A Prospective Evaluation of Modifiable Lifestyle Factors in Relation to Peripheral Artery Disease Risk

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WHAT THIS PAPER ADDS
There are limited data on the associations between modifiable lifestyle factors and peripheral artery disease risk in the healthy, community based population. This prospective cohort study found that individuals with healthy lifestyle factors, including avoidance of heavy alcohol consumption, a high adherence to a healthy diet, a moderate to high level of physical activity, and never smoking, had a 45% reduction in risk of symptomatic peripheral artery disease referred to secondary care compared with the remainder of the population. Approximately 40% of peripheral artery disease cases might be prevented if the population adopted these healthy lifestyle factors.

Objective: To examine the joint associations of multiple modifiable lifestyle factors with the risk of symptomatic peripheral artery disease (PAD) referred to secondary care in the healthy, community based population.

Methods: A prospective cohort study was conducted including 37 633 men from the Cohort of Swedish Men and 31 816 women from the Swedish Mammography Cohort who were free of clinically diagnosed PAD and 45 — 83 years of age at baseline. Healthy lifestyle factors were defined as avoidance of excessive alcohol consumption (≤2 drinks/day), high adherence to a healthy diet (modified Mediterranean diet score ≥4), moderate to high level of physical activity (≥30 minutes/day), and never smoking. PAD cases were ascertained by linkage with the Swedish National Patient Registry. Cox proportional hazards regression was used to analyse the data.

Results: During a mean of 18.1 years of follow up (from 1 January 1998 to 31 December 2019), 2 795 incident symptomatic PAD cases were ascertained. All healthy lifestyle factors were associated with a reduced PAD risk. Individuals who adhered to all four healthy lifestyle factors had a 45% (95% confidence interval [CI] 38 — 51) lower risk of PAD compared with the remainder of the population (0 — 3 healthy lifestyle factors) and a 71% (95% CI 61 — 79) lower risk of PAD compared with the group without any healthy lifestyle factor. Adherence to the combination of four healthy lifestyle factors was estimated to prevent 40% (95% CI 34 — 47) of PAD cases.

Conclusion: Healthy lifestyle factors were associated with a reduced risk of PAD.

Keywords: Cohort, Diet, Lifestyle, Peripheral artery disease, Population-attributable risk

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INTRODUCTION
Peripheral artery disease (PAD) is the third leading cause of atherosclerotic cardiovascular morbidity, and a larger burden of this disease is to be expected in the foreseeable future.1—4 Although the incidence of PAD has decreased slightly, which may in part be explained by reduced smoking prevalence,5,6 The presence of PAD leads to decreased quality of life and increased risk of limb loss, in additional to the subsequent risk of myocardial infarction, stroke and vascular dementia, as well as all cause and cardiovascular mortality.6—12

A cohort study of American men found that as many as 75% of PAD cases may be prevented if the population avoided four traditional cardiovascular risk factors, including smoking, hypertension, hypercholesterolaemia, and type 2 diabetes.12 Although the use of medications (e.g., antihypertensive and lipid and glucose lowering drugs), can be an important adjunct to attaining healthy cardiovascular profile, from the population wide perspective, identification of modifiable lifestyle factors is of the utmost importance for PAD prevention. In another study of 7 122 Spanish adults with existing cardiovascular disease
risk, it was estimated that four of five PAD cases could be prevented if the population adhered to the Mediterranean diet, consumed moderate amounts of alcohol, were physically active, and did not smoke.14 Yet, there are limited data available on the associations between modifiable lifestyle factors and PAD risk in the healthy, community based population.

A study was conducted to assess the association between the combination of four healthy lifestyle factors, including avoidance of excessive alcohol consumption, high adherence to a healthy diet, moderate to high level of physical activity, and avoidance of smoking, with PAD risk in two population based cohorts of Swedish adults.

