejection level was set at 0.05. Proportionality was tested using methodology based on Schoenfeld residuals. The models were run univariately and then repeated adjusting for the potential confounding effect of SES. The analyses were repeated stratifying by grouped year of birth in 5-year bands to examine birth cohort effects, and stratifying by length of service. All analyses were performed using Stata® v12.1.
RESULTS

After data cleansing to remove invalid or incomplete records, 56,205 (99.3%) veterans and 172,741 (99.9%) non-veterans were included in the analysis. Of the veterans included in the study, 5,235 (9.2%) were women, reflecting the gender balance of the Service population. The earliest date of entering service was January 1960 and the latest date of service was December 2012. The mean period of follow-up was 29.3 years, and there was a total of 6.7 million person-years of follow-up among veterans and non-veterans combined. PAD accounted for the hospitalisation or death of 696 (1.24%) veterans compared with 1,443 (0.84%) non-veterans. The difference was statistically highly significant in the Cox proportional hazard model (Figure 1), unadjusted HR 1.46, 95% CI 1.33-1.60, p<0.001 and HR 1.38, 95% CI 1.26-1.52, p<0.001 after adjusting for SES. Testing for non-proportionality of the hazards was non-significant, p=0.850.

PAD in veterans was more common in men than in women. There were 675 (1.32%) cases in male veterans compared with 1,347 (0.89%) in male non-veterans, and 21 (0.40%) in female veterans compared with 91 (0.46%) in non-veteran women (Table 1). The difference was statistically highly significant for men with the veterans at higher risk, unadjusted HR 1.47, 95% CI 1.34-1.64, p<0.001. The reduction in risk in female veterans was not statistically significant. The highest risk was in the 1950-1954 birth cohort but the increased risk persisted up to the 1960-1964 cohort, although it was not statistically significant in the latter (Table 1 and Figure 2). There was an increased risk for all lengths of military service except for 12 years’ and over, when it was similar to non-veterans, and the highest risk was in early service leavers (ESL) who left prior to completion of training. ESL born prior to 1960 were at especially high risk (Table 1).

Among people with a record of diabetes, 9.2% of veterans were recorded as having PAD, compared with 1.2% of the non-diabetic veteran population, whilst 6.9% of diabetic non-veterans were recorded with PAD compared with 0.8% overall. The increase in risk of comorbid PAD and diabetes in veterans compared with non-veterans was highly statistically significant, OR 1.33, 95% CI 1.13-1.58, p<0.001. Only 3.2% of veterans with PAD were
recorded as having PTSD, compared with 2.8% of non-veterans. The difference was not statistically significant, OR 1.15, 95% CI 0.67-1.99, p=0.607.

There were 179 deaths in veterans with a recorded diagnosis of PAD, equating to 25.9% of the cases, and 397 deaths (27.5%) in non-veterans. Mean survival from date of first record of PAD was 6.4 years in veterans and 6.0 years in non-veterans. The commonest cause of death in the veterans with PAD was ischaemic heart disease, representing 16.2% of the deaths, and in non-veterans it was lung cancer (15.1% of deaths). A further 5.6% of deaths in veterans and 3.3% in non-veterans were the result of stroke. Other notable causes of death, in both veterans and non-veterans, were oesophageal cancer (7.3% and 8.8% of the deaths respectively) and alcoholic liver disease (2.8% and 2.1% respectively). Despite the higher proportion of deaths, veterans with PAD were not at increased risk of comorbid alcoholic liver disease compared with non-veterans, OR 0.81, 95% CI 0.53-1.24, p=0.321, although they were at significantly increased risk of having a history of AMI, OR 1.22, 95% CI 1.05-1.43, p=0.011. Veterans with PAD were more likely to have received a prescription for nicotine replacement therapy although the difference did not achieve statistical significance, OR 1.16, 95% CI 0.98-1.37, p=0.091.
DISCUSSION

Main finding of this study

Analysis of data from the Scottish Veterans Health Study has shown that overall, veterans aged 40 years and over were at 46% increased risk of PAD compared with age-, sex- and geographically-matched people with no record of service. The increase in risk was only slightly attenuated after adjusting for SES. When analysed by birth cohort, the increase in risk was highest among veterans born between 1950 and 1954 although the risk was increased in all veterans born prior to 1965. Veterans with the shortest service, who left prior to completing the minimum military engagement (ESL), showed the greatest increase in risk, whilst veterans with over 12 years’ service were at no greater risk than people who had never served. Veterans had a non-significantly greater likelihood of having been prescribed NRT, suggesting that they were more likely to have been smokers.

