Original article

Anti-inflammatory diet and incident peripheral artery disease: Two prospective cohort studies

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S U M M A R Y
Background & aims: Systemic inflammation plays a role in peripheral artery disease (PAD), and therefore, an anti-inflammatory diet may reduce PAD risk. We examined the association between the anti-inflammatory diet and PAD risk by smoking status, a trigger of systemic inflammation.

Methods: The study was based on two cohorts of 82 295 Swedish adults aged 45–83 years (38 823 women from Swedish Mammography Cohort and 45 472 men from Cohort of Swedish Men). An anti-inflammatory diet index (AIDI; 0–17 scores) was used to estimate the anti-inflammatory potential of diet. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs).

Results: Over a median 22-year (interquartile range 7.5 years) follow-up period, 3413 PAD cases were ascertained. Compared with individuals in the lowest quartile of the AIDI (score ≤4), the HR of PAD for those in the highest quartile (score ≥8) was 0.84 (95% CI, 0.74–0.94). The inverse association was observed in current and past smokers but not in never smokers. The HR of PAD comparing extreme quartiles of the AIDI was 0.67 (95% CI, 0.53–0.86) in current smoker, 0.78 (95% CI, 0.63–0.97) in past smoker, and 1.00 (95% CI, 0.82–1.23) in never smokers. Among foods included in AIDI, high consumption of breakfast cereals, chocolate, red wine, and olive/canola oil, and low consumption of processed red meat and organ meats were associated with lower PAD risk.

Conclusions: The study suggests that adherence to a diet with high anti-inflammatory potential may lower PAD risk, especially in smokers.

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1. Introduction

Peripheral artery disease (PAD) contributes to significant worldwide morbidity, especially among the elderly [1]. Systemic inflammation has been revealed to facilitate and interact with atherosclerosis and thrombogenesis and to promote the development of PAD [2,3]. Certain dietary patterns (e.g., the Mediterranean diet [4]), food groups (e.g., fruits and vegetables [5]), and flavonoids [6] with anti-inflammatory potential have been associated with a decreased risk of PAD. However, whether a diet with a high anti-inflammatory potential is related to risk of PAD is unknown. A clear appraisal of this association can not only deepen the understanding of the role of diet in etiology of PAD, but also provide hints for the primary prevention of the disease.

A questionnaire-based anti-inflammatory diet index (AIDI) was developed to predict low-grade systemic chronic inflammation and the index showed robust associations with high-sensitivity C-reactive protein levels in 3503 Swedish women and subgroups defined by inflammatory-related factors [7]. Previous studies found that AIDI was associated with heart failure, abdominal aortic aneurysm, venous thromboembolism, and cardiovascular mortality [8–11], which is in line with findings from studies on dietary anti-

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inflammatory potentials assessed by other tools [12,13]. Here, we conducted a prospective analysis to assess the associations of AIDI [7] with risk of incident PAD using data from two population-based cohorts. The associations were examined by smoking status as smoking is a strong trigger of systemic inflammation and an important risk factor for this disease [14]. We also investigated the associations of individual food groups included in AIDI with PAD risk.

2. Methods

2.1. Study population

The study included participants from two Swedish population-based cohorts, that are, the Swedish Mammography Cohort (SMC) and the Cohort of Swedish Men (COSM), belonging to the national research infrastructure SIMPLER (www.simpler4health.se). The SMC was created in 1987–1990 when all women (n = 90 303) born in 1914–1949 and living in Västmanland and Uppland counties were invited to participate in a mammography screening programme. In the fall of 1997, a second extended questionnaire was sent to all SMC participants who were still alive and residing in the study area (n = 56 030). The COSM was established in the fall of 1997 when all men born 1918–1952 who were residing in Västmanland and Örebro counties were invited to participate in the study (n = 100 303). In 1997, 48 850 men (49% of those eligible from COSM) and 39 227 women (70% of those eligible from SMC) completed a questionnaire about diet and other lifestyle factors. With the exception of some sex-specific questions, the questionnaires were identical for both cohorts. Participants of these two cohorts well represented the Swedish population in 1997 concerning age distribution, educational level, prevalence of overweight and obesity, and smoking status [15]. Individuals with an incorrect or a missing personal identifier, previous cancer, previous peripheral artery disease, extreme energy intake, or who died before the start of follow-up (January 1, 1998) were excluded (Supplementary Fig. 1). The final study population included 82 295 participants. The study has been approved by the Swedish Ethical Review Authority (Dnr: 2019–03986). All participants have provided their informed consent.