**MATERIALS AND METHODS**

**Study design**

This was a prospective longitudinal cohort study with data from two Swedish cohort studies and nationwide Swedish registries. First, the associations between four individual modifiable lifestyle factors and PAD risk were explored, and then the combined effects of the four healthy lifestyle factors on this outcome were assessed. The population attributable risk was also calculated to estimate the proportion of PAD cases that could be prevented if the population adopted these healthy lifestyle factors.

**Study population**

The study population was from the National Research Infrastructure SIMPLER (Swedish Infrastructure for Medical Population based Life course Environmental Research), which includes the Cohort of Swedish Men (COSM) and the Swedish Mammography Cohort (SMC). In brief, the COSM invited all men who were born between the years 1914 and 1948 and residing in Västmanland or Örebro County, and 48 850 Swedish men (49% of the source population) aged 45 — 79 years responded in the late autumn of 1997. The SMC was initiated by inviting all women who were born between the years 1914 and 1948 and were living in Västmanland or Uppsala County in 1987 — 1990 to answer a questionnaire about diet and reproductive factors. Afterwards, SMC participants received an expanded questionnaire (similar to the questionnaire used in the COSM) in the autumn of 1997 and around 70% of the participants (39 227 Swedish women) aged 49 — 83 years were enrolled in the study. Recruited individuals were invited to complete a questionnaire on anthropometrics, education, lifestyle characteristics, and other potential risk factors for chronic diseases in the late autumn of 1997. The selected counties have similar economic status to other areas in Sweden and the cohorts represented the Swedish population in 1997 well concerning age distribution, educational level, prevalence of overweight and obesity, and smoking status.15 In the present study, participants were excluded with an incorrect or a missing personal identification number (n = 540), those with diagnosed cancer before 1 January 1998 (n = 4 383) as they may have changed their lifestyle, those who died before 1 January 1998 (n = 81), those with a prior clinical diagnosis of peripheral artery disease (n = 352), those with missing information on any of the four modifiable lifestyle factors (n = 12 968), and those with extreme energy intake (n = 304). After exclusions, 69 449 individuals (37 633 men and 31 816 women) remained for analysis as outlined in Figure 1. The study was approved by the Swedish Ethical Review Authority (Dnr: 2019-03986). All participants provided informed consent.

**Assessment of modifiable lifestyle factors**

Dietary information and alcohol consumption were collected by a validated and reproducible self administered semiquantitative food frequency questionnaire including questions on 96 commonly eaten foods and beverages.16,17

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**Figure 1.** Flow chart of the final study population of 69 449 participants from the Cohort of Swedish Men and from the Swedish Mammography Cohort free of clinically diagnosed peripheral artery disease (PAD) at baseline studied by number of healthy lifestyle factors.
The average intake frequency and serving size (the amount consumed for alcohol) were reported in the questionnaire. Intake of dietary fats was assessed by questions regarding type of fat used for dressing, cooking, and on sandwiches. A healthy diet was constructed, defined by a modified Mediterranean diet scale (m-MED score ranging from 0 to 7) by Trichopoulou and colleagues. One point was given if the intakes were above the median for a) fruit and vegetables; b) nuts and legumes; c) whole grains; d) fermented dairy products; and e) fish. Further, one point was given for f) intakes below the median of red and processed meat; and for g) use of olive or rapeseed oil for cooking. An m-MED score ≥ 4 indicated a high adherence to the Mediterranean diet pattern and was defined as a healthy diet. Alcohol consumption was measured by six alcoholic beverages, including light beer (alcohol by volume < 2.25%), beer (2.8% – 3.5%), strong beer (4.4% – 5.6%), wine (12% – 13.5%), fortified wine (15% – 22%), and liquor (40%). Avoidance of excessive alcohol consumption was defined as no more than two drinks per day, assuming that one standard drink contains 12 g of ethanol.

Smoking status and physical activity were considered as major modifiable non-dietary lifestyle factors. Individuals without past and current smoking were classified as never smokers. Participants reported their level of activity at work and home and during leisure time, including questions on time spent walking or bicycling (six pre-defined duration categories) and leisure time exercise (five pre-defined duration categories). The level of physical activity was considered to include both walking or bicycling and leisure time exercise and a moderate to high level of physical activity was defined as ≥ 30 minutes/day. Avoidance of excessive alcohol consumption, a high m-MED score, a moderate to high level of physical activity, and never smoking comprised the group with healthy lifestyle factors.