Tobacco smoking is the most important risk factor for PAD, and these findings are therefore consistent with the well-documented higher rates of smoking in serving personnel in the period when the veterans who demonstrated the highest risk in this study were serving,[11, 12] with the increase in prevalence of both never-smoking and ex-smoking in longer-serving senior ranks, [21] and with our earlier findings of increased risk of lung cancer, COPD, and AMI in veterans, in which the greatest increase in risk was in those born prior to 1960 and in those with the shortest service.[14, 15, 22] The study therefore adds further weight to our earlier hypothesis that increased rates of military smoking, especially among earlier- and shorter-serving military personnel, have resulted in a substantial burden of cardiovascular disease in veterans. Military smoking prevalence is also significantly positively correlated with low educational attainment and with deprivation,[23] both of which are linked to premature termination of service.[24] Secondhand smoke, to which many military personnel including non-smokers were exposed prior to the introduction of controls on indoor smoking, is also associated with an increased risk of PAD.[25] However it is likely that more senior personnel, who do not live in multi-occupancy barrack-rooms, may have had less exposure to secondhand smoke in their accommodation,[26] further supporting the finding that their risk of PAD is lower.

What is already known on this topic
Compared to ischaemic heart disease and stroke, public awareness of PAD is low,[27] even among people with a high prevalence of risk factors,[28] Furthermore, many cases of PAD (diagnosed by ankle brachial pressure index (ABPI)) are asymptomatic; in a study in Edinburgh, Scotland, 4.6% of a sample of people aged 55 to 74 years had symptoms of claudication but 8.0% had grossly abnormal results on testing despite being asymptomatic, whilst a further 16.6% showed moderately abnormal results. There was evidence of ischaemic heart disease in 54% of the participants with major asymptomatic PAD.[3]

There is a paucity of studies on PAD in veterans, but those which have been conducted demonstrate a substantial burden of disease. A US study reported over 60,000 lower limb amputations in Veterans Health Administration facilities in the decade 1989-1998, constituting 10% of all US male amputations; the predominant causes were diabetes and peripheral vascular disease, the latter accounting for over 14,000 amputations. Rates were significantly higher than in the general US male population.[2] Traumatic lower limb amputation in more recent veterans as a result of conflict has received much public attention; amputation for vascular disease is likely to affect greater numbers of veterans in the longer term but is rarely mentioned. A study of 4,462 Vietnam veterans aged 31 to 46 years showed an association between PAD (measured by ABPI) and hostility (measured by Cook-Medley Hostility Scale), the prevalence of PAD ranging from 0.7% in the lowest quartile of hostility to 1.6% in the highest quartile, even in this young, healthy population. The increase in risk of PAD persisted after adjusting for smoking, family history and other risk factors,[29] Our finding that only around 3% of both veterans and non-veterans with PAD had comorbid PTSD indicates that although this was not a major risk factor in our study, the prevalence of anger in military personnel [30] suggests that the association with hostility may be a contributory factor.

There have been few studies examining the reasons for premature separation from service in UK veterans, but Buckman et al. demonstrated that ESL are significantly more likely than people with longer service to exhibit a history of childhood adversity, low educational attainment, high levels of common mental disorders and alcohol misuse,[24] all of which have been shown to be associated with an increased risk of peripheral arterial disease or of cardiovascular disease overall.[3, 31, 32, 33] Lodge has also shown that the prevalence of smoking in serving personnel reduces with higher rank, which is closely linked to length of
service,[21] providing further evidence to underpin the inverse association between length of service and risk of PAD.