2.2. Assessment of anti-inflammatory diet

Dietary intake over the previous year was measured by a validated 96-item food frequency questionnaire at baseline in 1997. Participants were asked to report the frequency, on average, of consuming each item by using eight predefined frequency categories, ranging from “never” to “≥3 times per day”. Missing on intake frequency was treated as no consumption. An empirically developed AIDI that has been validated in a subgroup of the SMC (3503 women) was used to assess anti-inflammatory dietary potential [7]. The AIDI was based on frequency of consumption of 17 foods, including 12 foods with anti-inflammatory potential and five foods with pro-inflammatory potential. The 12 foods with anti-inflammatory potential were: sum of total fruits and vegetables (cut-off for getting 1 AIDI score ≥6 servings/day); tea (≥3 servings/day); coffee (≥2 servings/day); wholegrain foods (≥2 servings/day); breakfast cereals (≥1 servings/day); low-fat cheese (≥1 servings/day); olive oil and canola oil (≥0 servings/day); chocolate (≥1 servings/day); nuts (≥2 servings/week); legumes (≥2 servings/week); red wine (2–7 servings/week); and beer (2–14 servings/week). The five foods with pro-inflammatory potential were: unprocessed red meat (≤0.5 servings/day); processed red meat (≤0.5 servings/day); organ meats (0 servings/day); potato chips (0 servings/day); and soft-drink beverages (0 servings/day) [7]. Consumption of each food was scored as 1 when the cut-off criteria were met otherwise as 0. The AIDI score ranged from 0 to 17, where 0 indicates a diet with the lowest anti-inflammatory potential and 17 indicates a diet with the highest anti-inflammatory potential.

2.3. Ascertainment of cases and follow-up

Incident cases of PAD were defined by the clinical diagnosis based on codes from the 9th and 10th International Classification of Disease revision (Supplementary Table 1) with information identified by linkage of the cohorts to the Swedish Patient Register. The register has over 99% complete coverage of hospital-based inpatient and outpatient care [16]. Individuals were followed up from January 1, 1998 until the date of diagnosis of PAD, 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.

2.4. Assessment of covariables

Information on age, sex, body mass index, highest education attainment, smoking status, walking/cycling, leisure exercise, and dietary supplement use was reported in the 1997 questionnaire. Body mass index was calculated by body weight in kilogram divided by square of standing height in meter. Four categories, including primary school, high school, university and above, and unknown, were defined for highest education attainment. Smoking status was defined by information on current smoking status (never, current, and stopped) and smoking history, including years of smoking history and number of cigarettes smoked per day if stopped. We used combined time of walking/cycling and leisure exercise per day as an indicator for physical activity. Total energy intake was calculated by multiplying the frequency of consumption of each food by the energy content of age- and sex-specific serving sizes and summed up for all foods. Individual with missing data on body mass index, highest education attainment, smoking status, physical activity, or dietary supplement use were grouped as an individual group named missing. Missing was low for all these variables (<5%) except for physical activity (8.9%).

2.5. Statistical analysis

The AIDI score was divided into sex-specific quartiles. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) of PAD in groups defined by the quartiles of AIDI score or the quartiles of consumption for each food. The models treated age as the underlying time scale and sex as a strata variable. In addition to age and sex, the multivariable-adjusted models were adjusted for body mass index (≤18.5, 18.6–24.9, 25–29.9, ≥30 kg/m²), education attainment (<9, 9 to 12, >12 years), smoking status (never smoker, past smoker with <20, 20–40 and > 40 packs per year, and current smoker with <20, 20–40 and > 40 packs per year), physical activity (0–10, 11–30 and > 30 min per day), dietary supplement use (no use, irregular use and regular use) and total energy intake (kcal per day, continuous). Given that smoking is related to systemic inflammation [17,18], we examined the interaction between AIDI and smoking status first (by adding the interaction term of AIDI and smoking in the model) and we then performed the stratification analyses by smoking status (never, past, and current smokers). To rule out competing risk of death, we performed a competing risk analysis treating PAD diagnosis as the main outcome and death without PAD diagnosis as the competing outcome. We calculated the cumulative incidences by number of cases divided by person-years between quartiles as an indicator for absolute risk. The assumption of proportionality was examined using Schoenhed
residuals and found to be satisfied. 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). A p value below 0.05 was regarded as statistically significant.