Assessment of covariables

Information on age (continuous in years), sex (men and women), body mass index (continuous in kg/m²), education attainment (≤ 9, 10 – 12, > 12 years), and baseline cardiovascular risk factors (hypertension, hypercholesterolemia, and diabetes mellitus, self-reported status yes or no) was solicited in the 1997 questionnaire. Total energy intake (continuous in kcal/day) was calculated based on reported food intake and energy content in age and sex specific serving sizes of each food in the 96 food item questionnaire.

Statistical analysis

Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated using a Cox proportional hazards regression model with age as the underlying time scale and sex as a stratum variable where applicable. The assumption of proportionality was examined using Schoenfeld residuals and was found to be satisfied. All associations were adjusted for body mass index, educational attainment, baseline cardiovascular risk factors (hypertension, hypercholesterolemia, and diabetes mellitus), and total energy intake. Additional models were mutually adjusted for healthy lifestyle factors. Given that smoking is a strong risk factor for PAD, the association between the combination of the other three lifestyle factors and PAD risk by smoking status was examined. Assuming causal associations of healthy lifestyle factors with PAD, the population attributable risk was estimated based on associations derived from analyses using the remainder of the population as the reference group, which indicates the percentage of cases that potentially could be prevented if people adhered to these healthy lifestyle factors, using this formula: \(p(HR - 1)/(1 + p(HR - 1))\), where \(p\) is the prevalence of exposure and HR was estimated using the remainder of the population as the reference group. Stratified analyses were conducted by body mass index status (healthy and unhealthy body mass index), sex, and health status (with or without baseline cardiovascular risk factors). Given that baseline PAD cases without symptoms or treatments (at the early stage of PAD) might not be captured by registry data, a sensitivity analysis was performed excluding individuals who developed incident PAD within the first four years from the baseline \((n = 95\) cases). All statistical tests were two sided, and the analyses were performed in Stata/SE (version 15.0; StataCorp, Texas, USA) and R software (version 4.0.2). An association with a \(p\) value < .050 was deemed as statistically significant.

RESULTS

During a mean of 18.1 years and 1 258 993 person years of follow up, PAD was diagnosed in 2 795 individuals (1 621 men and 1 174 women). The incidence rate was 2.2 (2.4 in men and 2.0 in women) per 1000 person years. The mean age at diagnosis was 76.4 ± 8.8 years (75.8 ± 8.8 years in men and 77.1 ± 8.7 years in women). The baseline characteristics by number of any healthy lifestyle factors are displayed in Table 1. Participants who adhered to all four

Ascertaining of cases and follow up

Cases were ascertained as incident clinical diagnosis of symptomatic PAD referred to secondary care (called PAD in the following text), identified by linkage of the cohorts to the Swedish National Patient Registry. Before 2001, the registry included only data from the inpatient registry but since 2001, the registry also covered outpatient data, such as day surgery from both private and public caregivers. This registry has over 99% complete coverage of hospital based inpatient and outpatient care. Diagnostic codes from the International Classification of Diseases (ICD-9 and ICD-10) and procedure codes from Nordic Medico-Statistical Committee Classification of Surgical Procedures were used to define cases (Supplementary Table S1). The PAD diagnosis in the Swedish hospital setting is based on medical history and vascular examination results including the ankle brachial index test. Participants were followed up from the baseline (1 January 1998) to the date of PAD diagnosis, the date of surgery, date of death, or end of follow up (i.e., 31 December 2019), whichever came first. Death information was derived from the Swedish Death Registry.
healthy lifestyle factors were more likely to be women and to have a higher educational attainment, a healthy body mass index (18.5 – 25.0 kg/m²), and no cardiovascular risk factors compared with participants without any healthy lifestyle factor. They were also more likely to have a high intake of healthy foods and a low intake of foods regarded as less healthy.