What this study adds

We have shown that the burden of severe symptomatic PAD (resulting in secondary care admission or death) is substantially greater in older veterans than in non-veterans. We therefore conclude, based on the findings from a major population study in Scotland,[3] that there may be a similarly increased risk of a hidden burden of asymptomatic disease in veterans, with its associated risks of ischaemic heart disease, stroke and lower limb vascular compromise. The increased burden of severe symptomatic PAD which we have demonstrated indicates that healthcare providers caring for older veterans should be aware of their heightened risk, and should specifically enquire into risk factors and symptoms. Preventive measures aimed at minimising the risks of disease progression and complications encompass the general measures for cardiovascular prevention; smoking cessation, encouragement of physical activity, weight control, lipid management and blood pressure control,[34] and should be recommended for all veterans.

Limitations of this study

The major limitation of the study is that although the diagnoses were taken from hospital admission and death records, and are therefore likely to be reliable in respect of those events occurring within Scotland, only the most severe end of the spectrum of vascular disease has been captured. Similarly, the diagnoses of diabetes and stress/PTSD were based on in-patient and death records and are therefore inevitably incomplete. We have therefore made the assumption that the relative magnitude of severe disease in the veteran and non-veteran populations reflects the relative magnitude of total disease. Some loss to follow-up of subjects is likely to have occurred due to migration away from Scotland. Such losses could not be quantified and the assumption has been made that there was no systematic difference in this respect between veterans and non-veterans. There were no follow-up data prior to the start of linked health data collection in Scotland from 1 January 1981, although as the oldest veterans were only 36 years of age at that date and we used a landmark age of 40, this will not have affected our results. For those who are military veterans, we have not been able to link to in-service health or service records;
however as PAD is rare before middle age and most people have left military service by age 40 years, significant loss of relevant data is unlikely. We had no data on amputations and therefore we were unable to compare amputation rates in veterans and non-veterans. Because the dataset was derived from demographic, vital record and hospital admissions data, no information was available on personal lifestyle risk factors such as smoking which may have acted as confounders. Hence we were unable to directly analyse the impact of these factors or adjust for them, and there may therefore have been residual confounding. However it has been shown that a low ABPI, as an indicator of preclinical lower limb atherosclerosis, is associated with an increased risk of fatal and non-fatal cardiovascular disease which persists even after adjusting for lifestyle factors and comorbidities,[35,36] and therefore it is unlikely that adjusting for these factors would have changed our findings. We used NRT prescription as a proxy measure for smoking; although a novel measure, this has found utility in our earlier studies.[15,22] Veterans with Reserve service only could not be identified from NHS records and were therefore included amongst the non-veterans; this would have had the effect of reducing any observed differences between veterans and non-veterans.
Funding

No external funding.

Acknowledgements

We thank the NHS Central Registry (NHSCR) and the Information Services Division, NHS Scotland (ISD) for extracting and linking the dataset.

Declaration of Interest

The authors declare that they have no competing interests or relationships. BPB is a veteran and retired military medical officer.

Authors’ contributions

BPB conceived the idea and designed the study, with advice from JPP and DFM. BPB carried out the data analysis, which was overseen by DFM, and interpreted the findings. BPB wrote the first draft of the report, which was critically reviewed and edited by all authors. All authors approved the final article.

Data sharing

The Scottish Veterans Health Study remains in progress and the data are not currently available.
FIGURE LEGENDS

Fig. 1. Nelson-Aalen cumulative hazard plot of the risk of peripheral arterial disease by veteran status, landmark age 40 years

Fig. 2. Hazard ratios for peripheral arterial disease by birth cohort, veterans referent to non-veterans
REFERENCES


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HR hazard ratio; CI confidence interval
ESL Early Service Leavers – left before completing minimum engagement
*adjusted for Scottish Index of Multiple Deprivation
Intervals correspond to common terms of military engagement

**Table 1.** Cox proportional hazard model of the association between veteran status and risk of peripheral arterial disease, landmark age 40 years