3. Results

The median time of follow-up was 22 years (interquartile range 7.5 years, 1 474 822 person-years) and during this period 3413 PAD cases were ascertained. The incidence rate was 2.3 per 1000 person-years and the mean age at diagnosis was 76.2 ± 8.8 years.

The baseline characteristics of participants by quartiles of AIDI score are displayed in Table 1. Individuals with greater AIDI score were more likely to be women, tended to be younger, had lower body mass index, a higher education level, and higher levels of physical activity, and were more likely to regularly use dietary supplements but less likely to have a history of diabetes and hypertension compared with individuals with a low AIDI score.

An inverse association between anti-inflammatory potential of diet and risk of PAD was observed (Table 2). Compared with individuals in the lowest quartile of AIDI score, the HR of PAD for those in the highest quartile was 0.67 (95% CI, 0.53, 0.86) in current smokers, 0.78 (95% CI, 0.63, 0.97) in past smoker and 1.00 (95% CI, 0.82, 1.23) in never smokers. The cumulative incidence of PAD was 2.70 and 1.77 per 1000 person-year for two extreme quartiles of the AIDI score amongst past smokers, respectively, and 4.44 and 2.86 per 1000 person-year for two extreme quartiles of the AIDI score amongst current smokers, respectively. The associations remained in the competing risk analysis treating death without PAD diagnosis as a competing outcome (Supplementary Table 2).

The associations of AIDI with risk of PAD stratified by smoking status are presented in Fig. 1. We found a statistically significant interaction between AIDI and smoking status in relation to risk of PAD (p for interaction = 0.021). The inverse associations of higher anti-inflammatory potential of diet with lower risk of PAD were observed in past and current smokers but not in never smokers. The HR of PAD between extreme quartiles of the AIDI score was 0.67 (95% CI, 0.53, 0.86) in current smoker, 0.78 (95% CI, 0.63, 0.97) in past smoker and 1.00 (95% CI, 0.82, 1.23) in never smokers. The cumulative incidence of PAD was 2.70 and 1.77 per 1000 person-year for two extreme quartiles of the AIDI score amongst past smokers, respectively, and 4.44 and 2.86 per 1000 person-year for two extreme quartiles of the AIDI score amongst current smokers, respectively. The associations remained in the competing risk analysis treating death without PAD diagnosis as a competing outcome (Supplementary Table 2).