All studied modifiable healthy lifestyle factors were associated with a lower risk of PAD after adjustment for possible confounders (Fig. 1). The reduction in risk corresponded to 12% (95% CI 0 – 23) for avoidance of excessive alcohol consumption, 16% (95% CI 8 – 23) for high adherence to a healthy diet, 26% (95% CI 20 – 32) for being physically active and 54% (95% CI 51 – 58) for never smoking. The associations remained stable in the sensitivity analysis excluding individuals who developed incident PAD in four years after the baseline (Supplementary Table S2).

The associations between individual and combined healthy lifestyle factors were associated with a reduced risk of PAD in current smokers and possibly in past smokers, but not in never smokers (Supplementary Table S3). The population attributable risk of adopting all healthy lifestyle factors represented 16.8% of the study population. The associations persisted in the sensitivity analysis excluding individuals who developed incident PAD in the four years after the baseline (Supplementary Table S4). The population attributable risk of adopting all healthy lifestyle factors was 40% (95% CI 34 – 47), with never started smoking being the major contributing healthy lifestyle factor (Fig. 4).

The inverse association between the combined healthy lifestyle factors and risk of PAD remained consistent in the analysis stepwise adding lifestyle factors according to the magnitude of their association with PAD (from weakest to strongest association) (Fig. 3). Compared with the remainder of the study population, the risk of PAD was reduced by 12% (95% CI 0 – 23) for individuals with one healthy lifestyle factor (avoidance of excessive alcohol consumption) representing 92.4% of the study population and reduced by 45% (95% CI 38 – 51) for individuals with all healthy lifestyle factors representing 16.8% of the study population. The associations persisted in the sensitivity analysis excluding individuals who developed incident PAD in the four years after the baseline (Supplementary Table S5). The population attributable risk of adopting all healthy lifestyle factors was 40% (95% CI 34 – 47), with never started smoking being the major contributing healthy lifestyle factor (Fig. 4).

The associations between individual and combined healthy lifestyle factors and PAD were stratified by body mass index status, sex, and baseline health status (Fig. 5 and Supplementary Table S5). The associations were similar in individuals with or without healthy body mass index, in men or women, and in those with or without cardiovascular disease risk factors. An interaction was detected between smoking status and the combined score of three other lifestyle factors (p for interaction = .040). In the analysis stratified by smoking status, avoidance of excessive alcohol consumption, high adherence to a healthy diet, and high physical activity and the combination of three healthy lifestyle factors were associated with a reduced risk of PAD in current smokers and possibly in past smokers, but not in never smokers (Supplementary Table S6).

Table 1. Age standardised baseline characteristics of 69 449 participants by number of healthy lifestyle factors from the Cohort of Swedish Men and from the Swedish Mammography Cohort free of clinically diagnosed PAD at baseline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of any healthy lifestyle factors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (n=756)</td>
</tr>
<tr>
<td>Age – y</td>
<td>60.9±9.8</td>
</tr>
<tr>
<td>Male</td>
<td>390 (77.9)</td>
</tr>
<tr>
<td>Post-secondary education</td>
<td>119 (15.4)</td>
</tr>
<tr>
<td>Hypertension, hypercholesterolaemia, or diabetes</td>
<td>210 (28.5)</td>
</tr>
<tr>
<td>Healthy body mass index, 18.5–25.0 kg/m²</td>
<td>280 (36.3)</td>
</tr>
<tr>
<td>Avoidance of excessive alcohol, &lt;2 drinks/day</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Physical activity, &gt;30 min/d</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Never smoker</td>
<td>0 (0)</td>
</tr>
<tr>
<td>High adherence to m-MED diet</td>
<td>0 (0)</td>
</tr>
<tr>
<td>High intake of fruits and vegetables</td>
<td>145 (19.2)</td>
</tr>
<tr>
<td>High intake of nuts and legumes</td>
<td>228 (29.7)</td>
</tr>
<tr>
<td>High intake of whole grains</td>
<td>261 (34.6)</td>
</tr>
<tr>
<td>High intake of fermented dairy products</td>
<td>213 (28.2)</td>
</tr>
<tr>
<td>High intake of fish</td>
<td>281 (37.5)</td>
</tr>
<tr>
<td>Using olive or rapeseed oil in cooking</td>
<td>115 (14.9)</td>
</tr>
<tr>
<td>Low intake of red and processed meat</td>
<td>286 (37.8)</td>
</tr>
<tr>
<td>Energy intake = kcal/d</td>
<td>3 349±863</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean ± standard deviation. m-MED = modified Mediterranean diet; PAD = peripheral artery disease.
In two prospective cohorts comprising a total of 69,449 middle aged and older adults, it was found that individuals with healthy lifestyle factors, including avoidance of heavy alcohol consumption, a high adherence to a healthy diet, a moderate to high level of physical activity, and never smoking, had a 45% reduction in PAD risk compared with the remainder of the population and a 71% reduction in PAD risk compared with the group without any healthy lifestyle factor. The association was observed in men and women as well as in participants with and without hypertension, hypercholesterolemia, or diabetes. Approximately 40% of symptomatic PAD cases might be prevented if the population adopted these healthy lifestyle factors.

Associations between individual modifiable healthy lifestyle factors and risk of PAD have been investigated in several previous studies. No excessive alcohol consumption,14,24,25 a high adherence to a healthy diet,14 moderate to high level of physical activity,26 and never smoking,8,29 have previously been reported to be inversely associated with risk of prevalent and incident PAD, consistent with the present findings. With regard to the Mediterranean diet in relation to PAD, observational data are scarce and the results are conflicting with inverse14,26 and null findings.27 The present study found that individuals with high adherence to the Mediterranean diet had a lower PAD risk, confirming the results of the Prevención con Dieta Mediterránea randomised trial.28 Smoking has been established as one of the strongest risk factors for PAD and smoking cessation has been shown to improve various functional and physiological measures related to PAD, as well as reducing mortality in PAD patients.8,29 In a Mendelian randomisation study, genetic predisposition to smoking initiation exerted the strongest causal effect on PAD compared with 13 other cardiovascular endpoints.30 Likewise, another Mendelian randomisation study showed that among three common atherosclerotic cardiovascular diseases, genetically proxied lifetime exposure to cigarette smoking was associated with a significantly increased risk of PAD.31

### Figure 2

Hazard ratios (HR) of modifiable lifestyle factors association with peripheral artery disease (PAD) in 69,449 participants free of clinically diagnosed PAD at baseline. % indicates the percentage of cases in subgroup participants. All HRs were obtained from the model with mutual adjustment for modifiable lifestyle factors plus age, sex, body mass index, education level (< 9, 9 – 12, > 12 years), energy intake per day, self reported baseline cardiovascular risk factors (hypertension, hypercholesterolemia, or diabetes). CI = confidence interval.

<table>
<thead>
<tr>
<th>Exposure and group</th>
<th>No. of events (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 2 drinks/day (ref)</td>
<td>260 (4.90)</td>
<td>1.00</td>
</tr>
<tr>
<td>0–2 drinks/day</td>
<td>2 535 (3.95)</td>
<td>0.88 (0.77, 1.00)</td>
</tr>
<tr>
<td>Modified Mediterranean diet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low adherence (ref)</td>
<td>1 715 (4.43)</td>
<td>1.00</td>
</tr>
<tr>
<td>High adherence</td>
<td>1 080 (3.52)</td>
<td>0.84 (0.77, 0.91)</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30 min/day (ref)</td>
<td>820 (4.72)</td>
<td>1.00</td>
</tr>
<tr>
<td>≥ 30 min/day</td>
<td>1 975 (3.79)</td>
<td>0.74 (0.68, 0.80)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past or current smoker (ref)</td>
<td>1 884 (5.07)</td>
<td>1.00</td>
</tr>
<tr>
<td>Never-smoker</td>
<td>911 (2.82)</td>
<td>0.46 (0.42, 0.49)</td>
</tr>
</tbody>
</table>