Table 1
Age-standardized baseline characteristics of participants from the Swedish Mammography Cohort and the Cohort of Swedish Men by quartiles of the anti-inflammatory diet index.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Quartiles of AIDI</th>
<th>Total population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q 1</td>
<td>Q 2</td>
</tr>
<tr>
<td>AIDI, range (median), scores</td>
<td>0-4 (4)</td>
<td>5</td>
</tr>
<tr>
<td>Number of individuals</td>
<td>36681</td>
<td>20998</td>
</tr>
<tr>
<td>Male, %</td>
<td>62.9</td>
<td>54.2</td>
</tr>
<tr>
<td>Age, years, mean ± SD</td>
<td>61.4 ± 9.7</td>
<td>61.2 ± 9.6</td>
</tr>
<tr>
<td>BMI, kg/m², mean ± SD</td>
<td>25.7 ± 3.7</td>
<td>25.4 ± 3.6</td>
</tr>
<tr>
<td>University education, %</td>
<td>11.5</td>
<td>16.0</td>
</tr>
<tr>
<td>Never smoker, %</td>
<td>41.9</td>
<td>43.7</td>
</tr>
<tr>
<td>Physical activity, %</td>
<td>10.1</td>
<td>8.0</td>
</tr>
<tr>
<td>0–10 min/day</td>
<td>16.0</td>
<td>14.8</td>
</tr>
<tr>
<td>&gt;30 min/day</td>
<td>64.2</td>
<td>68.2</td>
</tr>
<tr>
<td>Dietary supplement use, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>14.3</td>
<td>17.2</td>
</tr>
<tr>
<td>Irregular</td>
<td>18.8</td>
<td>20.9</td>
</tr>
<tr>
<td>No use</td>
<td>58.9</td>
<td>53.7</td>
</tr>
<tr>
<td>Diabetes history, %</td>
<td>5.7</td>
<td>5.2</td>
</tr>
<tr>
<td>Hypertension history, %</td>
<td>23.0</td>
<td>21.7</td>
</tr>
<tr>
<td>Hypercholesterolemia history, %</td>
<td>11.2</td>
<td>11.4</td>
</tr>
<tr>
<td>Energy intake, kcal/day, mean ± SD</td>
<td>2297 ± 909</td>
<td>2181 ± 855</td>
</tr>
<tr>
<td>Servings/day, median ± IQR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruits and vegetables</td>
<td>3.45 ± 2.45</td>
<td>3.96 ± 2.96</td>
</tr>
<tr>
<td>Tea</td>
<td>0.00 ± 1.00</td>
<td>0.00 ± 1.00</td>
</tr>
<tr>
<td>Coffee</td>
<td>3.00 ± 2.57</td>
<td>3.00 ± 2.00</td>
</tr>
<tr>
<td>Wholegrain foods</td>
<td>8.28 ± 5.50</td>
<td>8.00 ± 5.15</td>
</tr>
<tr>
<td>Breakfast cereals</td>
<td>0.07 ± 0.21</td>
<td>0.07 ± 0.50</td>
</tr>
<tr>
<td>Low-fat cheese</td>
<td>0.00 ± 0.00</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>Chocolate</td>
<td>0.07 ± 0.15</td>
<td>0.07 ± 0.21</td>
</tr>
<tr>
<td>Unprocessed red meat</td>
<td>0.50 ± 0.30</td>
<td>0.35 ± 0.30</td>
</tr>
<tr>
<td>Processed red meat</td>
<td>0.63 ± 0.58</td>
<td>0.35 ± 0.43</td>
</tr>
<tr>
<td>Organ meats</td>
<td>0.13 ± 0.21</td>
<td>0.07 ± 0.21</td>
</tr>
<tr>
<td>French fries</td>
<td>0.07 ± 0.07</td>
<td>0.00 ± 0.07</td>
</tr>
<tr>
<td>Soft drinks</td>
<td>0.14 ± 1.00</td>
<td>0.02 ± 0.57</td>
</tr>
<tr>
<td>Servings/week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuts</td>
<td>0.00 ± 0.47</td>
<td>0.00 ± 0.47</td>
</tr>
<tr>
<td>Legumes</td>
<td>0.47 ± 0.47</td>
<td>0.47 ± 0.47</td>
</tr>
<tr>
<td>Wine</td>
<td>0.12 ± 0.58</td>
<td>0.12 ± 0.58</td>
</tr>
<tr>
<td>Beer</td>
<td>0.00 ± 1.58</td>
<td>0.00 ± 4.08</td>
</tr>
<tr>
<td>Use of olive/canola oil, %</td>
<td>17.49</td>
<td>41.29</td>
</tr>
</tbody>
</table>

AIDI, anti-inflammatory diet index; BMI, body mass index; IQR, interquartile range; SD, standard deviation. The maximum AIDI score is 17.
4. Discussion

In the population-based cohorts of middle-aged and older adults, adherence to a diet with high anti-inflammatory potential was associated with a lower risk of PAD. The inverse association was observed in past and current smokers but not in never smokers. Among foods included in AIDI, high consumption of breakfast cereals, chocolate, and red wine, use of olive/canola oil,
and low consumption of processed red meat and organ meats were associated with a lower risk of PAD. We are not aware of any previous prospective studies investigating the associations of anti-inflammatory diet with incident PAD.

Data on the association of AIDI with PAD are limited, but some previous studies have found that other healthy dietary patterns, such as the Mediterranean diet [4] and a diet rich in fruits and vegetables [19], were associated with a lower risk of PAD. Results of the Prevención con Dieta Mediterránea trial including 7447 participants with high cardiovascular risk (i.e., with type 2 diabetes mellitus or at least 3 cardiovascular risk factors) showed that the group with Mediterranean diet plus extra-virgin olive oil interventions had a 66% lower risk of PAD compared with the control group after a median follow-up of 4.8 years [4]. This inverse association was also found in a case-control study with type 2 diabetes patients [20]. A healthy diet rich in fruit and vegetables, fiber and unsaturated fatty acid was inversely associated with PAD risk in a cohort study of 26 010 adults followed up for 21.7 years. However, two other cohort studies failed to replicate a protective role of a healthy diet composed of a high intake of fruits and vegetables, fish and whole grains, and low intake of sodium and sugar-sweetened beverages in PAD development [21,22].

The study did not support an inverse association of fruit and vegetable intake with PAD risk, which is inconsistent with previous findings [5]. This null finding may be caused by inadequate power. Another possible explanation can be that pesticides contamination in fruit and vegetable counteracts the weak inverse association with PAD [23,24]. However, this hypothesis may also apply to other plant-based foods, like breakfast cereals that showed an inverse association with PAD risk. As the levels of pesticides decrease in the drying process (from fresh to dried fruits) [25], the inverse association for dried fruits might be clear and thus support the inverse association for breakfast cereals.

The beneficial associations of high consumption of breakfast cereals [26], use of olive/canola oil [4,27], and low consumption of processed red meat [28] with risk of PAD were in agreement with previous studies. Being different from wholegrain foods additionally including different breads, oatmeal, pasta, and wheat or oat bran, some breakfast cereals (muesli) contain dried fruits and nuts that might be inversely associated with PAD risk [5]. Our observed associations of chocolate, red wine and organ meats consumption with PAD risk were novel findings and needs verifications in future studies. A six-month double-blind, randomized clinical trial in PAD patients showed that the group with daily intake of cocoa beverages that contains 15 g of cocoa and 75 mg of epicatechin had a better walking performance compared to the placebo group [29]. In addition, a higher chocolate consumption has been associated with a lower risk of other atherosclerotic diseases, including coronary artery disease [30] and ischemic stroke [31]. Polyphenols in red wine has potentials to improve vascular function and reduce endothelial dysfunction [32].

Our results showed that consumption of diet with higher anti-inflammatory potential was associated with lower PAD risk in current and past smokers, but not in never smokers. Similarly, previous studies found that the inverse associations between an anti-inflammatory diet with risk of heart failure and all-cause and cardiovascular mortality were stronger in smokers compared to that in non-smokers [8,9]. These findings suggest that a diet with high anti-inflammatory potential may partially offset the inflammatory process or other cardio-detrimental pathways introduced by cigarette smoking.

Atherosclerosis and thrombosis are two important pathological bases of PAD development [33]. The relations of inflammation with atherosclerosis and thrombosis have been elucidated [34]. An interplay of inflammation and autoimmune response through myeloid cells in vessel wall plays a vital role in the development and progression of atherosclerosis [35]. Similarly, the interplay of innate immune cells, cytokines, and the coagulation cascade sets the pathological basis for thrombosis. Even though we did not assess the associations of AIDI with different inflammatory, atherosclerotic, and thrombotic biomarkers, the diet of high anti-inflammatory potentials, measured by AIDI, showed an association with systemic inflammation in the body. The lower concentrations of high sensitivity C-reactive protein in the group with higher AIDI score were associated with a slower progression of peripheral atherosclerosis [36] and a lower risk of PAD [37–39]. In addition, systemic inflammation modified by intake of anti-inflammatory foods may be associated with skeletal muscle structure, hemodynamic, insulin resistance and glucose metabolism [2] and therefore influence PAD risk.

There are several strengths of the present study, including a large number of participants and a long follow-up time, which resulted in a large number of PAD cases. The validity of questionnaire-based AIDI was high across all levels of high sensitivity C-reactive protein, age, and potential inflammatory risk factors [7]. An additional strength of the study is the detailed documentation on diet and confounders; however, residual confounding from healthy lifestyle and other dietary factors, might exist and bias our findings. Dietary information was self-reported, which might cause recall bias and misclassification. Since the follow-up information was obtained by linkage of participants with the Swedish Patient Register (a nationwide database), we might have lost very few participants who moved out from Sweden and never came back. Another shortcoming is that nearly 30% and 50% of invited participants in the SMC and COSM, respectively, did not return the baseline questionnaire and were not included in these cohorts. Individuals with a healthy diet and lifestyle might be more likely to participate than those with an unhealthy lifestyle. This would reduce the variance in the studied dietary exposures, and we cannot exclude that a stronger association between AIDI and PAD risk may have been observed if the reference group (lowest AIDI group) had included individuals with even lower adherence to the diet with anti-inflammatory potential. In addition, the included individuals might be general healthier than the overall community-dwelling middle-aged and old adults in Sweden. If so, this would reduce the representativeness of the sample population. The lack of information on inflammatory and coagulation biomarkers limited the exploration of underlying mechanisms linking the anti-inflammatory potential of diet to PAD. Additionally, lifestyle and dietary habits may have changed during the long follow-up, which may lead to misclassification and a corresponding conservative bias of our estimates.

In conclusion, the inverse association between AIDI and incident PAD observed suggests that adherence to a diet with high anti-inflammatory potential may lower the risk of PAD in current and past smokers.

Authors’ contributions

S.Y. 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., M.B., S.M.D., N.H., A.W., A.Å. and S.C.L. provided important comments to the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2022.04.002.

References