### Figure 3

Hazard ratios (HR) of peripheral artery disease (PAD) in the group with any combined healthy lifestyle factors compared with the group without any healthy lifestyle factor in 69,449 participants free of clinically diagnosed PAD at baseline. % indicates the percentage of cases in subgroup participants. All HRs were adjusted for age, sex, body mass index, education level (< 9, 9 – 12, > 12 years), total daily energy intake, and self reported baseline cardiovascular risk factors (hypertension, hypercholesterolemia or diabetes). CI = confidence interval.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of events (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without healthy lifestyle factors (ref)</td>
<td>48 (6.35)</td>
<td>1.00</td>
</tr>
<tr>
<td>Any 1 healthy lifestyle factor</td>
<td>499 (6.17)</td>
<td>0.91 (0.68, 1.23)</td>
</tr>
<tr>
<td>Any 2 healthy lifestyle factors</td>
<td>1 056 (4.66)</td>
<td>0.60 (0.45, 0.80)</td>
</tr>
<tr>
<td>Any 3 healthy lifestyle factors</td>
<td>878 (3.38)</td>
<td>0.39 (0.29, 0.53)</td>
</tr>
<tr>
<td>All 4 healthy lifestyle factors</td>
<td>314 (2.62)</td>
<td>0.29 (0.21, 0.39)</td>
</tr>
<tr>
<td>Additional one healthy lifestyle factor</td>
<td></td>
<td>0.68 (0.65, 0.71)</td>
</tr>
</tbody>
</table>
smoking had the strongest impact on PAD.31 The present cohort study confirmed the important role of smoking in the development of PAD and further observed that the population attributable risk due to past and current smoking contributed the greatest share of all studied modifiable lifestyle factors.

The association between a combined score of modifiable lifestyle factors and incident PAD has been examined in 7122 Spanish participants.14 The study supported a protective role of the combined healthy lifestyle factors in PAD prevention even though it had inadequate power in the analysis for the Mediterranean diet. The study was conducted in a high risk population with type 2 diabetes or at least three other risk factors (i.e., smoking, hypertension, hyperlipidaemia, overweight or obesity, and a family history of premature coronary heart disease).14 Thus, whether these findings could be generalised to overall healthy community based populations remained unestablished.

The present study not only confirms previous findings, but also provides new findings on the current knowledge. For example, there were limited data on the associations between other major lifestyle factors and PAD risk in smokers and non-smokers. In the present study, it was observed that promoting the other three healthy lifestyle factors (i.e., avoiding excessive alcohol consumption, adhering to a Mediterranean diet, and being physically active) generated more benefits in the prevention of PAD among current and past smokers who have a substantially higher incidence of PAD compared with never smokers. In addition, there was no study assessing the protective role of the combined healthy lifestyle factors.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of events (%)</th>
<th>HR (95% CI)</th>
<th>PAR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 healthy lifestyle factor</td>
<td>2535 (3.95)</td>
<td>0.88 (0.77, 1.00)</td>
<td>1 (0, 2)</td>
</tr>
<tr>
<td>2 healthy lifestyle factors</td>
<td>989 (3.47)</td>
<td>0.84 (0.78, 0.91)</td>
<td>10 (6, 15)</td>
</tr>
<tr>
<td>3 healthy lifestyle factors</td>
<td>766 (3.34)</td>
<td>0.77 (0.71, 0.84)</td>
<td>17 (11, 22)</td>
</tr>
<tr>
<td>4 healthy lifestyle factors</td>
<td>314 (2.62)</td>
<td>0.55 (0.49, 0.62)</td>
<td>40 (34, 47)</td>
</tr>
</tbody>
</table>

Figure 4. Hazard ratios (HR) of peripheral artery disease (PAD) in the group with combined healthy lifestyle factors compared with the remainder of the population among 69,449 participants free of clinically diagnosed PAD at baseline and the population attributable risk (PAR) estimates for the proportion of PAD cases that could be prevented if the population adopted the healthy lifestyle factors. % indicates the percentage of cases in subgroup participants. One healthy lifestyle factor includes avoidance of heavy alcohol consumption. Two healthy lifestyle factors include avoidance of heavy alcohol consumption and high adherence to modified Mediterranean diet. Three healthy lifestyle factors include avoidance of heavy alcohol consumption, high adherence to modified Mediterranean diet, and moderate to high physical activity. Four healthy lifestyle factors include avoidance of heavy alcohol consumption, high adherence to modified Mediterranean diet, moderate to high physical activity, and never smoking. All HRs were adjusted for age, sex, body mass index, education level (< 9, 10 – 12, > 12 years), total daily energy intake, self reported baseline cardiovascular risk factors (hypertension, hypercholesterolaemia, or diabetes) and healthy lifestyle factors which were not included in the combined healthy lifestyle factors. The reference groups were the remainder of the total study population, presenting 7.6%, 60.4%, 68.0%, and 83.2%, respectively, for each additional healthy lifestyle factor. CI = confidence interval.

<table>
<thead>
<tr>
<th>Stratification factor</th>
<th>No. of events (%)</th>
<th>HR (95% CI)</th>
<th>PAR (95% CI)</th>
</tr>
</thead>
</table>

Figure 5. Associations between combined healthy lifestyle factors and risk of peripheral artery disease (PAD) by body mass index (BMI) status, sex and baseline cardiovascular risk factor among 69,449 participants free of clinically diagnosed PAD at baseline and the population attributable risk (PAR) estimates for the proportion of PAD cases that could be prevented if the population adopted the healthy lifestyle factors. % indicates the percentage of cases in subgroup participants. Healthy lifestyle factors include avoidance of heavy alcohol consumption, high adherence to modified Mediterranean diet, and high physical activity in the analyses stratified by smoking status. Healthy lifestyle factors include all above factors plus never smoking in the analyses stratified by sex and health status. All hazard ratios (HRs) were adjusted for age, sex, BMI, educational level (< 9, 10 – 12, > 12 years), total daily energy intake, and self reported baseline cardiovascular risk factors (hypertension, hypercholesterolaemia, or diabetes) where applicable. The reference groups were the remainder of the subgroups stratified by BMI status, sex, and health status, presenting 80.0% for healthy BMI, 85% for unhealthy BMI, 87.1% for male, 77.6% for female, 82.0% for healthy and 86.0% for with baseline comorbid conditions. CI = confidence interval.
lifestyle factors in PAD prevention in an overall healthy community based population. Based on data from two large cohorts of participants from the general population, the present study strengthens the evidence of inverse associations between individual and combined healthy lifestyle factors and symptomatic PAD, and suggests that these associations might be applicable to both men and women as well as both populations at high and low cardiovascular risk.

Although four major lifestyle factors were identified for PAD prevention in this study, it may be difficult to maintain all four healthy lifestyle factors in the long term or to change current unhealthy lifestyle patterns to healthy ones to lower PAD risk, particularly for individuals without any of the healthy lifestyle factors. For both vascular specialists and patients, to increase adherence, it may help to make a sustainable PAD prevention strategy that improves lifestyle factors step by step and focuses on the major risk factor, such as smoking. In addition, it is vital to increase the patient’s awareness of the role of healthy lifestyle practices in PAD development.

There are strengths to the present study. It was a prospective cohort study with objective outcome data derived from registries. Thus, the recall bias related to outcome and differential loss to follow up were minimised. In addition, a large sample size along with a large number of cases ensured high statistical power to detect weak associations.

Several limitations need to be considered. Information on the exposure and covariables was collected by a self administrated questionnaire where measurement error might lead to misclassification of the exposures and covariables. Some individuals might have changed lifestyle behaviours during the follow up, which might also introduce misclassification of the exposures. Nevertheless, due to the prospective design, this misclassification is most likely non-differential with respect to the studied outcome (all included participants were free of PAD when completing the questionnaire) and would be expected to lead to attenuated associations. PAD cases were defined based on ICD codes and procedure codes with data from the Swedish Patient Registry. Even though the diagnosis of PAD in registry data has not been validated, the positive predictive values for inpatient registry diagnoses were generally high for most outcomes and the sensitivity was high for most surgical procedures. Given that most cases in this study were diagnosed by both ICD codes and surgical procedures, the specificity of case definition is probably high and should not be an issue. However, this study included PAD patients who required treatment and hospitalisation. Thus, the individuals with PAD at asymptomatic stages and symptomatic stages that were not treated invasively were not captured as cases in this study, which might introduce some outcome misclassifications. However, this bias was likely to be non-differential and therefore attenuated the associations. In addition, whether the clinical presentation of PAD captured, for example, intermittent claudication and chronic limb threatening ischaemia, in this study was unclear. More than 10% of individuals were excluded due to missing information on any of the four lifestyle factors. These exclusions might have introduced bias if individuals with few reported healthy lifestyle factors were less likely to respond to certain questions due to social stigmata or other reasons. If so, the study sample may not represent the population intended to be analysed (not a random sample) and this may influence the external validity of the findings. However, if the data were missed at random, this proportion of missing data generated no bias but reduced the power of the analysis. The present study had an observational design that could not infer the causality of the associations as residual confounding could not be ruled out. For example, there are limited data on medications for patients with other cardiovascular diseases at baseline and thus corresponding residual confounding might have affected the results. However, in the multivariable models, adjustments were made for baseline cardiovascular risk factors, including hypertension, hypercholesterolaemia, and diabetes mellitus, which should have strong correlations with cardiovascular issue related medications. The stratification analysis by health status did not detect any differences in the associations between modifiable lifestyle factors and PAD risk between individuals with and without baseline cardiovascular risk factor. All these may convey that confounding from medication use should be minimal. In addition, the present findings were based on two cohorts of middle aged and older (45 — 83 years) individuals of European descent. As Sweden treats the highest proportion of octogenarians for PAD among 11 Western countries, whether these associations could be generalised to young and middle aged populations needs further investigation. Similarly, interpretation of the findings in other ethnic groups should be cautious. Finally, the information on diet and lifestyle factors was assessed in the middle age of the population. More research is warranted to examine the effects of earlier exposure of healthy lifestyle factors on subsequent PAD risk.

In summary, the present study indicates that modifiable lifestyle factors play important roles in the prevention of PAD in both men and women. A healthy diet together with healthy lifestyle behaviours may prevent 40% of symptomatic PAD cases in the community based population. Avoidance of excessive alcohol consumption, high adherence to a healthy diet, and high physical activity were particularly beneficial in the prevention of PAD among current and past smokers who have a substantially increased risk of PAD.

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AUTHOR CONTRIBUTIONS
S.Y., S.M.D, A.Å., and S.C.L. conceived and designed the study. S.Y. undertook the statistical analyses and wrote the first draft of the manuscript. S.Y., S.M.D., N.H., A.Å., and S.C.L. provided important comments to the manuscript.

DATA SHARING
De-identified SIMPLER data are available for researchers upon application (http://www.simpler4health.se/).

CONFLICT OF INTEREST
None.

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APPENDIX A. SUPPLEMENTARY DATA
Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2022.04.004.

REFERENCES
A Rare Finding of Thrombosed Bilateral Giant External Iliac Vein Aneurysms

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A 70 year old man presented with severe left lower limb oedema and pain. He had a history of bilateral deep vein thrombosis 20 years ago. (A) Computed tomography phlebography revealed previously unknown bilateral thrombosed external iliac vein aneurysms (arrows), 45 mm and 63 mm on the right and left, respectively. The thrombus extended to both femoral veins being occlusive on the left side. (B) Transpopliteal catheter directed thrombolysis was performed on the symptomatic left side. Although venous aneurysm recanalisation was not achieved, the patient improved due to femoral vein and venous collateral blood clot lysis (arrowheads).